differed significantly between the time strata (Table 11-15 [f]: p=0.048). In the later tour stratum there was a significant positive association between current dioxin and the dermatology index (Est. RR=1.20, p=0.031). The percentages of Ranch Hands in this stratum who had at least one abnormality were 30.2, 40.3, and 38.6 percent for low, medium, and high current dioxin. In the earlier tour stratum the association was negative but nonsignificant (p=0.590).

Under the minimal assumption, the current dioxin-by-time interaction remained nonsignificant in the adjusted analysis of the dermatology index (Table 11-15 [g]: p=0.440). The interaction between current dioxin and time became marginally significant under the maximal assumption after adjusting for the presence of pre-SEA acne and the age-by-race interaction (Table 11-15 [h]: p=0.061). Within the later tour stratum, the association between current dioxin and the dermatology index also became marginally significant (Adj. RR=1.19, p=0.059) while the association in the earlier tour stratum remained nonsignificant (p=0.540).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the dermatology index, there was no significant difference in the percentage of participants with at least one abnormality among the four current dioxin categories (Table 11-15 [i]: p=0.479). After adjusting for significant covariate information, the overall contrast remained nonsignificant (Table 11-14 [j]: p=0.459). The individual contrasts also were nonsignificant.

Longitudinal Analysis

Physical Examination Variable

Dermatology Index

Longitudinal analyses of the percentage of participants who had an abnormal dermatology index at the 1987 examination were conducted to detect associations with initial dioxin in Ranch Hands, current dioxin and time since tour in Ranch Hands, and categorized current dioxin in Ranch Hands and Comparisons. Only participants with a normal dermatology index at the 1982 examination were included in these analyses. Table 11-16 presents the results of the longitudinal analyses.

For a specific longitudinal analysis (e.g., minimal assumption, initial dioxin analysis), the upper part of each subpanel of a table provides the percentages of participants with an abnormal dermatology index at each examination. The lower part of each subpanel presents sample sizes, percentages, relative risks, and associated 95 percent confidence intervals.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The longitudinal analysis of the percentage of Ranch Hands who had an abnormal dermatology index at the 1987 examination (and a normal dermatology index at the 1982 Baseline examination) displayed a nonsignificant association with initial dioxin for both the minimal and the maximal cohorts (Table 11-16 [a] and [b]: p=0.886 and p=0.787).

TABLE 11-16.

Longitudinal Analysis of Dermatology Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
a) Minimal	Low	28.3 (120)	42.4 (118)	20.3 (120)
	Medium	39.1 (248)	51.0 (243)	42.7 (248)
	High	38.5 (122)	50.4 (121)	35.3 (122)

Normal in 1982

Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	86	25.6	0.98 (0.80,1.22)	0.886
Medium	151	33.1		
High	75	25.3		

[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.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 11-16. (Continued)

Longitudinal Analysis of Dermatology Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
b) Maximal	Low	46.1 (167)	42.1 (164)	36.5 (167)
	Medium	35.5 (349)	50.6 (342)	40.4 (349)
	High	35.1 (174)	47.1 (172)	33.9 (174)

	Normal in 1982			
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	90	27.8	1.02 (0.87,1.20)	0.787
Medium	225	31.6		
High	113	23.9		

[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.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 11-16. (Continued)

Longitudinal Analysis of Dermatology Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal	≤18.6	1982	29.9 (67)	45.0 (120)	44.0 (50)
		1985	42.4 (66)	53.9 (117)	57.1 (49)
		1987	28.4 (67)	50.8 (120)	32.0 (50)
	>18.6	1982	29.6 (54)	33.9 (127)	31.9 (72)
		1985	50.9 (53)	44.0 (125)	47.2 (72)
		1987	33.3 (54)	37.8 (127)	34.7 (72)

Time (Yrs.)	Normal in 1982 Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
≤18.6	25.5 (47)	40.9 (66)	14.3 (28)	0.92 (0.64,1.32)	0.476[b] 0.655[c]
>18.6	23.7 (38)	28.6 (84)	30.6 (49)	1.09 (0.82,1.43)	0.560[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.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 11-16. (Continued)

