

## CHAPTER 11

### DERMATOLOGIC ASSESSMENT

#### INTRODUCTION

##### Background

Chloracne, a chronic acneiform eruption with a highly specific cutaneous distribution, was first described by Von Bettman in 1897 as an occupational disease found in German chemical industrial workers. It was not until 1957 that it became recognized as a very specific consequence of trichlorophenol exposure (1, 2).

Early animal researchers employed the rabbit's ear as a model for assaying the effects of chloracnegenic compounds (3, 4). Other researchers conducted experiments on hairless mice. These experiments have produced histopathologic changes similar to the changes that occur in humans exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), including hyperkeratotic changes in the sebaceous follicle with plugging of the orifice, hyperkeratinization of the stratum corneum, and keratin cyst formation (5, 6).

Most cases of chloracne have occurred in chemical plant workers or in victims of industrial accidents. Thousands of cases were reported in industrial workers during the 1930 to 1940 era; the earliest descriptions of chloracne-like disease date back to the turn of the century (7). Chronic conditions associated with severe chloracne include actinic elastosis, acne scars, and excessive hair growth (8, 9). The severity of chloracne appears to be dose-related, but may depend on the route of administration, age, genetic predisposition, and the presence of acne vulgaris and other skin disorders (8, 10, 11).

Monkeys who had been administered lethal doses of TCDD developed acneiform lesions of the lips, retention cysts of the Meibomian glands of the eyelids, facial alopecia, and loss of eyelashes (12). Other studies have demonstrated that TCDD induced squamous cell carcinomas in hamsters (13) and induced chloracne, hirsutism, and hyperpigmentation in association with suppression of selected androgens in rats (14). Domestic animals accidentally exposed to TCDD in contaminated soil have developed alopecia, mucous membrane inflammation, hyperkeratosis and ulcerative dermatitis (15, 16).

Recent research has defined a genetic basis for the dermal responses of selected laboratory animals exposed to TCDD. In one series of experiments, investigators found strain-specific differences in the cutaneous reactions of haired and hairless mice to the topical application of TCDD (17). The involvement of sebaceous glands and increased transglutaminase activity were noted in both strains while epidermal proliferation and hyperkeratinization occurred in the responsive (haired) strain only. Furthermore, in a subsequent study from the same laboratory, these TCDD-induced dermal changes were associated with an increased density of Langerhans cells in mouse skin unique to the responsive strain (18). Based on these and other studies (19, 20), it is clear that these strain-specific responses are determined genetically and that there is evidence that they may be mediated by the aryl hydroxylase (Ah) receptor (21, 22).

Of the industrial compounds known to cause chloracne (e.g., the chlorinated aromatic compounds), TCDD is by far the most potent. As summarized in a recent review article (23), numerous investigators have studied the pathogenesis of chloracne at the cellular level. In human epidermal cell-culture preparations, TCDD causes cell proliferation and differentiation into keratinocytes with excessive production of keratin (21, 24, 25, 26).

Studies of the application of dioxin to skin in human volunteers have defined the histopathologic changes that were described earlier in animals (27). Chloracne is characterized by a maculopapular rash of active comedones conforming to an eyeglass or facial butterfly distribution, often accompanied by chest, back, or periorbital lesions (8, 10). Clinically, the presence of chloracne, particularly in the chronic form, which can persist more than 30 years after exposure (9) can be strongly suspected on historical grounds though definitive diagnosis requires biopsy and histologic confirmation.

Many of the longitudinal studies designed to investigate the long-term health effects of TCDD exposure in humans have focused on populations from industrial accidents, particularly the 1976 explosion of a trichlorophenol plant in Seveso, Italy (28-33). In most cases, target organ abnormalities that occur in association with acute exposure to TCDD appear to resolve over time with no evidence for chronic hepatic biochemical or neurological abnormalities (9, 30, 33, 34). In addition, a recently published mortality study found no increased risk of malignancy among 323 industrial workers with chloracne (35).

The use of chloracne as a marker for TCDD exposure has been the subject of controversy. At issue is whether long-term health consequences occur at levels of exposure less than that required to produce chloracne. Also, recent studies of subjects with chloracne have found extreme variation in the body burden of dioxin as reflected in adipose tissue (36, 37, 38) and serum (39) levels.

Although the high incidence of dermatologic disease in Vietnam veterans has been well established (40), there is no objective evidence to support an association with herbicide exposure. In a study of American Legion veterans (41), a higher incidence of self-reported cutaneous disease was found in veterans who served in Vietnam. However, no attempt was made to confirm the historical findings by physical examination and the validity of the exposure indices employed have been questioned. In the Vietnam Experience Study conducted by the U.S. Centers for Disease Control the incidence of dermatologic disorders on physical examination was similar in Vietnam and non-Vietnam veterans (42). In the three examination cycles of the Air Force Health Study, Ranch Hand participants were found to have a slightly greater incidence of basal-cell skin cancers than Comparisons, though by longitudinal analysis the risk appears to be diminishing over time (43).

More detailed summaries of the pertinent scientific literature for the dermatologic assessment can be found in the report of the previous analyses of the 1987 examination data (44).

### **Summary of Previous Analyses of the 1987 Examination Data**

With the exception of more Ranch Hands reporting at least one occurrence of acne during their lifetime than Comparisons, no significant group differences were detected in the

dermatologic assessment. Subsequent analysis of the occurrence of acne indicated that, for participants with no history of acne before the start of the first Southeast Asia (SEA) tour, a higher percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour. However, the anatomic distribution of these lesions did not suggest chloracne as a cause. No cases of chloracne were diagnosed in the physical examination. Analyses were conducted on historical occurrence and duration of acne, six dermatologic disorders, a composite variable of other disorders, and a dermatology index of four disorders. All of these analyses found no significant group differences. The longitudinal analysis, based on the dermatology index, showed no significant differences between groups over time.

## **Parameters of the Dermatologic Assessment**

### ***Dependent Variables***

The dermatologic assessment was based on questionnaire and physical examination data.

#### **Questionnaire Data**

During the face-to-face health interview, each study participant was asked about occurrences of acne since the date of the last health interview. In addition, data regarding occurrence of acne were collected at the physical examination. This information was used to update data gathered through the 1985 examination, which was subsequently verified through medical records review. Information regarding the date of occurrence and location of occurrence also was collected and verified. The following variables were constructed from the self-reported acne data and analyzed in the dermatologic assessment and are defined below.

- Occurrence of Acne (Lifetime):
  - Yes: at least one occurrence of acne
  - No: no occurrences of acne.
- Acne Relative to SEA Tour of Duty:
  - Post-SEA: all occurrences were after the start of the first SEA tour
  - Pre/post-SEA: multiple occurrences, both before and after the start of the first SEA tour, or a case of acne that began before the start of the first SEA tour and ended after starting the SEA tour
  - Pre-SEA: last occurrence was before the start of the first SEA tour
  - None: no occurrences of acne.
- Location of Acne (post-SEA; post-SEA combined with pre/post-SEA):
  - Temples; eyes/eyelids; ears; temples and eyes; eyes and ears; temples and ears; temples, eyes, and ears; and other sites (cheeks, nose, forehead, jaw/chin, chest, and back)

If an individual had multiple site involvement for one or more of the seven specified sites and for the category "other sites," then site assignment went to the specified site(s) category.

The analysis of the occurrence of acne was based on responses from all of the participants of the 1987 examination. Acne relative to the SEA tour of duty was analyzed twice; once using all of the participants of the 1987 examination, and again using all participants of the 1987 examination stratified by pre-SEA occurrence (yes/no) of acne. Location of acne was analyzed twice. In one case, the location of acne was limited to the participants who had all their acne after the start of the first SEA tour (post-SEA). The second analysis was based on participants who had all their acne after the start of the first SEA tour or who had multiple occurrences, both before and after the start of the first tour, or a case of acne that began before the start of the first SEA tour and ended after starting the SEA tour (post-SEA combined with pre/post-SEA).

No participants were excluded for medical reasons from the analysis of these variables.

#### **Physical Examination Data**

Eight variables from the physical examination data were analyzed in the dermatologic assessment: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and the dermatology index. Depigmentation and hyperpigmentation were defined as areas of skin that were less or more pigmented relative to the rest of the integument. The variable "other abnormalities" was coded as yes/no. A participant was considered as abnormal (yes) for this variable if any of the following disorders were detected in the physical examination: jaundice, spider angiomas, palmar erythema, palmar keratoses, actinic keratoses, petechiae, ecchymoses, conjunctival abnormality, oral mucosal abnormality, fingernail abnormality, toenail abnormality, dermatographia, cutis rhomboidalis, nevus, or other abnormalities. Suspected melanoma, suspected basal cell carcinoma, and suspected squamous cell carcinoma, which were used in the classification of this variable in the previous 1987 report, were not used in this report because most of the other conditions under this variable do not relate to cancer. Skin malignancy is discussed in Chapter 7, Malignancy Assessment. The dermatology index was formed by counting the number of abnormalities present for the following conditions: comedones, acneiform lesions, acneiform scars, and inclusion cysts. This dermatology index was then dichotomized as no abnormalities (normal) and at least one abnormality (abnormal). All other variables were coded as yes/no.

No participants were excluded for medical reasons from the analysis of these variables.

#### ***Covariates***

The covariates age and race were used in adjusted statistical analyses of the occurrence of acne and location of acne. Presence of pre-SEA acne (yes/no) was a stratification variable in the analysis of acne relative to SEA tour. Time reference to SEA (pre/post-SEA and post-SEA) was a stratification variable in the analysis of location of acne. The covariates age, race, and presence of pre-SEA acne were used in adjusted statistical analyses of all physical examination variables in the dermatologic assessment. Age was used in its continuous form for modeling purposes for all dependent variables and dichotomized for interaction summaries.

### ***Relation to Baseline, 1985, and 1987 Studies***

The variables analyzed in this report were also analyzed in the 1985 and 1987 studies. Duration of acne was analyzed in the 1985 and 1987 studies but was not analyzed in this report. To conduct a thorough analysis of the occurrence and location of acne, the data used in this report have been updated to incorporate information from the physical examination and all information has been verified clinically. Time references to SEA and the presence of pre-SEA acne also have been updated and verified. Also different from the previous studies is the variable "other abnormalities," which no longer includes suspected melanoma, suspected basal cell carcinoma, and suspected squamous cell carcinoma. Except for depigmentation, which was a refinement in the analysis of the 1985 study, the variables analyzed in the 1985 and 1987 studies were the same variables analyzed in the Baseline study.

The longitudinal analysis for the dermatologic assessment was based on the dermatology index. For this analysis, the dermatology index was dichotomized as no abnormalities and at least one abnormality.

### **Statistical Methods**

Table 11-1 summarizes the statistical analyses that were performed for the dermatologic assessment. The first part of this table describes the dependent variables analyzed and identifies the candidate covariates and the statistical methods used. Chapter 4, Statistical Methods, describes basic statistical analysis methods. The second part of this table further describes the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Appendix J-1 contains graphical displays of dermatology dependent variables versus initial dioxin for the minimal and maximal Ranch Hand cohorts, and dermatology dependent variables versus current dioxin for Ranch Hands and Comparisons. Appendix J-2 presents graphics for the dioxin-by-covariate interactions determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

Three statistical models were used to examine the association between a dermatology dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch 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 the time since each Ranch Hand's tour of duty in SEA. 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 dermatology 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 (44). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

**TABLE 11-1.**  
**Statistical Analysis for the Dermatologic Assessment**  
**Dependent Variables**

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analysis
Occurrence of Acne (Lifetime)	Q/PE-V	D	Yes No	AGE,RACE	U:LR A:LR
Acne Relative to SEA Tour	Q/PE-V/ MIL	D	Pre-SEA Pre/Post-SEA Post-SEA None	AGE,RACE, SEAACNE	U:LR,CS,FT A:LR
Location of Acne	Q/PE-V	D	Temples Eyes Ears Other Sites	TIMESEA, AGE,RACE	U:LR A:LR
Comedones	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Acneiform Lesions	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Acneiform Scars	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Depigmentation	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Inclusion Cysts	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Hyperpigmentation	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Other Abnormalities	PE	D	Yes No	AGE,RACE, SEAACNE	U:LR A:LR
Dermatology Index	PE	D	Abnormal: $\geq 1$ Normal: 0	AGE,RACE, SEAACNE	U:LR A:LR L:OR

**TABLE 11-1. (Continued)**  
**Statistical Analysis for the Dermatologic Assessment**  
**Covariates**

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Time Reference to SEA (TIMESEA)	Q-PE-V/ MIL	D	Pre/Post-SEA Post-SEA
Presence of Pre-SEA Acne (SEAACNE)	Q-PE-V/ MIL	D	Yes No

**Abbreviations**

Data Source: MIL--Air Force military records  
PE--1987 SCRF physical examination  
Q/PE-V--Questionnaire and physical examination (verified)

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

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

Statistical Methods: CS--Chi-square contingency table test  
FT--Fisher's exact test  
LR--Logistic regression analysis  
OR--Chi-square test on the odds ratio

## RESULTS

### Exposure Analysis

#### *Questionnaire Variables*

Figure 11-1 shows the occurrence of acne by time for the 1,670 participants.

