TABLE 10-37. (Continued)

Analysis of Creatine Kinase (Discrete)

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	7.8	All Categories		0.099
Unknown	341	5.3	Unknown vs. Background	0.66 (0.38,1.13)	0.127
Low	193	5.2	Low vs. Background	0.64 (0.32,1.28)	0.209
High	186	3.8	High vs. Background	0.46 (0.21,1.02)	0.057
Total	1,499				

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	779	All Categories		0.154**	DXCAT*RACE (p=0.011)
					ALC (p=0.135)
Unknown	339	Unknown vs. Background	0.76 (0.43,1.35)**	0.345**	AGE*DC (p<0.001)
Low	191	Low vs. Background	0.56 (0.26,1.20)**	0.134**	
High	185	High vs. Background	0.48 (0.21,1.10)**	0.083**	
Total	1,494				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); 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.

noted for Blacks (Appendix Table I-1: 54.3%, 25.0%, 0.0%, and 25.0% for the background, unknown, low, and high current dioxin categories, p=0.001), but not for non-Blacks (4.9%, 4.6%, 4.9%, and 2.8% for the corresponding current dioxin categories, p=0.664). After excluding the interaction, the overall contrast became nonsignificant (p=0.154), although the relative risk for the high versus background contrast remained marginally less than 1 (Table 10-37 [j]: Adj. RR=0.48, 95% C.I.: [0.21,1.10], p=0.083).

Longitudinal Analysis

Laboratory Examination Variables

For the gastrointestinal assessment, longitudinal analyses were conducted to evaluate the association between various measures of dioxin (initial dioxin, current dioxin and time since tour, categorized current dioxin) and the change between the 1982 Baseline examination and the 1987 examination in levels of AST, ALT, and GGT. For a specific longitudinal analysis of AST, ALT, or GGT (e.g., minimal assumption, initial dioxin analysis), the left side of each subpanel of a table provides the means and sample sizes for participants with laboratory values at each examination. Based on the difference between 1987 and 1982 laboratory values, the right side of each subpanel presents slopes, standard errors, and associated p-values (for models using initial dioxin or models using current dioxin and time), or differences of examination mean changes, 95 percent confidence intervals, and associated p-values (for models using categorized current dioxin). The reported statistics for all three examinations are presented for all participants who were compliant at both the 1982 and 1987 examinations. Tables 10-38, 10-39, and 10-40 present the results of the longitudinal analyses of AST, ALT, and GGT.

AST (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

For both the minimal and the maximal cohorts, the longitudinal analyses did not display a significant association between initial dioxin and the change in AST between the 1982 and 1987 examinations (Table 10-38 [a] and [b]: p=0.475 and p=0.245, respectively).

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

The longitudinal analysis of the change in AST did not detect a significant current dioxin-by-time since tour interaction for either the minimal or the maximal cohorts (Table 10-38 [c] and [d]: p=0.870 and p=0.723).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The change in mean levels of AST between the 1982 Baseline examination and the 1987 examination did not differ significantly among the four current dioxin categories (Table 10-38 [e]: p=0.268).

TABLE 10-38.

Longitudinal Analysis of AST (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Mean[a]/(n) Examination 1982	1985	1987	Slope (Std. Error)[b]	p-Value
a) Minimal (R^2=0.001)	Low	33.9 (124)	35.3 (121)	26.9 (124)	-0.0080 (0.0112)	0.475
	Medium	33.1 (252)	33.8 (248)	25.7 (252)		
	High	34.4 (123)	34.4 (121)	26.2 (123)		
b) Maximal (R^2=0.002)	Low	32.0 (169)	32.6 (166)	24.9 (169)	-0.0093 (0.0080)	0.245
	Medium	33.2 (356)	34.4 (349)	26.3 (356)		
	High	34.0 (177)	34.3 (174)	26.2 (177)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 AST and natural logarithm of 1982 AST versus log_2 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.