Longitudinal Analysis of Dermatology Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
d) Maximal	≤18.6	1982	42.4 (92)	39.4 (180)	46.1 (76)
		1985	39.3 (89)	47.7 (176)	56.0 (75)
		1987	31.5 (92)	41.1 (180)	38.2 (76)
	>18.6	1982	41.9 (74)	31.8 (170)	32.7 (98)
		1985	54.8 (73)	48.2 (168)	42.3 (97)
		1987	47.3 (74)	34.7 (170)	35.7 (98)

Time (Yrs.)	Normal in 1982 Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
≤18.6	26.4 (53)	33.0 (109)	24.4 (41)	1.02 (0.78,1.32)	0.844[b] 0.907[c]
>18.6	32.6 (43)	25.9 (116)	28.8 (66)	1.05 (0.85,1.30)	0.650[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.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 11-16. (Continued)

Longitudinal Analysis of Dermatology Index

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Percent Abnormal/(n) in 1987 Current Dioxin 1982	1985	1987
Background	36.3 (658)	47.8 (655)	38.3 (658)
Unknown	39.4 (307)	46.8 (301)	38.1 (307)
Low	39.0 (187)	51.1 (184)	44.4 (187)
High	38.5 (174)	48.3 (172)	36.8 (174)

Normal in 1982

Current Dioxin Category	n in 1987	Percent Abnormal in 1987	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	419	30.1	All Categories		0.572
Unknown	186	28.5	Unknown vs. Background	0.93 (0.63,1.36)	0.695
Low	114	35.1	Low vs. Background	1.26 (0.81,1.95)	0.306
High	107	27.1	High vs. Background	0.86 (0.54,1.39)	0.548

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.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

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

Under the minimal and the maximal assumptions, the current dioxin-by-time since tour interaction was nonsignificant in the longitudinal analysis of the dermatology index (Table 11-16 [c] and [d]: p=0.476 and p=0.844). Thus, the association between current dioxin and the dermatology index did not differ for the two time strata.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the longitudinal analysis of the dermatology index, there was not a significant difference among the percentages of participants with an abnormal 1987 dermatology index (among those with a normal dermatology index at the 1982 Baseline examination) in the four current dioxin categories (Table 11-16 [e]: p=0.572).

DISCUSSION

When studying biological effects of herbicides in humans, particular emphasis must be placed on the dermatologic examination. Of the organ systems subjected to analysis, only the skin has a generally acknowledged clinical endpoint. That endpoint is chloracne, which has been related conclusively to topical dioxin exposure. The intact skin is a protective barrier but can serve, by cutaneous absorption, as a significant portal of entry through which internal organ systems are placed at risk for toxicity from the efforts of a wide range of industrial chemicals.

In dermatologic practice, as in all clinical disciplines, history can be more important to accurate diagnosis than objective physical findings. This is particularly true in the case of chloracne which, apart from the characteristic cutaneous distribution, has no clinical hallmark that distinguishes it from other more common acneiform eruptions. In the current study, examiners strictly were forbidden from taking an occupational history. Though at obvious variance with traditional practice, such restrictions were essential to the elimination of observer bias. During the examinations, dermatologists were instructed to biopsy lesions that were thought to be skin-cancer suspicious. Though blinded to the participants' herbicide exposure status, examiners performed a similar number of biopsies in the Ranch Hand (19) and Comparison (20) groups.

Because chloracne is rare in clinical practice, few dermatologists encounter it in a lifetime of practice. Experimental dose-response studies in animals and studies in humans have confirmed that the concentrations of TCDD required to produce overt lesions are far greater than that to which participants in the current study were likely to have been exposed in SEA. In the Seveso, Italy industrial explosion, for example, chloracne was associated with serum TCDD levels ranging from 828 ppt to 27,821 ppt (39). These levels contrast with a range of 26 ppt to 5,002 ppt and a median of 100 ppt, based on 742 Ranch Hands in this study. Chloracne was not detected in any of the participants at the 1987 physical examination. It is not surprising, therefore, that in the three examination cycles completed to date, no evidence of active chloracne has been detected. Recognizing the remote possibility that chloracne may have occurred in acute form and resolved, emphasis in data collection was placed on the presence of chronic cutaneous conditions such as scarring and pigmentation, which are recognized as complications of all forms of acne.