#### Occurrence of Acne (Lifetime)

##### *Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)*

The association between initial dioxin and the lifetime occurrence of acne was not significant in the unadjusted minimal and maximal analyses (Table 11-2 [a] and [b]:  $p=0.430$  and  $p=0.787$ ). The association remained nonsignificant after the model had been adjusted for significant covariates (Table 11-2 [c] and [d]: minimal assumption,  $p=0.188$ ; maximal assumption,  $p=0.406$ ).

##### *Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time*

In the unadjusted analysis of the lifetime occurrence of acne, the interaction between current dioxin and time since tour was nonsignificant under the minimal assumption (Table 11-2 [e]:  $p=0.115$ ). Under the maximal assumption, however, the association between current dioxin and the lifetime occurrence of acne differed significantly between the time strata (Table 11-2 [f]:  $p=0.006$ ). Within the later tour stratum ( $\text{time} \leq 18.6$  years) there was a significant positive association (Est. RR=1.21,  $p=0.025$ ). In the earlier tour stratum ( $\text{time} > 18.6$  years) the association was negative but nonsignificant ( $p=0.110$ ). The percentages of Ranch Hands in the later tour stratum who reported at least one occurrence of acne in their lifetime were 49.1, 57.6, and 62.7 percent for low, medium, and high current dioxin.

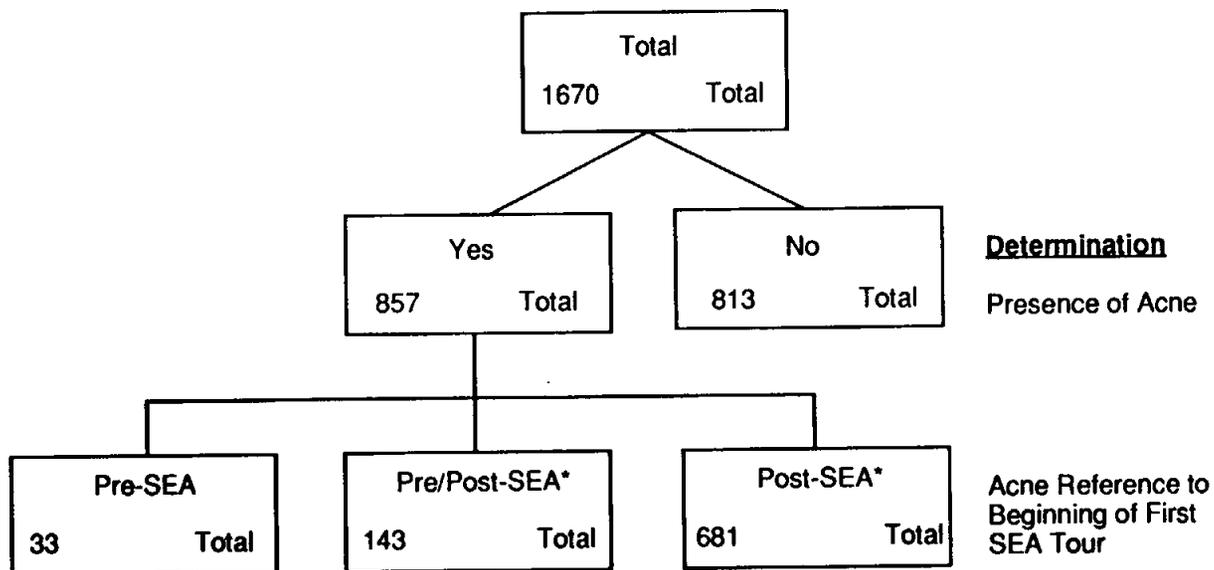
In the adjusted minimal analysis, the current dioxin-by-time interaction remained nonsignificant (Table 11-2 [g]:  $p=0.131$ ). Under the maximal assumption, the interaction between current dioxin and time remained significant (Table 11-2 [h]:  $p=0.006$ ). However, after the model had been adjusted for age, the association between current dioxin and lifetime occurrence of acne became only marginally significant in the later tour stratum (Adj. RR=1.17,  $p=0.078$ ) and became significant in the earlier tour stratum (Adj. RR=0.85,  $p=0.040$ ). In the earlier tour stratum, the percentages of Ranch Hands who reported at least one occurrence of acne in their lifetime decreased over the low, medium, and high levels of current dioxin (57.0%, 50.3%, and 42.3%).

##### *Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The percentage of participants who reported at least one occurrence of acne in their lifetime did not differ significantly among the four current dioxin categories (Table 11-2 [i]:  $p=0.819$ ). Even after adjusting for significant covariate information, the overall difference and individual contrasts remained nonsignificant (Table 11-2 [j]:  $p > 0.35$  for all contrasts).

#### Acne Relative to SEA Tour

Participants with acne were further classified as to when they had acne relative to their duty in SEA. Of the 857 participants with acne, 33 had all occurrences of acne prior to the



\* Analysis of location of acne performed for these participants.

- Yes to Acne** - Reported acne on Baseline and/or 1985 study and/or 1987 study.
- No to Acne** - Never had acne.
- Pre-SEA Acne** - Participants with acne who had all occurrences of acne before the start of first SEA tour (as determined from military records).
- Pre/Post-SEA Acne** - Participants with acne who had multiple occurrences, both before and after the start of first SEA tour, or a case of acne that began before the start of first SEA tour and ended after starting SEA tour.
- Post-SEA Acne** - Participants with acne who had all occurrences of acne after the start of first SEA tour.

**FIGURE 11-1. Occurrence of Acne by Time for 1987 Examination Participants (Ranch Hands and Comparisons)**

**TABLE 11-2.**

**Analysis of Occurrence of Acne (Lifetime)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	54.6	0.94 (0.82,1.09)	0.430
	Medium	260	52.3		
	High	131	54.2		
b) Maximal (n=742)	Low	185	54.1	0.99 (0.89,1.09)	0.787
	Medium	371	54.7		
	High	186	48.4		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c) Minimal (n=521)	0.91 (0.78,1.05)		0.188	AGE (p=0.022)	
d) Maximal (n=742)	0.96 (0.86,1.06)		0.406	AGE (p=0.006)	

<sup>a</sup>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 11-2. (Continued)**  
**Analysis of Occurrence of Acne (Lifetime)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	<u>Percent Yes/(n) Current Dioxin</u>			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	55.6 (72)	60.2 (128)	63.0 (54)	1.16 (0.91,1.47)	0.115 <sup>b</sup> 0.236 <sup>c</sup>
	>18.6	55.2 (58)	45.5 (132)	45.5 (77)	0.90 (0.75,1.10)	0.306 <sup>c</sup>
f) Maximal (n=742)	≤18.6	49.1 (106)	57.6 (191)	62.7 (83)	1.21 (1.02,1.44)	0.006 <sup>b</sup> 0.025 <sup>c</sup>
	>18.6	57.0 (79)	50.3 (179)	42.3 (104)	0.89 (0.77,1.03)	0.110 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.10 (0.86,1.41)	0.131 <sup>b</sup> 0.447 <sup>c</sup>	AGE (p=0.096)
	>18.6	0.87 (0.71,1.06)	0.171 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.17 (0.98,1.39)	0.006 <sup>b</sup> 0.078 <sup>c</sup>	AGE (p=0.017)
	>18.6	0.85 (0.73,0.99)	0.040 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-2. (Continued)****Analysis of Occurrence of Acne (Lifetime)****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	786	50.3	All Categories		0.819
Unknown	345	51.0	Unknown vs. Background	1.03 (0.80,1.33)	0.814
Low	196	54.1	Low vs. Background	1.17 (0.85,1.60)	0.338
High	187	51.3	High vs. Background	1.04 (0.76,1.44)	0.790
Total	1,514				

**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	786	All Categories		0.638	AGE*RACE (p=0.023)
Unknown	345	Unknown vs. Background	1.07 (0.83,1.39)	0.596	
Low	196	Low vs. Background	1.16 (0.84,1.59)	0.357	
High	187	High vs. Background	0.91 (0.65,1.25)	0.552	
Total	1,514				

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

start of their first SEA tour (pre-SEA), 143 participants had acne before and after the start of their first SEA tour (pre/post-SEA), and 681 participants had acne only after the start of their first SEA tour (post-SEA). These categories are used to assist the reader in identifying the contrasts in subsequent analyses. Additionally, the word “versus” is used when describing these contrasts to assist the reader in differentiating participants considered to be “yes” responses from those considered to be “no” responses. For example, in the analysis of post-SEA acne versus none, participants with post-SEA acne are considered to be “yes” and participants without acne are considered to be “no.”

To assess whether the occurrence of acne after the start of the first SEA tour was associated with dioxin, analyses were conducted that contrasted participants with acne after the start of the first SEA tour with participants who did not have acne after the start of the first SEA tour. The analysis of acne after the start of the first SEA tour also was performed after stratifying by occurrence of acne before the start of the first SEA tour; one stratum consisted of all participants with pre-SEA acne (pre/post-SEA versus pre-SEA), and the other consisted of all participants without pre-SEA acne (post-SEA versus none). This analysis was done to determine if occurrence of acne before the start of the first SEA tour had any effect on occurrence of acne after the start of the first SEA tour. The two analyses that were conducted are listed below:

- Participants who had acne only after the start of their first SEA tour (post-SEA) combined with those who had acne both before and after the start of their first SEA tour (pre/post-SEA) versus participants who did not have acne after the start of their first SEA tour (post-SEA and none)
- Participants who had acne after the start of their first SEA tour versus participants who did not have acne after the start of their first SEA tour, stratified by occurrence of acne prior to their first SEA tour
  - Participants without acne prior to their first SEA tour: post-SEA versus no acne
  - Participants with acne prior to their first SEA tour: pre/post-SEA versus pre-SEA.

The results of these analyses are presented below.

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The association between initial dioxin and post-SEA acne was nonsignificant based on unadjusted analyses when Ranch Hands who had post-SEA acne only or who had acne both before and after the start of their SEA tour (pre/post-SEA) were contrasted with Ranch Hands who did not have acne after the start of their SEA tour (pre-SEA and none) (Table 11-3 [a1] and [b1]: minimal assumption,  $p=0.623$ ; maximal assumption,  $p=0.839$ ). In the adjusted analysis, the association remained nonsignificant (Table 11-3 [c1] and [d1]: minimal,  $p=0.333$ ; maximal,  $p=0.750$ ).

In the subset of Ranch Hands who did not have acne before their first SEA tour the association between initial dioxin and post-SEA acne was nonsignificant in the unadjusted analysis (Table 11-3 [a2] and [b2]: minimal assumption,  $p=0.292$ ; maximal assumption,

**TABLE 11-3.**

**Analysis of Acne Relative to SEA Tour  
(Pre/Post-SEA and Post-SEA versus Pre-SEA and None)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Pre/Post-SEA Post-SEA</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a1) Minimal (n=521)	Low	130	51.5	0.97 (0.84,1.11)	0.623
	Medium	260	51.5		
	High	131	53.4		
b1) Maximal (n=742)	Low	185	51.4	1.01 (0.91,1.12)	0.839
	Medium	371	52.8		
	High	186	47.9		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c1) Minimal (n=521)	0.93 (0.80,1.08)	0.333	AGE (p=0.043)
d1) Maximal (n=742)	0.98 (0.88,1.09)	0.750	AGE (p=0.012)

<sup>a</sup>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 11-3. (Continued)**  
**Analysis of Acne Relative to SEA Tour**  
**(Post-SEA versus None)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Post-SEA	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a2) Minimal (n=468)	Low	118	50.0	0.92 (0.79,1.07)	0.292
	Medium	235	47.2		
	High	115	47.8		
b2) Maximal (n=671)	Low	168	49.4	0.97 (0.86,1.08)	0.531
	Medium	334	49.7		
	High	169	43.2		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c2) Minimal (n=468)	0.92 (0.79,1.07)	0.292	- -
d2) Maximal (n=671)	0.95 (0.85,1.06)	0.353	AGE (p=0.112)

<sup>a</sup>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 11-3. (Continued)**  
**Analysis of Acne Relative to SEA Tour**  
**(Pre/Post-SEA versus Pre-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Pre/Post-SEA	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a3) Minimal (n=53)	Low	12	66.7	1.82 (0.78,4.25)	0.111
	Medium	25	92.0		
	High	16	93.8		
b3) Maximal (n=71)	Low	17	70.6	1.92 (1.04,3.53)	0.013
	Medium	37	81.1		
	High	17	94.1		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
Assumption	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c3) Minimal (n=53)	****	****	INIT*AGE (p=0.003) INIT*RACE (p=0.009)
d3) Maximal (n=71)	****	****	INIT*AGE (p=0.007) INIT*RACE (p=0.016)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (p≤0.01); adjusted relative risk, confidence interval, and p-value not presented.

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.

INIT: Log<sub>2</sub> (initial dioxin).

**TABLE 11-3. (Continued)**

**Analysis of Acne Relative to SEA Tour  
(Pre/Post-SEA and Post-SEA versus Pre-SEA and None)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Pre/Post-SEA and Post-SEA (n) <u>Current Dioxin</u>			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e1) Minimal (n=521)	≤18.6	52.8 (72)	58.6 (128)	63.0 (54)	1.21 (0.95,1.55)	0.062 <sup>b</sup> 0.116 <sup>c</sup>
	>18.6	53.5 (58)	44.7 (132)	44.2 (77)	0.91 (0.75,1.10)	0.318 <sup>c</sup>
f1) Maximal (n=742)	≤18.6	45.3 (106)	55.0 (191)	62.7 (83)	1.27 (1.07,1.51)	0.001 <sup>b</sup> 0.005 <sup>c</sup>
	>18.6	55.7 (79)	49.2 (179)	41.4 (104)	0.89 (0.77,1.03)	0.108 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g1) Minimal (n=521)	≤18.6	1.21 (0.95,1.55)	0.062 <sup>b</sup> 0.116 <sup>c</sup>	--
	>18.6	0.91 (0.75,1.10)	0.318 <sup>c</sup>	
h1) Maximal (n=742)	≤18.6	1.23 (1.04,1.46)	0.001 <sup>b</sup> 0.019 <sup>c</sup>	AGE (p=0.030)
	>18.6	0.86 (0.74,0.99)	0.043 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-3. (Continued)**  
**Analysis of Acne Relative to SEA Tour**  
**(Post-SEA versus None)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Post-SEA/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e2) Minimal (n=468)	≤18.6	50.8 (65)	53.2 (109)	57.5 (47)	1.13 (0.88,1.47)	0.101 <sup>b</sup> 0.340 <sup>c</sup>
	>18.6	51.9 (54)	41.9 (124)	39.1 (69)	0.86 (0.70,1.06)	0.157 <sup>c</sup>
f2) Maximal (n=671)	≤18.6	44.3 (97)	51.2 (166)	56.9 (72)	1.19 (0.99,1.42)	0.006 <sup>b</sup> 0.058 <sup>c</sup>
	>18.6	54.1 (74)	47.0 (168)	36.2 (94)	0.85 (0.73,1.00)	0.045 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g2) Minimal (n=468)	≤18.6	1.13 (0.88,1.47)	0.101 <sup>b</sup> 0.340 <sup>c</sup>	--
	>18.6	0.86 (0.70,1.06)	0.157 <sup>c</sup>	
h2) Maximal (n=671)	≤18.6	1.19 (0.99,1.42)	0.006 <sup>b</sup> 0.058 <sup>c</sup>	--
	>18.6	0.85 (0.73,1.00)	0.045 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-3. (Continued)**

**Analysis of Acne Relative to SEA Tour  
(Pre/Post-SEA versus Pre-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Pre/Post-SEA (n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e3) Minimal (n=53)	≤18.6	71.4 (7)	89.5 (19)	100.0 (7)	4.81 (0.74,31.46)	0.184 <sup>b</sup> 0.101 <sup>c</sup>
	>18.6	75.0 (4)	87.5 (8)	87.5 (8)	1.30 (0.49,3.40)	0.598 <sup>c</sup>
f3) Maximal (n=71)	≤18.6	55.6 (9)	80.0 (25)	100.0 (11)	3.56 (1.21,10.43)	0.072 <sup>b</sup> 0.021 <sup>c</sup>
	>18.6	80.0 (5)	81.8 (11)	90.0 (10)	1.15 (0.56,2.37)	0.701 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g3) Minimal (n=53)	≤18.6	4.81 (0.74,31.46)		0.184 <sup>b</sup> 0.101 <sup>c</sup>	--	
	>18.6	1.30 (0.49,3.40)		0.598 <sup>c</sup>		
h3) Maximal (n=71)	≤18.6	3.56 (1.21,10.43)		0.072 <sup>b</sup> 0.021 <sup>c</sup>	--	
	>18.6	1.15 (0.56,2.37)		0.701 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-3. (Continued)**

**Analysis of Acne Relative to SEA Tour  
(Pre/Post-SEA and Post-SEA versus Pre-SEA and None)**

**i1) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Pre/Post-SEA and Post-SEA	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	48.2	All Categories		0.691
Unknown	345	48.4	Unknown vs. Background	1.01 (0.78,1.30)	0.954
Low	196	52.6	Low vs. Background	1.19 (0.87,1.63)	0.278
High	187	50.8	High vs. Background	1.11 (0.81,1.53)	0.525
Total	1,514				

**j1) 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	786	All Categories		0.732**	DXCAT*RACE (p=0.022)
Unknown	345	Unknown vs. Background	1.05 (0.81,1.35)**	0.725**	AGE*RACE (p=0.006)
Low	196	Low vs. Background	1.18 (0.86,1.63)**	0.295**	
High	187	High vs. Background	0.97 (0.70,1.34)**	0.858**	
Total	1,514				

\*\*Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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.  
 DXCAT: Categorized current dioxin.

**TABLE 11-3. (Continued)**

**Analysis of Acne Relative to SEA Tour  
(Post-SEA versus None)**

**i2) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Post-SEA	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	700	44.1	All Categories		0.771
Unknown	310	45.5	Unknown vs. Background	1.06 (0.81,1.38)	0.693
Low	175	48.6	Low vs. Background	1.20 (0.86,1.67)	0.293
High	166	45.2	High vs. Background	1.04 (0.74,1.47)	0.809
Total	1,351				

**j2) 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	700	All Categories		0.660	AGE*RACE (p=0.019)
Unknown	310	Unknown vs. Background	1.09 (0.83,1.42)	0.554	
Low	175	Low vs. Background	1.19 (0.85,1.66)	0.300	
High	166	High vs. Background	0.94 (0.66,1.33)	0.727	
Total	1,351				

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

**TABLE 11-3. (Continued)**

**Analysis of Acne Relative to SEA Tour  
(Pre/Post-SEA versus Pre-SEA)**

**i3) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Pre/Post-SEA	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	86	81.4	All Categories		0.245
Unknown	35	74.3	Unknown vs. Background	0.66 (0.26,1.68)	0.522
Low	21	85.7	Low vs. Background	1.37 (0.36,5.24)	0.918
High	21	95.2	High vs. Background	4.57 (0.67,31.30)	0.210
Total	163				

**j3) 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	86	All Categories		0.336	AGE (p=0.119)
Unknown	35	Unknown vs. Background	0.76 (0.29,1.99)	0.582	
Low	21	Low vs. Background	1.32 (0.34,5.06)	0.690	
High	21	High vs. Background	4.13 (0.51,33.66)	0.185	
Total	163				

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

p=0.531). Under the minimal assumption, no covariates were retained in the adjusted analysis. Under the maximal assumption, age was retained but the association between initial dioxin and post-SEA acne remained nonsignificant (p=0.353).

In the subset of Ranch Hands with acne prior to their first SEA tour, there was a significant positive association in the unadjusted analysis between initial dioxin and post-SEA acne under the maximal assumption, but not under the minimal assumption (Table 11-3 [a3] and [b3]: minimal assumption, p=0.111; maximal assumption, Est. RR=1.92, p=0.013). Among Ranch Hands with acne before their first SEA tour, the percentages under the maximal assumption who also had acne after the start of their SEA tour increased over the low, medium, and high initial dioxin categories (70.6%, 81.1%, and 94.1%).

In the minimal and maximal adjusted analyses, there were significant interactions between initial dioxin and age (Table 11-3 [c3] and [d3]: minimal assumption, p=0.003; maximal assumption, p=0.007), and between initial dioxin and race (minimal assumption, p=0.009; maximal assumption, p=0.016). Under the minimal assumption, there were only two Blacks—both in the low initial dioxin category—with acne both before and after their first SEA tour. For the younger non-Blacks, the association between initial dioxin and post-SEA acne was nonsignificant (Appendix Table J-1: p=0.511). For the older non-Blacks, just two Ranch Hands had acne only before their first SEA tour, both of whom were in the low initial dioxin category. Under the maximal assumption, just one Black Ranch Hand had acne only before the start of his SEA tour. For the younger non-Blacks, the association between initial dioxin and post-SEA acne was not significant (p=0.294). For the older non-Blacks, there was a significant positive association between initial dioxin and post-SEA acne (Adj. RR=9.69, p=0.039). Within this stratum, there were only three Ranch Hands in the low initial dioxin category, three in the medium category, and none in the high category who had only pre-SEA acne.

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

When the Ranch Hands with acne before and after the start of their first SEA tour were included with Ranch Hands with acne only after the start of their first SEA tour, the current dioxin-by-time since tour interaction was marginally significant in unadjusted analyses under the minimal assumption (Table 11-3 [e1]: p=0.062) and significant for the maximal unadjusted analysis (Table 11-3 [f1]: p=0.001). Under the minimal assumption, the association between current dioxin and post-SEA acne was nonsignificant within both time strata (Table 11-3 [e1]: p=0.116 for time<sub>≤</sub>18.6 years; p=0.318 for time<sub>></sub>18.6 years). Under the maximal assumption, there was a significant positive association in the later tour stratum (Table 11-3 [f1]: Est. RR=1.27, p=0.005), but the association was negative but nonsignificant in the earlier tour stratum (p=0.108). The percentages of Ranch Hands in the later tour stratum who had either post-SEA acne or pre/post-SEA acne were 45.3, 55.0, and 62.7 percent for low, medium, and high current dioxin.

In the adjusted analysis, no covariates were retained in the minimal model, so the results were the same as in the unadjusted analysis. Under the maximal assumption, after age was included in the model, the current dioxin-by-time interaction (Table 11-3 [h1]: p=0.001) and the positive association between current dioxin and post-SEA acne within the later tour stratum (Adj. RR=1.23, p=0.019) remained significant. Within the earlier tour stratum, the negative association between current dioxin and post-SEA acne became

significant as well (Adj. RR=0.86, p=0.043). The percentages of post-SEA or pre/post-SEA acne occurrences in this stratum were 55.7, 49.2, and 41.4 percent for low, medium, and high current dioxin.

In the unadjusted analysis of the Ranch Hands without acne prior to the start of their first SEA tour, the interaction between current dioxin and time since tour was nonsignificant under the minimal assumption (Table 11-3 [e2]: p=0.101), but was significant under the maximal assumption (Table 11-3 [f2]: p=0.006). Under the maximal assumption, there was a marginally significant positive association between current dioxin and post-SEA acne when time was 18.6 years or less (Est. RR=1.19, p=0.058) and a significant negative association when time was greater than 18.6 years (Est. RR=0.85, p=0.045). Among the Ranch Hands without pre-SEA acne, the percentages with post-SEA acne were 44.3, 51.2, and 56.9 percent for low, medium, and high current dioxin in the later tour stratum. In the earlier tour stratum, the corresponding percentages were 54.1, 47.0, and 36.2 percent. No covariates were retained in the adjusted analyses under either assumption, so the results remained the same as in the unadjusted analyses.