Of the 454 Ranch Hand participants with a verified history of acne, 366 only developed lesions subsequent to active duty in Vietnam. With few exceptions, the historical and physical examination variables that were associated positively with the current level of serum dioxin were limited to those participants with service in Vietnam after 1968 (i.e., ≤18.6 years). Within this subgroup, in a pattern consistent with a dose response, participants with higher levels of serum dioxin had a significantly increased incidence of the lifetime occurrence of acne relative to participants with lower levels (p=0.025). In contrast, a negative association was noted for participants with service prior to 1968. Furthermore, in both time strata, similar negative and positive associations were noted with respect to the development of acne subsequent to active duty in Vietnam. These results were not statistically significant.

The results of the analyses of the physical examination variables were consistent with the historical variables. Significant associations were limited to the later time stratum in which the incidence of acneiform scars and hyperpigmentation increased significantly (p=0.002 and p=0.007, respectively) in relation to the current level of serum dioxin. In contrast, in Ranch Hand participants now more removed from active duty in Vietnam, none of the physical examination variables was associated positively with the current body burden of dioxin. Finally, the longitudinal analysis of the dermatology index revealed no significant group differences between Ranch Hands and Comparisons.

SUMMARY

The dermatologic assessment was based on the occurrence of acne (lifetime and relative to SEA tour); location of acne; six dermatologic disorders (comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, and hyperpigmentation); other abnormalities; and a dermatology index based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts. Each of these dependent variables was analyzed for associations with initial dioxin, current dioxin and time since tour, and categorized current dioxin. Tables 11-17, 11-18, and 11-19 summarize the results.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses, none of the dermatology variables showed a significant association with initial dioxin under the minimal assumption. Under the maximal assumption, there was a significant positive association between post-SEA acne and initial dioxin when only those Ranch Hands who had pre-SEA acne were included in the analysis (i.e., pre/post-SEA acne versus pre-SEA acne) (p=0.013).

In the adjusted analysis of pre/post-SEA acne versus pre-SEA acne, there were significant interactions between initial dioxin and age and between initial dioxin and race under both assumptions. These interactions could have been caused by or affected by the sparseness of data in each stratum. Under the minimal assumption, there was also a significant interaction between initial dioxin and age in the analysis of the location of acne when only Ranch Hands with post-SEA acne were included in the analysis. The association between initial dioxin and the location of acne was positive but nonsignificant for the younger Ranch Hands and negative and nonsignificant for the older Ranch Hands.

TABLE 11-17.

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

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Occurrence of Acne (Lifetime)	ns	ns	ns	ns
Acne Relative to SEA Tour				
Pre/Post-SEA and Post SEA vs. Pre-SEA and None	ns	NS	ns	ns
Post-SEA vs. None	ns	ns	ns	ns
Pre/Post-SEA vs. Pre-SEA	NS	+0.013	****	****
Location of Acne (Post-SEA)	NS	ns	** (NS)	ns
Location of Acne (Pre/Post-SEA and Post-SEA)	NS	ns	NS	ns
Physical Examination				
Comedones	NS	NS	NS*	NS
Acneiform Lesions	ns	NS*	ns	NS
Acneiform Scars	NS	NS*	NS	NS
Depigmentation	ns	NS	ns	NS
Inclusion Cysts	ns	ns*	ns	ns*
Hyperpigmentation	NS	+0.008	NS	** (+0.005)
Other Abnormalities	ns	ns*	ns	ns
Dermatology Index	NS	NS	NS	NS

+: Relative risk 1.00 or greater for discrete analysis.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table J-1 for a detailed description of this interaction.
** (0.005): Log_2 (initial 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 J-1 for a detailed description of this interaction.
****: Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); refer to Appendix Table J-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 11-18.