In the unadjusted analysis of the Ranch Hands with acne prior to the start of their first SEA tour, the current dioxin-by-time since tour interaction was nonsignificant under the minimal analysis (Table 11-3 [e3]: p=0.184), but was marginally significant under the maximal assumption (Table 11-3 [f3]: p=0.072). Under the maximal assumption, the association between current dioxin and post-SEA acne was significant when time was 18.6 years or less (Est. RR=3.56, p=0.021), but was nonsignificant when time was greater than 18.6 years (p=0.701). Within the later tour stratum, the percentages of Ranch Hands with post-SEA acne as well as pre-SEA acne were 55.6, 80.0, and 100.0 percent for low, medium, and high current dioxin. In the adjusted analyses, no covariates were retained in the model under either assumption, so the results were the same as in the unadjusted analyses.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of participants with post-SEA acne only or with acne both before and after the start of their SEA tour versus participants without acne after the start of their SEA tour, there was no significant difference among the four current dioxin categories (Table 11-3 [i1]: p=0.691). In the adjusted analysis, there was a significant interaction between categorized current dioxin and race (Table 11-3 [j1]: p=0.022). In the Black stratum, the percentages of participants with either post-SEA acne or pre/post-SEA acne differed significantly among the current dioxin categories (Appendix Table J-1: p=0.037). The percentages in the background, unknown, low, and high categories were 52.1, 75.0, 25.0, and 37.5 percent. The percentage in the unknown category was marginally higher than the percentage in the background category (Adj. RR=3.62, 95% C.I.: [0.83,15.82], p=0.088); the percentage in the low category was marginally lower than the percentage in the background category (Adj. RR=0.29, 95% C.I.: [0.07,1.24], p=0.095). There was no significant difference between the high and background categories (p=0.420). In the non-Black stratum, the percentages of participants with either post-SEA acne or pre/post-SEA acne did not differ significantly among the current dioxin categories (Appendix Table J-1: p=0.482). Without the categorized current dioxin-by-race interaction in the model, the overall contrast of the four current dioxin categories was nonsignificant (Table 11-3 [j1]: p=0.732).

In the analysis of participants with post-SEA acne versus participants with no occurrences of acne, the overall contrast of the four current dioxin categories was nonsignificant in the unadjusted and adjusted models (Table 11-3 [i2] and [j2]: unadjusted,  $p=0.771$ ; adjusted,  $p=0.660$ ).

In the unadjusted analysis of the participants with pre-SEA acne, the percentages of participants who also had post-SEA acne did not differ significantly among the current dioxin categories (Table 11-3 [i3]:  $p=0.245$ ). In the adjusted analysis, the overall contrast remained nonsignificant (Table 11-3 [j3]:  $p=0.336$ ).

#### **Location of Acne**

The location of acne was analyzed for the participants in the post-SEA acne category and those in the post-SEA and pre/post-SEA categories combined. Tables 11-4 and 11-5 present the spatial distributions of acne with primary emphasis on the temples, around the eyes, or on the ears. The distributions provided in Table 11-4 are limited to the participants in the post-SEA only category. Table 11-5 shows the distributions of acne by location for the participants in the post-SEA and the pre/post-SEA categories combined.

Due to the sparse numbers at individual sites, the analyses presented below were performed on the contrast of participants with acne on the temples, eyes, ears, or any combination of these sites, versus the participants with acne on other sites.

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the post-SEA acne category, there was no significant association between location of acne and initial dioxin in the unadjusted analysis (Table 11-6 [a1] and [b1]: minimal assumption,  $p=0.611$ ; maximal assumption,  $p=0.554$ ). Under the minimal assumption, a significant interaction between initial dioxin and age was present in the adjusted analysis (Table 11-6 [c1]:  $p=0.016$ ). After dividing the Ranch Hands into two age strata (born $\geq$ 1942 and born $<$ 1942), the association between initial dioxin and location of acne was positive for the younger Ranch Hands and negative for the older Ranch Hands, but neither association was significant (Appendix Table J-1: born $\geq$ 1942:  $p=0.118$ ; born $<$ 1942:  $p=0.206$ ). Without this interaction in the model, the association between initial dioxin and the location of acne was nonsignificant (Table 11-6 [c1]:  $p=0.581$ ). Under the maximal assumption, no covariates were retained in the adjusted model so the results remained the same as in the unadjusted analysis.

When the post-SEA acne category was combined with the pre/post-SEA acne category, the association between initial dioxin and location of acne was nonsignificant under both assumptions (Table 11-6 [a2] and [b2]: minimal assumption,  $p=0.289$ ; maximal assumption,  $p=0.808$ ). In the adjusted minimal analysis, the association remained nonsignificant (Table 11-6 [c2]:  $p=0.207$ ). No covariates were retained in the adjusted maximal analysis so the results remained unchanged.

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted minimal analysis of the post-SEA acne category there was a significant interaction between current dioxin and time since tour (Table 11-6 [e1]:  $p=0.021$ ). In the later tour stratum, the association between current dioxin and location of acne was

**TABLE 11-4.**  
**Location of Post-SEA Acne\***

Location	<u>Minimal Assumption</u>			<u>Maximal Assumption</u>		
	Total	<u>Time (yrs.)</u>		Total	<u>Time (yrs.)</u>	
		≤18.6	>18.6		≤18.6	>18.6
Temples Only	28	15	13	44	21	23
Eyes Only	0	0	0	1	0	1
Ears Only	3	1	2	7	4	3
Temples and Eyes	2	2	0	4	3	1
Temples and Ears	5	1	4	6	2	4
Eyes and Ears	0	0	0	1	1	0
Temples, Eyes, and Ears	3	1	2	3	1	2
Other Sites	184	98	86	256	137	119

Location	<u>Current Dioxin Category</u>			
	Background	Unknown	Low	High
Temples Only	29	25	12	6
Eyes Only	5	1	0	0
Ears Only	7	5	1	0
Temples and Eyes	2	3	1	1
Temples and Ears	4	2	3	2
Eyes and Ears	1	1	0	0
Temples, Eyes, and Ears	0	0	0	3
Other Sites	261	104	68	63

\*Total indicates sample size used in the log<sub>2</sub> (initial dioxin) analysis; total sample size is broken down by time since tour to indicate sample sizes used in the log<sub>2</sub> (current dioxin) and time analysis; sample size given for each category used in categorized current dioxin analysis.

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 11-5.**

**Location of Post-SEA and Pre/Post-SEA Acne\***

Location	<u>Minimal Assumption</u>			<u>Maximal Assumption</u>		
	Total	<u>Time (yrs.)</u>		Total	<u>Time (yrs.)</u>	
		≤18.6	>18.6		≤18.6	>18.6
Temples Only	39	21	18	62	30	32
Eyes Only	1	0	1	2	0	2
Ears Only	3	1	2	7	4	3
Temples and Eyes	2	2	0	4	3	1
Temples and Ears	7	2	5	8	3	5
Eyes and Ears	0	0	0	1	1	0
Temples, Eyes, and Ears	5	2	3	5	2	3
Other Sites	214	119	95	291	162	129

Location	<u>Current Dioxin Category</u>			
	Background	Unknown	Low	High
Temples Only	45	34	17	11
Eyes Only	6	1	0	1
Ears Only	11	5	1	0
Temples and Eyes	2	3	1	1
Temples and Ears	9	3	3	3
Eyes and Ears	2	1	0	0
Temples, Eyes, and Ears	4	1	1	4
Other Sites	300	119	80	75

\*Total indicates sample size used in the log<sub>2</sub> (initial dioxin) analysis; total sample size is broken down by time since tour to indicate sample sizes used in the log<sub>2</sub> (current dioxin) and time analysis; sample size given for each category used in categorized current dioxin analysis.

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 11-6.**

**Analysis of Location of Acne  
(Post-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Temples/ Eyes/Ears	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a1) Minimal (n=225)	Low	59	17.0	1.08 (0.81,1.42)	0.611
	Medium	111	18.9		
	High	55	18.2		
b1) Maximal (n=322)	Low	83	26.5	0.94 (0.76,1.16)	0.554
	Medium	166	19.9		
	High	73	15.1		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks		
c1) Minimal (n=225)	1.09 (0.81,1.46)**	0.581**	INIT*AGE (p=0.016) RACE (p=0.081)		
d1) Maximal (n=322)	0.94 (0.76,1.16)	0.554	-		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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 11-6. (Continued)**  
**Analysis of Location of Acne**  
**(Pre/Post-SEA and Post-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Temples/ Eyes/Ears</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a2) Minimal (n=271)	Low	67	17.9	1.14 (0.90,1.44)	0.289
	Medium	134	20.9		
	High	70	24.3		
b2) Maximal (n=380)	Low	95	29.5	0.98 (0.82,1.17)	0.808
	Medium	196	21.9		
	High	89	20.2		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c2) Minimal (n=271)	1.17 (0.92,1.48)		0.207	RACE (p=0.142)	
d2) Maximal (n=380)	0.98 (0.82,1.17)		0.808	--	

<sup>a</sup>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 11-6. (Continued)**  
**Analysis of Location of Acne**  
**(Post-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Temples, Eyes, Ears/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e1) Minimal (n=225)	≤18.6	24.2 (33)	17.2 (58)	7.4 (27)	0.71 (0.43,1.17)	0.021 <sup>b</sup> 0.177 <sup>c</sup>
	>18.6	14.3 (28)	17.3 (52)	29.6 (27)	1.42 (1.00,2.03)	0.051 <sup>c</sup>
f1) Maximal (n=322)	≤18.6	23.3 (43)	21.2 (85)	9.8 (41)	0.76 (0.54,1.07)	0.083 <sup>b</sup> 0.113 <sup>c</sup>
	>18.6	27.5 (40)	19.0 (79)	23.5 (34)	1.11 (0.85,1.44)	0.458 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g1) Minimal (n=225)	≤18.6	0.71 (0.43,1.17)	0.021 <sup>b</sup> 0.177 <sup>c</sup>	--
	>18.6	1.42 (1.00,2.03)	0.051 <sup>c</sup>	
h1) Maximal (n=322)	≤18.6	0.76 (0.54,1.07)	0.083 <sup>b</sup> 0.113 <sup>c</sup>	--
	>18.6	1.11 (0.85,1.44)	0.458 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-6. (Continued)**  
**Analysis of Location of Acne**  
**(Pre/Post-SEA and Post-SEA)**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Temples, Eyes, Ears/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e2) Minimal (n=271)	≤18.6	26.3 (38)	18.7 (75)	11.8 (34)	0.84 (0.57,1.24)	0.037 <sup>b</sup> 0.386 <sup>c</sup>
	>18.6	12.9 (31)	22.0 (59)	35.3 (34)	1.42 (1.03,1.94)	0.030 <sup>c</sup>
f2) Maximal (n=380)	≤18.6	25.0 (48)	22.9 (105)	13.5 (52)	0.84 (0.63,1.11)	0.141 <sup>b</sup> 0.213 <sup>c</sup>
	>18.6	31.8 (44)	21.6 (88)	30.2 (43)	1.10 (0.87,1.38)	0.433 <sup>c</sup>
<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>		p-Value	Covariate Remarks	
g2) Minimal (n=271)	≤18.6	0.84 (0.57,1.24)		0.037 <sup>b</sup> 0.386 <sup>c</sup>	--	
	>18.6	1.42 (1.03,1.94)		0.030 <sup>c</sup>		
h2) Maximal (n=370)	≤18.6	0.84 (0.63,1.11)		0.141 <sup>b</sup> 0.213 <sup>c</sup>	--	
	>18.6	1.10 (0.87,1.38)		0.433 <sup>c</sup>		

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-6. (Continued)**  
**Analysis of Location of Acne**  
**(Post-SEA)**

**i1) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Temples/Eyes/Ears	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	309	15.5	All Categories		0.060
Unknown	141	26.2	Unknown vs. Background	1.93 (1.19,3.14)	0.008
Low	85	20.0	Low vs. Background	1.36 (0.74,2.51)	0.327
High	75	16.0	High vs. Background	1.04 (0.52,2.06)	0.921
Total	610				

**j1) 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	309	All Categories		0.060	--
Unknown	141	Unknown vs. Background	1.93 (1.19,3.14)	0.008	
Low	85	Low vs. Background	1.36 (0.74,2.51)	0.327	
High	75	High vs. Background	1.04 (0.52,2.06)	0.921	
Total	610				

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

**TABLE 11-6. (Continued)**  
**Analysis of Location of Acne**  
**(Pre/Post-SEA and Post-SEA)**

**i2) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Temples/Eyes/Ears	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	379	20.8	All Categories		0.241
Unknown	167	28.7	Unknown vs. Background	1.53 (1.01,2.32)	0.045
Low	103	22.3	Low vs. Background	1.09 (0.65,1.85)	0.743
High	95	21.1	High vs. Background	1.01 (0.58,1.76)	0.964
Total	744				

**j2) 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	379	All Categories		0.193	AGE (p=0.118)
Unknown	167	Unknown vs. Background	1.55 (1.02,2.36)	0.039	
Low	103	Low vs. Background	1.09 (0.64,1.84)	0.757	
High	95	High vs. Background	0.94 (0.54,1.65)	0.840	
Total	744				

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

negative but nonsignificant ( $p=0.177$ ). In the earlier tour stratum, there was a marginally significant positive association between current dioxin and time (Est. RR=1.42,  $p=0.051$ ). Among Ranch Hands with early tours and acne only after the start of their SEA tour, the percentages with acne on the temples, eyes, ears, or a combination of these sites were 14.3, 17.3, and 29.6 percent for low, medium, and high current dioxin. Under the maximal assumption, the current dioxin-by-time interaction was marginally significant (Table 11-6 [f1]:  $p=0.083$ ). However, the association between current dioxin and location of acne was nonsignificant in both time strata (time $\leq$ 18.6:  $p=0.113$ ; time $>$ 18.6:  $p=0.458$ ). In the adjusted analyses, no covariates were retained in the model.

When the Ranch Hands with acne both before and after the start of their first SEA tour were included in the analysis, the current dioxin-by-time since tour interaction was significant under the minimal assumption (Table 11-6 [e2]:  $p=0.037$ ). The association between current dioxin and location of acne was negative but nonsignificant in the later tour stratum ( $p=0.386$ ) and significantly positive in the earlier tour stratum (Est. RR=1.42,  $p=0.030$ ). Within the earlier tour stratum, the percentage of Ranch Hands used in this analysis with acne on the temples, eyes, ears, or a combination of these sites increased with current dioxin (12.9%, 22.0%, and 35.3% for low, medium, and high current dioxin). Under the maximal assumption, the current dioxin-by-time interaction was not significant (Table 11-6 [f2]:  $p=0.141$ ). There were no covariates retained in the adjusted model under either assumption, so the results were the same as the unadjusted results.

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

When the unadjusted analysis of the location of acne was restricted to the post-SEA acne category, the overall contrast of the four current dioxin categories was marginally significant (Table 11-6 [i1]:  $p=0.060$ ). Of the participants with post-SEA acne only, the percentages with acne on the temples, eyes, ears, or a combination of these sites were 15.5, 26.2, 20.0, and 16.0 percent in the background, unknown, low, and high categories. The percentage in the unknown category was significantly greater than the percentage in the background category (Est. RR=1.93, 95% C.I.: [1.19,3.14],  $p=0.008$ ), but the low and high categories were not significantly different from the background category (low versus background:  $p=0.327$ ; high versus background:  $p=0.921$ ). The adjusted analysis did not retain any covariates, so the results remained unchanged.

When the participants in the pre/post-SEA acne category were included in the unadjusted analysis, the overall contrast became nonsignificant (Table 11-6 [i2]:  $p=0.241$ ). However, the percentage of participants used in this analysis with acne on the temples, eyes, ears, or a combination of these sites in the unknown current dioxin category (28.7%) was significantly greater than the percentage in the background category (20.8%) (Est. RR=1.53, 95% C.I.: [1.01,2.32],  $p=0.045$ ). After the model was adjusted for age, the overall contrast remained nonsignificant (Table 11-6 [j2]:  $p=0.193$ ) and the contrast between the unknown and background categories remained significant (Adj. RR=1.55, 95% C.I.: [1.02,2.36],  $p=0.039$ ). The low and high versus background category contrasts were also nonsignificant.

## ***Physical Examination Variables***

### **Comedones**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The association between initial dioxin and comedones was not significant in the unadjusted minimal or the unadjusted maximal analysis (Table 11-7 [a] and [b]:  $p=0.335$  and  $p=0.398$ ).

Under the minimal assumption, the association between initial dioxin and comedones became marginally significant after adjustment for age and race (Table 11-7 [c]: Adj. RR=1.18,  $p=0.076$ ). The percentages of Ranch Hands with comedones for the low, medium, and high initial dioxin categories were 16.9, 22.7, and 19.1 percent. Under the maximal assumption, the association with comedones remained nonsignificant in the adjusted model (Table 11-7 [d]:  $p=0.157$ ).

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analysis of comedones, the current dioxin-by-time since tour interaction was nonsignificant under the minimal and maximal assumptions (Table 11-7 [e] and [f]:  $p=0.708$  and  $p=0.939$ ).

Under the minimal assumption, after adjustment for age and race, the interaction between current dioxin and time remained nonsignificant (Table 11-7 [g]:  $p=0.862$ ). However, for Ranch Hands in the earlier tour stratum the relative risk of comedones became marginally significant (Adj. RR=1.24,  $p=0.074$ ). In this stratum, the percentages of Ranch Hands with comedones were 19.0, 18.2, and 23.4 percent for low, medium, and high current dioxin. Under the maximal assumption, the current dioxin-by-time interaction remained nonsignificant in the adjusted analysis (Table 11-7 [h]:  $p=0.909$ ).

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of comedones, no significant difference was exhibited among the four current dioxin categories (Table 11-7 [i]:  $p=0.779$ ). After adjusting the model for covariate information, the difference remained nonsignificant (Table 11-7 [j]:  $p=0.898$ ).

### **Acneiform Lesions**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The association between acneiform lesions and initial dioxin was not significant under the minimal assumption in the unadjusted analysis (Table 11-8 [a]:  $p=0.763$ ). Under the maximal assumption, however, the relative risk was marginally significant (Table 11-8 [b]: Est. RR=1.17,  $p=0.080$ ). In the low, medium, and high initial dioxin categories the percentages of Ranch Hands who had acneiform lesions were 4.9, 10.8, and 9.1 percent.

In the adjusted analysis, the association between acneiform lesions and initial dioxin remained nonsignificant under the minimal assumption (Table 11-8 [c]:  $p=0.243$ ). After age

**TABLE 11-7.**  
**Analysis of Comedones**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=521)	Low	130	16.9	1.09 (0.92,1.30)	0.335
	Medium	260	22.7		
	High	131	19.1		
b) Maximal (n=742)	Low	185	19.5	1.06 (0.93,1.20)	0.398
	Medium	371	21.6		
	High	186	18.8		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
Assumption			Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=521)			1.18 (0.98,1.41)	0.076	AGE (p=0.002) RACE (p=0.141)
d) Maximal (n=742)			1.10 (0.96,1.26)	0.157	AGE (p=0.003)

<sup>a</sup>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 11-7. (Continued)**

**Analysis of Comedones**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	12.5 (72)	28.9 (128)	13.0 (54)	1.04 (0.79,1.39)	0.708 <sup>b</sup> 0.761 <sup>c</sup>
	>18.6	19.0 (58)	18.2 (132)	23.4 (77)	1.12 (0.89,1.41)	0.335 <sup>c</sup>
f) Maximal (n=742)	≤18.6	19.8 (106)	22.5 (191)	16.9 (83)	1.06 (0.86,1.29)	0.939 <sup>b</sup> 0.595 <sup>c</sup>
	>18.6	22.8 (79)	17.9 (179)	22.1 (104)	1.04 (0.87,1.25)	0.632 <sup>c</sup>

**Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted**

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.20 (0.90,1.61)	0.862 <sup>b</sup> 0.221 <sup>c</sup>	AGE (p=0.001) RACE (p=0.121)
	>18.6	1.24 (0.98,1.57)	0.074 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.13 (0.92,1.38)	0.909 <sup>b</sup> 0.256 <sup>c</sup>	AGE (p=0.002)
	>18.6	1.11 (0.93,1.33)	0.263 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-7. (Continued)**

**Analysis of Comedones**

**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	786	22.8	All Categories		0.779
Unknown	345	21.5	Unknown vs. Background	0.93 (0.68,1.26)	0.623
Low	196	23.5	Low vs. Background	1.04 (0.72,1.51)	0.836
High	187	19.8	High vs. Background	0.84 (0.56,1.24)	0.377
Total	1,514				

**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	786	All Categories		0.898	SEAACNE (p=0.059) AGE*RACE (p=0.023)
Unknown	345	Unknown vs. Background	0.92 (0.67,1.25)	0.575	
Low	196	Low vs. Background	1.05 (0.72,1.52)	0.807	
High	187	High vs. Background	0.92 (0.61,1.38)	0.685	
Total	1,514				

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

**TABLE 11-8.**

**Analysis of Acneiform Lesions**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	10.0	0.97 (0.77,1.22)	0.763
	Medium	260	11.5		
	High	131	10.7		
b) Maximal (n=742)	Low	185	4.9	1.17 (0.98,1.39)	0.080
	Medium	371	10.8		
	High	186	9.1		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c) Minimal (n=521)	0.86 (0.67,1.11)		0.243	AGE (p=0.004) RACE*SEAACNE (p=0.039)	
d) Maximal (n=742)	1.11 (0.93,1.32)		0.270	AGE (p=0.009) RACE*SEAACNE (p=0.042)	

<sup>a</sup>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 11-8. (Continued)**  
**Analysis of Acneiform Lesions**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	9.7 (72)	13.3 (128)	11.1 (54)	1.06 (0.74,1.51)	0.507 <sup>b</sup> 0.752 <sup>c</sup>
	>18.6	12.1 (58)	9.9 (132)	9.1 (77)	0.90 (0.65,1.25)	0.527 <sup>c</sup>
f) Maximal (n=742)	≤18.6	1.9 (106)	12.0 (191)	9.6 (83)	1.39 (1.06,1.81)	0.110 <sup>b</sup> 0.016 <sup>c</sup>
	>18.6	6.3 (79)	10.1 (179)	9.6 (104)	1.03 (0.81,1.32)	0.792 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	0.89 (0.61,1.29)	0.621 <sup>b</sup> 0.530 <sup>c</sup>	AGE (p=0.003) RACE*SEAACNE (p=0.045)
	>18.6	0.78 (0.55,1.12)	0.179 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.26 (0.96,1.66)	0.124 <sup>b</sup> 0.091 <sup>c</sup>	AGE (p=0.009) RACE*SEAACNE (p=0.044)
	>18.6	0.95 (0.74,1.23)	0.709 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-8. (Continued)**  
**Analysis of Acneiform Lesions**

**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	786	11.3	All Categories		0.111
Unknown	345	7.0	Unknown vs. Background	0.59 (0.37,0.94)	0.026
Low	196	11.7	Low vs. Background	1.04 (0.64,1.70)	0.871
High	187	9.6	High vs. Background	0.83 (0.49,1.42)	0.505
Total	1,514				

**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	786	All Categories		0.137	SEAACNE (p<0.001) AGE*RACE (p=0.043)
Unknown	345	Unknown vs. Background	0.63 (0.39,1.01)	0.055	
Low	196	Low vs. Background	1.03 (0.63,1.70)	0.893	
High	187	High vs. Background	0.68 (0.39,1.18)	0.170	
Total	1,514				

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

and the interaction between race and the presence of pre-SEA acne were included in the model for the maximal analysis, the association became nonsignificant (Table 11-8 [d]:  $p=0.270$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The association between acneiform lesions and current dioxin did not differ significantly between the time since tour strata in the unadjusted analyses under either the minimal or the maximal assumption (Table 11-8 [e] and [f]:  $p=0.507$  and  $p=0.110$ ). However, under the maximal assumption, there was a significant association between acneiform lesions and current dioxin when time was 18.6 years or less (Table 11-8 [f]: Est. RR=1.39,  $p=0.016$ ). Within this stratum, 1.9, 12.0, and 9.6 percent of the Ranch Hands with low, medium, and high current dioxin had acneiform lesions.

After the models had been adjusted for significant covariate information, the current dioxin-by-time interactions remained nonsignificant (Table 11-8 [g] and [h]: minimal assumption,  $p=0.621$ ; maximal assumption,  $p=0.124$ ). Under the maximal assumption, the association between acneiform lesions and current dioxin for Ranch Hands with a later tour (time $\leq$ 18.6 years) became marginally significant after age and the race-by-presence of pre-SEA acne interaction were included in the model (Table 11-8 [h]:  $p=0.091$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of acneiform lesions, the overall contrast of the four current dioxin categories was nonsignificant (Table 11-8 [i]:  $p=0.111$ ). However, there was a significant difference between the unknown and background categories (Est. RR=0.59, 95% C.I.: [0.37,0.94],  $p=0.026$ ). The percentages of acneiform lesion occurrences for the background, unknown, low, and high current dioxin categories were 11.3, 7.0, 11.7, and 9.6 percent.