Summary of Current Dioxin and Time Analyses for Dermatology 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						
Occurrence of Acne (Lifetime)	ns	NS	ns	-0.006	+0.025	ns
Acne Relative to SEA Tour						
Pre/Post-SEA and Post-SEA vs. Pre-SEA and None	ns*	NS	ns	-0.001	+0.005	ns
Post-SEA vs. None	ns	NS	ns	-0.006	NS*	-0.045
Pre/Post-SEA vs. Pre-SEA	ns	NS	NS	ns*	+0.021	NS
Location of Acne (Post-SEA)	+0.021	ns	NS*	NS*	ns	NS
Location of Acne (Pre/Post-SEA and Post-SEA)	+0.037	ns	+0.030	NS	ns	NS
Physical Examination						
Comedones	NS	NS	NS	ns	NS	NS
Acneiform Lesions	ns	NS	ns	ns	+0.016	NS
Acneiform Scars	ns*	+0.009	NS	-0.030	+0.002	NS
Depigmentation	ns	NS	ns	ns*	NS	ns
Inclusion Cysts	NS	ns	NS	NS	ns	ns
Hyperpigmentation	NS	NS	NS	ns	+0.007	NS
Other Abnormalities	ns	ns	ns	ns	ns	ns*
Dermatology Index	ns	NS	NS	-0.048	+0.031	ns

-: C*T: Relative risk for ≤18.6 category greater than relative risk for >18.6 category.
≤18.6 and >18.6: Relative risk less than 1.00.
+: C*T: Relative risk for ≤18.6 category less than relative risk for >18.6 category.
≤18.6 and >18.6: Relative risk 1.00 or greater.
NS/ns: Not significant (p>0.10).
NS*/ns*: Marginally significant (0.05<p≤0.10).
Note: P-value given if p≤0.05.
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 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour more 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 11-18. (Continued)

Summary of Current Dioxin and Time Analyses for Dermatology 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						
Occurrence of Acne (Lifetime)	ns	NS	ns	-0.006	NS*	-0.040
Acne Relative to SEA Tour						
Pre/Post-SEA and Post-SEA vs. Pre-SEA and None	ns*	NS	ns	-0.001	+0.019	-0.043
Post-SEA vs. None	ns	NS	ns	-0.006	NS*	-0.045
Pre/Post-SEA vs. Pre-SEA	ns	NS	NS	ns*	+0.021	NS
Location of Acne (Post-SEA)	+0.021	ns	NS*	NS*	ns	NS
Location of Acne (Pre/Post-SEA and Post-SEA)	+0.037	ns	+0.030	NS	ns	NS
Physical Examination						
Comedones	NS	NS	NS*	ns	NS	NS
Acneiform Lesions	ns	ns	ns	ns	NS*	ns
Acneiform Scars	ns*	+0.047	ns	-0.032	+0.016	ns
Depigmentation	ns	NS	ns	ns*	NS*	ns
Inclusion Cysts	NS	ns	NS	NS	ns	ns
Hyperpigmentation	ns	NS*	NS*	ns	+0.003	NS
Other Abnormalities	ns	ns	ns	ns	ns	ns
Dermatology Index	ns	NS	NS	ns*	NS*	ns

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

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

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 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour more 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 relaive risk for ≤18.6 category greater than relative risk for >18.6 category, or relative risk less than 1.00.

TABLE 11-19.

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

Variable	All	Unadjusted		
		Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Occurrence of Acne (Lifetime)	NS	NS	NS	NS
Acne Relative to SEA Tour				
Pre/Post-SEA and Post-SEA vs. Pre-SEA and None	NS	NS	NS	NS
Post-SEA vs. None	NS	NS	NS	NS
Pre/Post-SEA vs. Pre-SEA	NS	ns	NS	NS
Location of Acne (Post-SEA)	NS*	+0.008	NS	NS
Location of Acne (Pre/Post-SEA and Post-SEA)	NS	+0.045	NS	NS
Physical Examination				
Comedones	NS	ns	NS	ns
Acneiform Lesions	NS	-0.026	NS	ns
Acneiform Scars	NS	NS	NS*	NS*
Depigmentation	NS	ns	ns	NS
Inclusion Cysts	0.041	NS	NS*	ns*
Hyperpigmentation	0.037	-0.028	ns	NS
Other Abnormalities	NS	NS	ns	ns
Dermatology Index	NS	NS	NS	ns