Following the adjustment for significant covariates (the presence of pre-SEA acne and the age-by-race interaction), the overall contrast remained nonsignificant (Table 11-8 [j]:  $p=0.137$ ). However, the relative risk under the unknown versus background contrast became only marginally significant (Adj. RR=0.63, 95% C.I.: [0.39,1.01],  $p=0.055$ ).

**Acneiform Scars**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

No significant association was shown to exist between acneiform scars and current dioxin under the minimal assumption based on the unadjusted analysis (Table 11-9 [a]:  $p=0.105$ ). Under the maximal assumption, however, this association was marginally significant with a relative risk greater than 1 (Table 11-9 [b]: Est. RR=1.17,  $p=0.058$ ). The percentages of Ranch Hands in the low, medium, and high initial dioxin categories who had acneiform scars were 9.7, 11.3, and 12.4 percent.

In the adjusted minimal analysis, the association between acneiform scars and initial dioxin remained nonsignificant (Table 11-9 [c]:  $p=0.273$ ). After the model in the maximal

**TABLE 11-9.**  
**Analysis of Acneiform Scars**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	7.7	1.19 (0.97,1.47)	0.105
	Medium	260	13.1		
	High	131	13.7		
b) Maximal (n=742)	Low	185	9.7	1.17 (1.00,1.37)	0.058
	Medium	371	11.3		
	High	186	12.4		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>	<b>Covariate Remarks</b>
c) Minimal (n=521)	1.14 (0.91,1.43)	0.273	AGE*SEAACNE (p=0.032)
d) Maximal (n=742)	1.12 (0.94,1.33)	0.200	AGE*SEAACNE (p=0.049)

<sup>a</sup>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 11-9. (Continued)**  
**Analysis of Acneiform Scars**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	2.8 (72)	18.0 (128)	14.8 (54)	1.54 (1.12,2.12)	0.100 <sup>b</sup> 0.009 <sup>c</sup>
	>18.6	6.9 (58)	12.9 (132)	10.4 (77)	1.07 (0.79,1.44)	0.666 <sup>c</sup>
f) Maximal (n=742)	≤18.6	5.7 (106)	12.0 (191)	16.9 (83)	1.46 (1.15,1.85)	0.030 <sup>b</sup> 0.002 <sup>c</sup>
	>18.6	12.7 (79)	9.5 (179)	12.5 (104)	1.02 (0.81,1.28)	0.888 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.43 (1.01,2.03)	0.097 <sup>b</sup> 0.047 <sup>c</sup>	AGE*SEAACNE (p=0.034)
	>18.6	0.97 (0.69,1.34)	0.833 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.38 (1.06,1.78)	0.032 <sup>b</sup> 0.016 <sup>c</sup>	AGE*SEAACNE (p=0.047)
	>18.6	0.94 (0.74,1.21)	0.644 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-9. (Continued)**  
**Analysis of Acneiform Scars**

**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	786	9.5	All Categories		0.151
Unknown	345	11.0	Unknown vs. Background	1.17 (0.78,1.77)	0.447
Low	196	13.8	Low vs. Background	1.51 (0.95,2.43)	0.084
High	187	14.4	High vs. Background	1.60 (1.00,2.57)	0.051
Total	1,514				

**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	786	All Categories		0.182	AGE (p=0.028) SEAACNE (p<0.001)
Unknown	345	Unknown vs. Background	1.27 (0.82,1.95)	0.284	
Low	196	Low vs. Background	1.58 (0.96,2.60)	0.070	
High	187	High vs. Background	1.53 (0.92,2.52)	0.098	
Total	1,514				

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

analysis had been adjusted for significant covariate information (specifically the age-by-presence of pre-SEA acne interaction), the association between acneiform scars and initial dioxin became nonsignificant (Table 11-9 [d]:  $p=0.200$ ).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted minimal analysis, there was a marginally significant difference in the association between acneiform scars and current dioxin between the time since tour strata (Table 11-9 [e]:  $p=0.100$ ). When time did not exceed 18.6 years, the association was significant (Est. RR=1.54,  $p=0.009$ ). For low, medium, and high levels of current dioxin the percentages of men with acneiform scars were 2.8, 18.0, and 14.8 percent. When time was greater than 18.6 years, the association between acneiform scars and current dioxin was not significant ( $p=0.666$ ). Under the maximal assumption, the association between acneiform scars and current dioxin was significantly different between the time strata (Table 11-9 [f]:  $p=0.030$ ). The association was significant when time was 18.6 years or less (Est. RR=1.46,  $p=0.002$ ) and nonsignificant when time was greater than 18.6 years ( $p=0.888$ ). In the later tour stratum (time $\leq$ 18.6 years), the percentages of Ranch Hands with low, medium, and high current dioxin who had acneiform scars were 5.7, 12.0, and 16.9 percent.

After adjusting the models for significant covariate information, the current dioxin-by-time interaction remained marginally significant under the minimal assumption (Table 11-9 [g]:  $p=0.097$ ) and significant under the maximal assumption (Table 11-9 [h]:  $p=0.032$ ). The association between acneiform scars and current dioxin when time was 18.6 years or less remained significant under both assumptions (Table 11-9 [g] and [h]: minimal assumption: Adj. RR=1.43,  $p=0.047$ ; maximal assumption: Adj. RR=1.38,  $p=0.016$ ). When time was greater than 18.6 years, the association remained nonsignificant under both assumptions (minimal assumption,  $p=0.833$ ; maximal assumption,  $p=0.644$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of acneiform scars, the overall contrast of the four current dioxin categories was nonsignificant (Table 11-9 [i]:  $p=0.151$ ). However, there were marginally significant differences between the low and background categories (Est. RR=1.51, 95% C.I.: [0.95,2.43],  $p=0.084$ ) and between the high and background categories (Est. RR=1.60, 95% C.I.: [1.00,2.57],  $p=0.051$ ). In both cases, the percentage of men with acneiform scars in the Ranch Hand category exceeded the percentage in the background category. The percentages for the background, unknown, low, and high categories were 9.5, 11.0, 13.8, and 14.4 percent.

After adjusting for significant covariates, the overall contrast remained nonsignificant (Table 11-9 [j]:  $p=0.182$ ). The contrasts between the low and background categories (Adj. RR=1.58, 95% C.I.: [0.96,2.60],  $p=0.070$ ) and between the high and background categories (Adj. RR=1.53, 95% C.I.: [0.92,2.52],  $p=0.098$ ) remained marginally significant.

## **Depigmentation**

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The association between depigmentation and initial dioxin was not significant in the unadjusted minimal analysis and in the unadjusted maximal analysis (Table 11-10 [a] and

**TABLE 11-10.**  
**Analysis of Depigmentation**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=521)	Low	130	8.5	0.91 (0.68,1.21)	0.498
	Medium	260	6.5		
	High	131	7.6		
b) Maximal (n=742)	Low	185	3.2	1.06 (0.86,1.30)	0.599
	Medium	371	7.6		
	High	186	7.5		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
Assumption			Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=521)			0.93 (0.69,1.24)	0.606	RACE (p=0.109)
d) Maximal (n=742)			1.06 (0.86,1.31)	0.581	RACE (p=0.123)

<sup>a</sup>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 11-10. (Continued)**

**Analysis of Depigmentation**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	11.1 (72)	3.9 (128)	11.1 (54)	1.05 (0.68,1.62)	0.381 <sup>b</sup> 0.813 <sup>c</sup>
	>18.6	8.6 (58)	7.6 (132)	5.2 (77)	0.81 (0.53,1.22)	0.308 <sup>c</sup>
f) Maximal (n=742)	≤18.6	1.9 (106)	6.8 (191)	8.4 (83)	1.30 (0.94,1.79)	0.087 <sup>b</sup> 0.110 <sup>c</sup>
	>18.6	6.3 (79)	7.8 (179)	6.7 (104)	0.89 (0.66,1.19)	0.433 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.09 (0.70,1.69)	0.346 <sup>b</sup> 0.695 <sup>c</sup>	RACE (p=0.100)
	>18.6	0.82 (0.54,1.24)	0.344 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.32 (0.95,1.82)	0.076 <sup>b</sup> 0.094 <sup>c</sup>	RACE (p=0.110)
	>18.6	0.88 (0.65,1.19)	0.414 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-10. (Continued)**

**Analysis of Depigmentation**

**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	786	5.7	All Categories		0.702
Unknown	345	4.9	Unknown vs. Background	0.85 (0.48,1.51)	0.588
Low	196	5.6	Low vs. Background	0.98 (0.50,1.93)	0.951
High	187	7.5	High vs. Background	1.33 (0.72,2.48)	0.366
Total	1,514				

**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	786	All Categories		0.536	AGE (p=0.057) RACE (p=0.100)
Unknown	345	Unknown vs. Background	0.86 (0.48,1.53)	0.610	
Low	196	Low vs. Background	0.98 (0.50,1.94)	0.965	
High	187	High vs. Background	1.50 (0.80,2.83)	0.209	
Total	1,514				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

[b]:  $p=0.498$  and  $p=0.599$ ). In the adjusted analyses, this association was also nonsignificant (Table 11-10 [c] and [d]: minimal assumption,  $p=0.606$ ; maximal assumption,  $p=0.581$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted minimal analysis of depigmentation, the interaction between current dioxin and time since tour was not significant (Table 11-10 [e]:  $p=0.381$ ). Under the maximal assumption, however, the current dioxin-by-time interaction was marginally significant (Table 11-10 [f]:  $p=0.087$ ). The relative risk was greater than 1 when time was no more than 18.6 years and was less than 1 when time was more than 18.6 years, although both risks were nonsignificant (time $\leq$ 18.6:  $p=0.110$ ; time $>$ 18.6:  $p=0.433$ ).

Under the minimal assumption, the current dioxin-by-time interaction remained nonsignificant in the adjusted analysis of depigmentation (Table 11-10 [g]:  $p=0.346$ ). When race was included in the maximal analysis, the current dioxin-by-time interaction remained marginally significant (Table 11-10 [h]:  $p=0.076$ ). However, the risk of depigmentation became marginally significant within the later tour stratum (Adj. RR=1.32,  $p=0.094$ ). In the earlier tour stratum the risk remained less than 1 but nonsignificant ( $p=0.414$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted model, no significant difference in the percentages of depigmentation was detected among the four current dioxin categories (Table 11-10 [i]:  $p=0.702$ ). Even after adjusting for covariate information, the difference remained nonsignificant (Table 11-10 [j]:  $p=0.536$ ).

**Inclusion Cysts**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

The association between initial dioxin and inclusion cysts was not significant in the unadjusted analysis under the minimal assumption (Table 11-11 [a]:  $p=0.615$ ). Under the maximal assumption, however, the association was marginally significant, with a relative risk less than 1 (Table 11-11 [b]: Est. RR=0.86,  $p=0.098$ ). The percentages of Ranch Hands in the low, medium, and high initial dioxin categories who had inclusion cysts decreased as initial dioxin increased (13.5%, 12.7%, and 5.9%, respectively).

In the adjusted minimal analysis, the association between initial dioxin and inclusion cysts remained nonsignificant (Table 11-11 [c]:  $p=0.557$ ). The relative risk remained marginally less than 1 under the maximal assumption after adjusting the model for significant covariates (Table 11-11 [d]: Adj. RR=0.85,  $p=0.075$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analysis, the association between current dioxin and inclusion cysts did not differ significantly between the two time since tour strata under either assumption (Table 11-11 [e] and [f]: minimal assumption,  $p=0.305$ ; maximal assumption,  $p=0.923$ ). After adjusting the models under both assumptions for significant covariates, the interaction

**TABLE 11-11.**  
**Analysis of Inclusion Cysts**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
a) Minimal (n=521)	Low	130	5.4	0.94 (0.73,1.20)	0.615
	Medium	260	13.9		
	High	131	5.3		
b) Maximal (n=742)	Low	185	13.5	0.86 (0.72,1.03)	0.098
	Medium	371	12.7		
	High	186	5.9		

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>			
Assumption	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
c) Minimal (n=521)	0.93 (0.72,1.19)	0.557	SEAACNE (p=0.009)
d) Maximal (n=742)	0.85 (0.71,1.02)	0.075	SEAACNE (p=0.003)

<sup>a</sup>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 11-11. (Continued)**

**Analysis of Inclusion Cysts**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	6.9 (72)	14.8 (128)	0.0 (54)	0.78 (0.50,1.21)	0.305 <sup>b</sup> 0.270 <sup>c</sup>
	>18.6	5.2 (58)	12.1 (132)	9.1 (77)	1.03 (0.75,1.42)	0.840 <sup>c</sup>
f) Maximal (n=742)	≤18.6	12.3 (106)	12.0 (191)	4.8 (83)	0.82 (0.61,1.10)	0.923 <sup>b</sup> 0.179 <sup>c</sup>
	>18.6	20.3 (79)	10.6 (179)	7.7 (104)	0.84 (0.65,1.07)	0.147 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	0.76 (0.49,1.18)	0.297 <sup>b</sup> 0.223 <sup>c</sup>	SEAACNE (p=0.003)
	>18.6	1.01 (0.73,1.39)	0.943 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	0.80 (0.59,1.06)	0.870 <sup>b</sup> 0.124 <sup>c</sup>	SEAACNE (p=0.003)
	>18.6	0.82 (0.64,1.05)	0.111 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-11. (Continued)**

**Analysis of Inclusion Cysts**

**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	786	10.4	All Categories		0.041
Unknown	345	12.5	Unknown vs. Background	1.22 (0.83,1.81)	0.316
Low	196	14.8	Low vs. Background	1.49 (0.95,2.35)	0.086
High	187	6.4	High vs. Background	0.59 (0.31,1.10)	0.098
Total	1,514				

**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	786	All Categories		0.070	AGE (p=0.062) RACE (p=0.072) SEAACNE (p=0.066)
Unknown	345	Unknown vs. Background	1.19 (0.80,1.77)	0.384	
Low	196	Low vs. Background	1.51 (0.95,2.38)	0.080	
High	187	High vs. Background	0.63 (0.33,1.18)	0.148	
Total	1,514				

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

between current dioxin and time remained nonsignificant (Table 11-11 [g] and [h]: minimal assumption,  $p=0.297$ ; maximal assumption,  $p=0.870$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of inclusion cysts, the overall contrast showed a significant difference among the four current dioxin categories (Table 11-11 [i]:  $p=0.041$ ). The percentages of participants in the background, unknown, low, and high categories who had inclusion cysts were 10.4, 12.5, 14.8, and 6.4 percent. The risk of inclusion cysts was marginally greater than 1 when contrasting the low and background categories (Est. RR=1.49, 95% C.I.: [0.95,2.35],  $p=0.086$ ) and was marginally less than 1 when contrasting the high and background categories (Est. RR=0.59, 95% C.I.: [0.31,1.10],  $p=0.098$ ).

The overall contrast in the adjusted analysis of inclusion cysts became marginally significant after age, race, and the presence of pre-SEA acne were accounted for in the model (Table 11-11 [j]:  $p=0.070$ ). The relative risk remained marginally significant under the low versus background contrast (Adj. RR=1.51, 95% C.I.: [0.95,2.38],  $p=0.080$ ), but became nonsignificant but still less than 1 under the high versus background contrast ( $p=0.148$ ).

**Hyperpigmentation**

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

Under the unadjusted analysis for the minimal assumption, no significant association was exhibited between initial dioxin and hyperpigmentation (Table 11-12 [a]:  $p=0.319$ ). Under the maximal assumption, however, the risk of hyperpigmentation was significantly greater than 1 (Table 11-12 [b]: Est. RR=1.22,  $p=0.008$ ). The percentages of hyperpigmentation in the low, medium, and high initial dioxin categories were 8.7, 14.8, and 18.3 percent.

The association between initial dioxin and hyperpigmentation remained nonsignificant in the adjusted minimal analysis (Table 11-12 [c]:  $p=0.159$ ). In the adjusted maximal analysis, significant interactions between initial dioxin and age (Table 11-12 [d]:  $p=0.029$ ) and between initial dioxin and the presence of pre-SEA acne ( $p=0.048$ ) were present. Age was then divided into two strata—born in or after 1942 and born before 1942—to explore these interactions. Within the younger-age stratum, the interaction between initial dioxin and the presence of pre-SEA acne remained significant; consequently, the presence of pre-SEA acne was dichotomized as yes or no and analyzed further. For those who had pre-SEA acne, there were only two Ranch Hands who also had hyperpigmentation, both of whom were in the high initial dioxin category. For those who did not have pre-SEA acne, the association between initial dioxin and hyperpigmentation was not significant (Appendix Table J-1:  $p=0.883$ ). Within the older-age stratum, the initial dioxin-by-presence of pre-SEA acne interaction was not significant, and no further stratification was pursued. Within this stratum, the risk of hyperpigmentation was significantly greater than 1 (Adj. RR=1.47,  $p<0.001$ ), with the percentages in the low, medium, and high initial dioxin categories equal to 4.4, 15.9, and 21.7 percent. Without these two interactions in the adjusted maximal analysis, the risk of hyperpigmentation was significantly greater than 1 (Table 11-12 [d]: Adj. RR=1.25,  $p=0.005$ ).

**TABLE 11-12.**

**Analysis of Hyperpigmentation**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	13.9	1.10 (0.91,1.33)	0.319
	Medium	260	16.9		
	High	131	17.6		
b) Maximal (n=742)	Low	185	8.7	1.22 (1.06,1.40)	0.008
	Medium	371	14.8		
	High	186	18.3		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c) Minimal (n=521)	1.15 (0.95,1.40)		0.159	RACE (p<0.001) SEAACNE (p=0.012)	
d) Maximal (n=742)	1.25 (1.07,1.45)**		0.005**	INIT*AGE (p=0.029) INIT*SEAACNE (p=0.048) RACE (p<0.001)	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

\*\*Log<sub>2</sub> (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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 11-12. (Continued)**  
**Analysis of Hyperpigmentation**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	13.9 (72)	20.3 (128)	16.7 (54)	1.14 (0.85,1.53)	0.961 <sup>b</sup> 0.390 <sup>c</sup>
	>18.6	10.3 (58)	14.4 (132)	19.5 (77)	1.15 (0.89,1.48)	0.286 <sup>c</sup>
f) Maximal (n=742)	≤18.6	5.7 (106)	15.7 (191)	21.7 (83)	1.35 (1.09,1.68)	0.305 <sup>b</sup> 0.007 <sup>c</sup>
	>18.6	12.7 (79)	12.3 (179)	18.3 (104)	1.16 (0.95,1.41)	0.145 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.32 (0.96,1.82)	0.808 <sup>b</sup> 0.084 <sup>c</sup>	AGE (p=0.097) RACE (p<0.001)
	>18.6	1.26 (0.96,1.64)	0.090 <sup>c</sup>	SEAACNE (p=0.014)
h) Maximal (n=742)	≤18.6	1.42 (1.13,1.79)	0.216 <sup>b</sup> 0.003 <sup>c</sup>	RACE (p<0.001) SEAACNE
	>18.6	1.17 (0.96,1.44)	0.123 <sup>c</sup>	(p=0.002)

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-12. (Continued)**  
**Analysis of Hyperpigmentation**

**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	786	16.0	All Categories		0.037
Unknown	345	11.0	Unknown vs. Background	0.65 (0.44,0.95)	0.028
Low	196	14.3	Low vs. Background	0.87 (0.56,1.36)	0.548
High	187	19.8	High vs. Background	1.29 (0.86,1.94)	0.217
Total	1,514				

**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	786	All Categories		0.049	RACE (p<0.001)
Unknown	345	Unknown vs. Background	0.68 (0.46,1.00)	0.052	
Low	196	Low vs. Background	0.87 (0.56,1.36)	0.541	
High	187	High vs. Background	1.35 (0.89,2.03)	0.157	
Total	1,514				

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

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analysis of hyperpigmentation, the interaction between current dioxin and time since tour was nonsignificant under the minimal and maximal assumptions (Table 11-12 [e] and [f]:  $p=0.961$  and  $p=0.305$ ). However, under the maximal assumption, the risk of hyperpigmentation was significantly greater than 1 when time since tour was no more than 18.6 years (Table 11-12 [f]: Est. RR=1.35,  $p=0.007$ ). Within this time stratum, the percentages of hyperpigmentation were 5.7, 15.7, and 21.7 percent for low, medium, and high current dioxin.

The current dioxin-by-time interaction remained nonsignificant in the adjusted analyses of hyperpigmentation (Table 11-12 [g] and [h]: minimal assumption,  $p=0.808$ ; maximal assumption,  $p=0.216$ ). In the minimal analysis, however, the risk of hyperpigmentation became marginally significant in both time strata after the model was adjusted for age, race, and the presence of pre-SEA acne (time $\leq$ 18.6 years: Adj. RR=1.32,  $p=0.084$ ; time $>$ 18.6 years: Adj. RR=1.26,  $p=0.090$ ). Within the later tour stratum, the percentages of Ranch Hands with hyperpigmentation for low, medium, and high current dioxin were 13.9, 20.3, and 16.7 percent. The corresponding percentages in the earlier tour stratum were 10.3, 14.4, and 19.5 percent, respectively. Under the maximal assumption, the risk in the later tour stratum remained significantly greater than 1 after adjusting for significant covariates (Table 11-12 [h]: Adj. RR=1.42,  $p=0.003$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The percentages of hyperpigmentation differed significantly among the four current dioxin categories in the unadjusted analysis (Table 11-12 [i]:  $p=0.037$ ). The percentages in the background, unknown, low, and high current dioxin categories were 16.0, 11.0, 14.3, and 19.8 percent. Under the unknown versus background contrast, the risk of hyperpigmentation was significantly less than 1 (Adj. RR=0.65, 95% C.I.: [0.44,0.95],  $p=0.028$ ). The risk, however, was nonsignificant under the low versus background contrast ( $p=0.548$ ) and the high versus background contrast ( $p=0.217$ ).

After the model was adjusted for race, the overall contrast of the four current dioxin categories remained significant (Table 11-12 [j]:  $p=0.049$ ). However, the risk of hyperpigmentation under the unknown versus background contrast became only marginally significant in the adjusted analysis (Adj. RR=0.68, 95% C.I.: [0.46,1.00],  $p=0.052$ ). The risks under the other two contrasts remained nonsignificant (low versus background:  $p=0.541$ ; high versus background:  $p=0.157$ ).

### **Other Abnormalities**

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the unadjusted minimal analysis, no significant association was detected between initial dioxin and the composite variable containing all other dermatologic abnormalities (Table 11-13 [a]:  $p=0.226$ ). However, under the maximal assumption, the association was marginally significant with a relative risk less than 1 (Table 11-13 [b]: Est. RR=0.89,  $p=0.057$ ). The percentages of Ranch Hands with at least one abnormality in the category of other dermatologic disorders were 76.2, 76.8, and 71.0 percent for low, medium, and high initial dioxin.

**TABLE 11-13.**

**Analysis of Other Abnormalities**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Yes</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	76.2	0.91 (0.77,1.06)	0.226
	Medium	260	73.1		
	High	131	71.0		
b) Maximal (n=742)	Low	185	76.2	0.89 (0.79,1.00)	0.057
	Medium	371	76.8		
	High	186	71.0		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c) Minimal (n=521)	0.96 (0.81,1.13)		0.616	AGE (p<0.001) RACE (p=0.020)	
d) Maximal (n=742)	0.94 (0.83,1.06)		0.308	AGE (p<0.001) RACE (p=0.007)	

<sup>a</sup>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 11-13. (Continued)**  
**Analysis of Other Abnormalities**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	75.0 (72)	71.9 (128)	68.5 (54)	0.88 (0.69,1.14)	0.928 <sup>b</sup> 0.338 <sup>c</sup>
	>18.6	84.5 (58)	72.0 (132)	71.4 (77)	0.87 (0.70,1.08)	0.199 <sup>c</sup>
f) Maximal (n=742)	≤18.6	77.4 (106)	73.8 (191)	68.7 (83)	0.87 (0.73,1.05)	0.821 <sup>b</sup> 0.141 <sup>c</sup>
	>18.6	81.0 (79)	77.1 (179)	73.1 (104)	0.85 (0.72,1.00)	0.052 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	0.96 (0.74,1.26)	0.872 <sup>b</sup> 0.791 <sup>c</sup>	AGE (p<0.001) RACE (p=0.019)
	>18.6	0.94 (0.75,1.17)	0.574 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	0.93 (0.77,1.13)	0.864 <sup>b</sup> 0.470 <sup>c</sup>	AGE (p<0.001) RACE (p=0.006)
	>18.6	0.91 (0.77,1.09)	0.304 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-13. (Continued)**  
**Analysis of Other Abnormalities**

**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	786	74.6	All Categories		0.154
Unknown	345	78.8	Unknown vs. Background	1.27 (0.94,1.72)	0.121
Low	196	71.9	Low vs. Background	0.87 (0.62,1.24)	0.455
High	187	71.1	High vs. Background	0.84 (0.59,1.20)	0.337
Total	1,514				

**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	786	All Categories		0.583	AGE (p<0.001) RACE (p<0.001)
Unknown	345	Unknown vs. Background	1.17 (0.86,1.60)	0.324	
Low	196	Low vs. Background	0.88 (0.61,1.26)	0.477	
High	187	High vs. Background	1.02 (0.71,1.47)	0.922	
Total	1,514				

Note: Background (Comparisons): Current Dioxin  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands):  $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$ .  
 High (Ranch Hands): Current Dioxin  $> 33.3 \text{ ppt}$ .