-: Relative risk less than 1.00.
+: Relative risk 1.00 or greater.
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 11-19. (Continued)

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

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Questionnaire				
Occurrence of Acne (Lifetime)	NS	NS	NS	ns
Acne Relative to SEA Tour				
Pre/Post-SEA and Post-SEA vs. Pre-SEA and None	** (NS)	** (NS)	** (NS)	** (ns)
Post-SEA vs. None	NS	NS	NS	ns
Pre/Post-SEA vs. Pre-SEA	NS	ns	NS	NS
Location of Acne (Post-SEA)	NS*	+0.008	NS	NS
Location of Acne (Pre/Post-SEA and Post-SEA)	NS	+0.039	NS	ns
Physical Examination				
Comedones	NS	ns	NS	ns
Acneiform Lesions	NS	ns*	NS	ns
Acneiform Scars	NS	NS	NS*	NS*
Depigmentation	NS	ns	ns	NS
Inclusion Cysts	NS*	NS	NS*	ns
Hyperpigmentation	0.049	ns*	ns	NS
Other Abnormalities	NS	NS	ns	NS
Dermatology Index	NS	NS	NS	ns

+: Relative risk 1.00 or greater.
NS/ns: Not significant ($p>0.10$).
NS*/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 J-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.

In the unadjusted analyses of the physical examination variables, there were marginally significant positive associations between initial dioxin and acneiform lesions (p=0.080) and between initial dioxin and acneiform scars (p=0.058) under the maximal assumption. Inclusion cysts was also marginally associated with initial dioxin, but with a relative risk less than 1 (p=0.098). Hyperpigmentation displayed a significant positive association with initial dioxin under the maximal assumption (p=0.008), and the variable consisting of other abnormalities showed a marginally significant negative association with initial dioxin (p=0.057).

Under the minimal assumption, the positive association between initial dioxin and comedones became marginally significant in the adjusted analysis (p=0.076). Under the maximal assumption, the negative association between initial dioxin and inclusion cysts remained marginally significant (p=0.075). Also under the maximal assumption, in the adjusted analysis of hyperpigmentation, there were significant interactions between initial dioxin and age and between initial dioxin and the presence of pre-SEA acne. For the older Ranch Hands there was a significant positive association between initial dioxin and hyperpigmentation (p<0.001). For the younger Ranch Hands, the association was nonsignificant for those who did not have pre-SEA acne. Without these interactions in the adjusted maximal analysis of hyperpigmentation, the association with initial dioxin was significant and positive (p=0.005).

The longitudinal analysis of the dermatology index displayed a nonsignificant association with initial dioxin.

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

In the unadjusted maximal analysis of lifetime occurrence of acne, the current dioxin-by-time since tour interaction was significant (p=0.006). The association between occurrence of acne and current dioxin was significantly positive in the later tour stratum (p=0.025) and was negative, but nonsignificant, in the earlier tour stratum.

In the minimal analysis of acne relative to SEA tour, the current dioxin-by-time interaction was marginally significant for the participants with either post-SEA acne only or with pre/post-SEA acne (p=0.062). The association between post-SEA acne and current dioxin was positive in the later tour stratum and negative in the earlier tour stratum, but was not statistically significant in both strata. Under the maximal assumption, the current dioxin-by-time interaction was significant in the analysis that contrasted Ranch Hands with either post-SEA acne only or with pre/post-SEA acne versus Ranch Hands without post-SEA acne (p=0.001), and the stratified analysis that excluded pre-SEA acne (p=0.006). In the stratified analysis of the Ranch Hands with at least one occurrence of acne before their first SEA tour, the current dioxin-by-time interaction was marginally significant (p=0.072). In the first two analyses, the association with current dioxin was positive and either significant or marginally significant within the later tour stratum, and was negative within the earlier tour stratum. In the other analysis, the association between post-SEA acne and current dioxin was positive in both time strata, but was significant only in the later tour stratum.