In the adjusted minimal analysis, the association between initial dioxin and other abnormalities remained nonsignificant (Table 11-13 [c]:  $p=0.616$ ). After adjusting the model in the maximal analysis for age and race, the association between initial dioxin and other abnormalities became nonsignificant (Table 11-13 [d]:  $p=0.308$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The association between current dioxin and other abnormalities was not significantly different between the time since tour strata under either the minimal or the maximal assumption (Table 11-13 [e] and [f]:  $p=0.928$  and  $p=0.821$ ). Under the maximal assumption, however, there was a marginally significant negative association between current dioxin and other abnormalities within the earlier tour stratum (Table 11-13 [f]: Est. RR=0.85,  $p=0.052$ ). Within this stratum, the percentages of Ranch Hands with low, medium, and high current dioxin with at least one of the other abnormalities were 81.0, 77.1, and 73.1 percent.

After adjusting for significant covariates, the current dioxin-by-time interaction remained nonsignificant under both assumptions (Table 11-13 [g] and [h]: minimal assumption,  $p=0.872$ ; maximal assumption,  $p=0.864$ ). The association in the earlier tour stratum, under the maximal assumption, became nonsignificant after the model was adjusted for age and race (Table 11-13 [h]:  $p=0.304$ ).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

In the unadjusted analysis of other abnormalities, the overall contrast of the four current dioxin categories showed no significant difference in the percentages of participants who had at least one of the other dermatologic abnormalities (Table 11-13 [i]:  $p=0.154$ ). After the model was adjusted for significant covariates, the overall contrast remained nonsignificant (Table 11-13 [j]:  $p=0.583$ ).

***Dermatology Index***

The dermatology index was formed by counting the number of abnormalities present for the following conditions: comedones, acneiform lesions, acneiform scars, and inclusion cysts. Table 11-14 shows the frequencies of the number of abnormalities. For the analyses presented below, the dermatology index was dichotomized as normal (no abnormalities) and abnormal (at least one abnormality).

***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the unadjusted analysis of the dermatology index, classified as either no abnormalities or more than one abnormality, there was no significant association with initial dioxin under the minimal and maximal assumptions (Table 11-15 [a] and [b]:  $p=0.410$  and  $p=0.246$ ). When the analysis was adjusted for significant covariate information, the association remained nonsignificant under both assumptions (Table 11-15 [c] and [d]: minimal assumption,  $p=0.471$ ; maximal assumption,  $p=0.324$ ).

***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted minimal analysis of the dermatology index, the current dioxin-by-time since tour interaction was not significant (Table 11-15 [e]:  $p=0.431$ ). Under the maximal assumption, however, the association between current dioxin and the dermatology index

**TABLE 11-14.**  
**Dermatology Index Frequencies\***

Dermatology Index	<u>Minimal Assumption</u>			<u>Maximal Assumption</u>		
	Total	<u>Time (yrs.)</u>		Total	<u>Time (yrs.)</u>	
		≤18.6	>18.6		≤18.6	>18.6
0	323	153	170	464	239	225
1	139	72	67	198	102	96
2	45	23	22	59	29	30
3	10	2	8	17	6	11
4	4	4	0	4	4	0

Dermatology Index	<u>Current Dioxin Category</u>			
	Background	Unknown	Low	High
0	487	213	110	117
1	204	97	57	50
2	67	25	22	16
3	25	8	4	4
4	3	2	3	0

\*Total indicates sample size used in the log<sub>2</sub> (initial dioxin) analysis; total sample size is broken down by time since tour to indicate sample sizes used in the log<sub>2</sub> (current dioxin) and time analysis; sample size given for each category used in categorized current dioxin analysis.

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 11-15.**

**Analysis of Dermatology Index**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Unadjusted</b>					
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>n</b>	<b>Percent Abnormal</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
a) Minimal (n=521)	Low	130	31.5	1.06 (0.92,1.23)	0.410
	Medium	260	42.3		
	High	131	35.9		
b) Maximal (n=742)	Low	185	35.7	1.07 (0.96,1.19)	0.246
	Medium	371	39.9		
	High	186	34.4		
<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin) - Adjusted</b>					
<b>Assumption</b>	<b>Adj. Relative Risk (95% C.I.)<sup>a</sup></b>		<b>p-Value</b>	<b>Covariate Remarks</b>	
c) Minimal (n=521)	1.06 (0.91,1.23)		0.471	SEAACNE (p<0.001)	
d) Maximal (n=742)	1.06 (0.95,1.19)		0.324	SEAACNE (p<0.001) AGE*RACE (p=0.041)	

<sup>a</sup>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 11-15. (Continued)**

**Analysis of Dermatology Index**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Unadjusted</b>						
Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
		Low	Medium	High		
e) Minimal (n=521)	≤18.6	26.4 (72)	50.8 (128)	31.5 (54)	1.17 (0.92,1.48)	0.431 <sup>b</sup> 0.202 <sup>c</sup>
	>18.6	34.5 (58)	37.1 (132)	36.4 (77)	1.03 (0.85,1.25)	0.763 <sup>c</sup>
f) Maximal (n=742)	≤18.6	30.2 (106)	40.3 (191)	38.6 (83)	1.20 (1.02,1.42)	0.048 <sup>b</sup> 0.031 <sup>c</sup>
	>18.6	46.8 (79)	34.6 (179)	36.5 (104)	0.96 (0.83,1.11)	0.590 <sup>c</sup>

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time - Adjusted</b>				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) <sup>a</sup>	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	1.15 (0.90,1.46)	0.440 <sup>b</sup> 0.265 <sup>c</sup>	SEAACNE (p<0.001)
	>18.6	1.01 (0.83,1.24)	0.892 <sup>c</sup>	
h) Maximal (n=742)	≤18.6	1.19 (0.99,1.42)	0.061 <sup>b</sup> 0.059 <sup>c</sup>	SEAACNE (p<0.001)
	>18.6	0.95 (0.81,1.11)	0.540 <sup>c</sup>	

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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 11-15. (Continued)**  
**Analysis of Dermatology Index**

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	38.0	All Categories		0.479
Unknown	345	38.3	Unknown vs. Background	1.01 (0.78,1.31)	0.944
Low	196	43.9	Low vs. Background	1.27 (0.93,1.75)	0.135
High	187	37.4	High vs. Background	0.97 (0.70,1.35)	0.878
Total	1,514				

**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	786	All Categories		0.459	SEAACNE (p<0.001) AGE*RACE (p=0.010)
Unknown	345	Unknown vs. Background	1.02 (0.78,1.33)	0.900	
Low	196	Low vs. Background	1.29 (0.93,1.78)	0.122	
High	187	High vs. Background	0.98 (0.70,1.37)	0.896	
Total	1,514				

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

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<sub>2</sub> (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**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin)</b>				
<b>Assumption</b>	<b>Initial Dioxin</b>	<b>Percent Abnormal/(n) Examination</b>		
		<b>1982</b>	<b>1985</b>	<b>1987</b>
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)
<hr/> <b>Normal in 1982</b> <hr/>				
<b>Initial Dioxin</b>	<b>n in 1987</b>	<b>Percent Abnormal in 1987</b>	<b>Est. Relative Risk (95% C.I.)<sup>a</sup></b>	<b>p-Value</b>
Low	86	25.6	0.98 (0.80,1.22)	0.886
Medium	151	33.1		
High	75	25.3		

<sup>a</sup>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**

<b>Ranch Hands - Log<sub>2</sub> (Initial Dioxin)</b>				
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)
<u>Normal in 1982</u>				
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
Low	90	27.8	1.02 (0.87,1.20)	0.787
Medium	225	31.6		
High	113	23.9		

<sup>a</sup>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**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time</b>					
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			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
	Low	Medium	High		
≤18.6	25.5 (47)	40.9 (66)	14.3 (28)	0.92 (0.64,1.32)	0.476 <sup>b</sup> 0.655 <sup>c</sup>
>18.6	23.7 (38)	28.6 (84)	30.6 (49)	1.09 (0.82,1.43)	0.560 <sup>c</sup>

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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**

<b>Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time</b>					
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			Est. Relative Risk (95% C.I.) <sup>a</sup>	p-Value
	Low	Medium	High		
≤18.6	26.4 (53)	33.0 (109)	24.4 (41)	1.02 (0.78,1.32)	0.844 <sup>b</sup> 0.907 <sup>c</sup>
>18.6	32.6 (43)	25.9 (116)	28.8 (66)	1.05 (0.85,1.30)	0.650 <sup>c</sup>

<sup>a</sup>Relative risk for a twofold increase in dioxin.

<sup>b</sup>Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

<sup>c</sup>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**

<b>e) Ranch Hands and Comparisons by Current Dioxin Category</b>					
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)		
<u>Normal in 1982</u>					
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  $\leq 10$  ppt.  
 Unknown (Ranch Hands): Current Dioxin  $\leq 10$  ppt.  
 Low (Ranch Hands): 15 ppt < Current Dioxin  $\leq 33.3$  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<sub>2</sub> (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.,  $\leq 18.6$  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 - $\text{Log}_2$ (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)

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
<b>Questionnaire</b>				
Occurrence of Acne (Lifetime)	ns	ns	ns	ns
<u>Acne Relative to SEA Tour</u>				
Pre/Post-SEA and Post SEA vs. Pre-SEA and None	ns	NS	ns	ns
Post-SEA vs. None Pre/Post-SEA	ns	ns	ns	ns
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
<b>Physical Examination</b>				
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 ( $0.05 < p \leq 0.10$ ).

\*\* (NS):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Appendix Table J-1 for a detailed description of this interaction.

\*\* (0.005):  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $0.01 < p \leq 0.05$ ); 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.

\*\*\*\*:  $\text{Log}_2$  (initial dioxin)-by-covariate interaction ( $p \leq 0.01$ ); refer to Appendix Table J-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

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)**

Variable	Unadjusted					
	Minimal			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
<b>Questionnaire</b>						
Occurrence of Acne (Lifetime)	ns	NS	ns	-0.006	+0.025	ns
<u>Acne Relative to SEA Tour</u>						
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
<b>Physical Examination</b>						
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<sub>2</sub> (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour 18.6 years or less.

>18.6: Log<sub>2</sub> (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)**

Variable	Minimal			Adjusted			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
<b>Questionnaire</b>									
Occurrence of Acne (Lifetime)	ns	NS	ns	-0.006	NS*	-0.040			
<b>Acne Relative to SEA Tour</b>									
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			
<b>Physical Examination</b>									
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≤0.10).

Note: P-value given if p≤0.05.

C\*T: Log<sub>2</sub> (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log<sub>2</sub> (current dioxin) hypothesis test for Ranch Hands with time since end of tour 18.6 years or less.

>18.6: Log<sub>2</sub> (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 11-19.**

**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
<b>Questionnaire</b>				
Occurrence of Acne (Lifetime)	NS	NS	NS	NS
<u>Acne Relative to SEA Tour</u>				
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
<b>Physical Examination</b>				
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 ( $0.05 < p \leq 0.10$ ).

Note: P-value given if  $p \leq 0.05$ .

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	Low versus Background	High versus Background
<b>Questionnaire</b>				
Occurrence of Acne (Lifetime)	NS	NS	NS	ns
<u>Acne Relative to SEA Tour</u>				
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
<b>Physical Examination</b>				
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 ( $0.05 < p \leq 0.10$ ).

\*\* (NS)/\*\* (ns): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Appendix Table J-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

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 - $\text{Log}_2$ (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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