In the adjusted analysis of the lifetime occurrence of acne, the interaction between current dioxin and time remained significant (p=0.006). However, the positive association

with current dioxin became only marginally significant in the later tour stratum (p=0.078) and the negative association in the earlier tour stratum became significant (p=0.040). In the analysis of the occurrence of acne, significant covariates were retained only in the analysis that contrasted the post-SEA and the pre/post-SEA categories with the Ranch Hands without post-SEA acne. In this analysis, the association with current dioxin differed significantly between the time strata (p=0.001), was significantly positive in the later tour stratum (p=0.019), and was significantly negative in the earlier tour stratum (p=0.043).

In the unadjusted minimal analysis of the location of acne, the interaction between current dioxin and time was significant in the analysis that included only post-SEA acne (p=0.021) and the analysis that also included pre/post-SEA acne (p=0.037). The association between current dioxin and location of acne was negative, but nonsignificant, in the later tour stratum and positive and either significant or marginally significant in the earlier tour stratum. Under the maximal assumption, the current dioxin-by-time interaction was only marginally significant in the analysis that included only post-SEA acne (p=0.083) and was nonsignificant in the analysis that also included pre/post-SEA acne.

No covariates were retained in the adjusted analyses of the location of acne, so the results were identical to those in the unadjusted analyses.

In the unadjusted minimal analyses of the physical examination variables, the current dioxin-by-time interaction was marginally significant only in the analysis of acneiform scars (p=0.100). In this analysis, the association between current dioxin and acneiform scars was significantly positive for the Ranch Hands who served a late tour (p=0.009) and was positive but nonsignificant for those who served an early tour. In the analysis of acneiform scars, the current dioxin-by-time interaction was significant under the maximal assumption (p=0.030) with a significant positive association between acneiform scars and current dioxin in the later tour stratum (p=0.002). The current dioxin-by-time interaction was marginally significant in the unadjusted maximal analysis of depigmentation (p=0.076). In the unadjusted analysis of the dermatology index, the current dioxin-by-time interaction was significant (p=0.048) where the association with current dioxin was significantly positive in the later tour stratum (p=0.031). Within the later tour stratum, there were also significant positive associations between current dioxin and acneiform lesions (p=0.016) and between current dioxin and hyperpigmentation (p=0.007) under the maximal assumption.

In the adjusted analyses of the physical examination variables, acneiform scars was the only variable to have a marginally significant current dioxin-by-time interaction under the minimal assumption (p=0.097). The association between current dioxin and acneiform scars was significantly positive in the later tour stratum (p=0.047) and was negative, but nonsignificant, in the earlier tour stratum. In the adjusted analysis of comedones, there was a marginally significant positive association with current dioxin in the earlier tour stratum under the minimal assumption (p=0.074). There was also a marginally significant positive association between current dioxin and hyperpigmentation within both time strata under the minimal assumption (time$\leq$18.6 years: p=0.084; time>18.6 years: p=0.090). Under the maximal assumption, the current dioxin-by-time interaction was significant in the adjusted analysis of acneiform scars (p=0.032) and was marginally significant in the adjusted analyses of depigmentation (p=0.076) and the dermatology index (p=0.061). Within the later tour stratum, the association with current dioxin was significantly positive in the analysis of

acneiform scars (p=0.016) and was marginally significant and positive in the analyses of acneiform lesions (p=0.091), depigmentation (p=0.094), and the dermatology index (p=0.059). Within the earlier tour stratum, the association with current dioxin was negative but nonsignificant in all four of these analyses. There was also a significant positive association between current dioxin and hyperpigmentation (p=0.003) within the later tour stratum of the adjusted maximal analyses.

The current dioxin-by-time since tour interaction was not significant in the longitudinal analysis of the dermatology index.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analyses of the occurrence of acne (both lifetime and relative to SEA tour), the overall contrast of the four current dioxin categories was nonsignificant. The overall contrast was marginally significant in the analysis of the location of acne when the analysis was restricted to post-SEA acne only (p=0.060). In this analysis, the percentage of participants with acne on the temples, eyes, ears, or a combination of these sites in the unknown category was significantly greater than the percentage in the background category (p=0.008). The percentage in the unknown category also was significantly greater than the percentage in the background category in the analysis of the location of acne that combined the post-SEA acne and the pre/post-SEA acne categories (p=0.045). In both analyses of the location of acne, the percentage of Ranch Hands in the high current dioxin category with acne on the temples, eyes, ears, or a combination of these sites was greater than the percentage of Comparisons in the background category, but the difference was nonsignificant.

In the adjusted analysis of the occurrence of acne relative to SEA tour, there was a significant interaction between categorized current dioxin and race when the post-SEA and pre/post-SEA categories were contrasted with the participants without any post-SEA acne (p=0.022). There was a significant difference among the current dioxin categories in the Black stratum (p=0.037) but not in the non-Black stratum.

In the adjusted analysis of the location of acne that included only the post-SEA acne category, no covariates were retained in the model and adjusted results are the same as unadjusted results. When the participants who had both pre- and post-SEA acne also were included in the analysis, the percentage of participants in the unknown category who had acne on the temples, eyes, ears, or a combination of these sites was significantly greater than the percentage in the background category (p=0.039). In the high versus background contrast, the relative risk was less than 1, but nonsignificant.

In the unadjusted analyses of the physical examination variables, the percentages of participants with inclusion cysts and the percentages with hyperpigmentation differed significantly among the four current dioxin categories (inclusion cysts: p=0.041; hyperpigmentation: p=0.037). In the analysis of inclusion cysts, the percentage in the low category was marginally greater than the percentage in the background category (p=0.086) and the percentage in the high category was marginally less than the percentage in the background category (p=0.098). In the analysis of hyperpigmentation, the percentage in the unknown category was significantly less than the percentage in the background category (p=0.028). There was also a significant relative risk that was less than 1 for the unknown

versus background category contrast in the analysis of acneiform lesions (p=0.026). In the analysis of acneiform scars, there was a marginally significant relative risk that was greater than 1 for the low versus background category (p=0.094) and for the high versus background category contrasts (p=0.051).

In the adjusted analyses of the physical examination variables, the overall contrast became marginally significant in the analysis of inclusion cysts (p=0.070), but remained significant in the analysis of hyperpigmentation (p=0.049). In the adjusted analyses of acneiform lesions and hyperpigmentation, there was a marginally significant relative risk greater than 1 between the unknown and background categories (acneiform lesions: p=0.055; hyperpigmentation: p=0.052). There was a marginally significant relative risk greater than 1 between the low and background categories in the adjusted analyses of acneiform scars and inclusion cysts (acneiform scars: p=0.070; inclusion cysts: p=0.080). Between the high and background categories, there was a marginally significant relative risk greater than 1 in the adjusted analysis of acneiform scars (p=0.098).

In the longitudinal analysis of the dermatology index the overall contrast of the four current dioxin categories was not significant.

CONCLUSION

In general, the occurrence and location of acne were not associated with initial dioxin. However, in the stratified analysis of acne relative to SEA tour, the association with initial dioxin was negative in the stratum consisting of Ranch Hands without pre-SEA acne (post-SEA versus none) and was positive in the pre-SEA acne stratum (pre/post-SEA versus pre-SEA). Of the physical examination variables, only hyperpigmentation had a significant positive association with initial dioxin under the maximal assumption.

The association between current dioxin and the occurrence of acne (lifetime), under the maximal assumption, differed between the time since tour strata with a positive association for Ranch Hands with a later tour and a negative association for those with an early tour. The same pattern was exhibited in the analysis of acne relative to SEA tour. In the stratified analysis of acne relative to SEA tour the association with current dioxin, within the earlier tour stratum, was similar to the association with initial dioxin; negative for Ranch Hands without pre-SEA acne and positive for those with pre-SEA acne. Several of the physical examination variables also had significant or marginally significant positive associations with current dioxin in the later tour stratum but nonsignificant associations in the earlier tour stratum. In contrast, the association between current dioxin and location of acne was negative in the later tour stratum and positive in the earlier tour stratum. No significant differences were found between the low and background current dioxin categories nor between the high and background categories for any of the variables. No cases of chloracne were defined, nor were there any dermatologic endpoints consistently related to the current body burden of dioxin.

The longitudinal analysis of the dermatology index showed no significant associations with dioxin.

In summary, there is no consistent evidence in these data to suggest a dioxin effect on the dermatologic system.

CHAPTER 11

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