TABLE 10-38. (Continued)

Longitudinal Analysis of AST (U/L) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
c) Minimal (R^2=0.002)	≤18.6	1982	33.6 (69)	31.6 (123)	34.4 (50)	-0.0120 (0.0182)	0.870[c] 0.511[d]
		1985	33.7 (67)	34.4 (121)	33.6 (49)		
		1987	25.6 (69)	25.2 (123)	25.0 (50)		
	>18.6	1982	35.1 (55)	34.0 (129)	34.8 (73)	-0.0081 (0.0149)	0.585[d]
		1985	36.0 (54)	33.8 (127)	34.9 (72)		
		1987	28.8 (55)	26.3 (129)	26.9 (73)		
d) Maximal (R^2=0.004)	≤18.6	1982	32.3 (93)	32.1 (183)	33.5 (78)	-0.0152 (0.0125)	0.723[c] 0.224[d]
		1985	33.0 (90)	34.0 (179)	34.1 (77)		
		1987	25.8 (93)	24.8 (183)	25.6 (78)		
	>18.6	1982	31.4 (76)	34.9 (172)	33.8 (100)	-0.0094 (0.0108)	0.388[d]
		1985	31.3 (75)	35.4 (170)	34.1 (98)		
		1987	24.3 (76)	27.6 (172)	27.0 (100)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 AST and natural logarithm of 1982 AST versus log_2 dioxin.

[c]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[d]Test of significance for slope equal to 0 (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.

TABLE 10-38. (Continued)

Longitudinal Analysis of AST (Continuous)

e) Ranch Hands and Comparisons by Current Dioxin Category

Category	Mean[a]/(n) Examination 1982	1985	1987	Contrast	Difference of Examination Mean Change (95% C.I.)[e]	p-Value[f]
Background	33.1 (677)	33.9 (671)	25.6 (677)	All Categories		0.268
Unknown	31.3 (311)	32.4 (306)	25.0 (311)	Unknown vs. Background	1.2 --	0.109
Low	33.3 (189)	34.2 (187)	25.3 (189)	Low vs. Background	-0.5 --	0.503
High	33.7 (178)	34.1 (175)	26.4 (178)	High vs. Background	0.2 --	0.595
	(R^2=0.003)					

[a]Transformed from natural logarithm scale.

[e]Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 10-39.

Longitudinal Analysis of ALT (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Mean[a]/(n) Examination 1982	1985	1987	Slope (Std. Error)[b]	p-Value
a) Minimal (R^2<0.001)	Low	21.8 (124)	23.7 (121)	21.2 (124)	-0.0072 (0.0176)	0.684
	Medium	21.2 (252)	22.9 (248)	21.5 (252)		
	High	23.7 (123)	24.3 (121)	23.2 (123)		
b) Maximal (R^2=0.004)	Low	18.0 (169)	19.4 (166)	18.8 (169)	-0.0213 (0.0129)	0.099
	Medium	20.9 (356)	23.0 (349)	21.4 (356)		
	High	23.2 (177)	24.0 (174)	22.8 (177)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 ALT and natural logarithm of 1985 ALT versus log_2 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.

TABLE 10-39. (Continued)

Longitudinal Analysis of ALT (U/L) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
c) Minimal							0.797[c]
(R^2=0.001)	≤18.6	1982	21.9 (69)	20.2 (123)	25.0 (50)	-0.0047 (0.0288)	0.871[d]
		1985	22.2 (67)	23.7 (121)	25.3 (49)		
		1987	20.0 (69)	21.5 (123)	22.3 (50)		
	>18.6	1982	22.6 (55)	21.1 (129)	24.2 (73)	-0.0142 (0.0235)	0.545[d]
		1985	25.2 (54)	22.3 (127)	24.0 (72)		
		1987	22.7 (55)	21.5 (129)	23.8 (73)		
d) Maximal							0.749[c]
(R^2=0.006)	≤18.6	1982	18.2 (93)	20.4 (183)	23.4 (78)	-0.0305 (0.0202)	0.132[d]
		1985	19.9 (90)	22.5 (179)	24.9 (77)		
		1987	19.7 (93)	20.4 (183)	22.7 (78)		
	>18.6	1982	17.2 (76)	22.0 (172)	22.5 (100)	-0.0219 (0.0175)	0.211[d]
		1985	18.3 (75)	23.9 (170)	23.3 (98)		
		1987	17.6 (76)	22.3 (172)	23.6 (100)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 ALT and natural logarithm of 1985 ALT versus log_2 dioxin.

[c]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[d]Test of significance for slope equal to 0 (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.

TABLE 10-39. (Continued)

Longitudinal Analysis of ALT (U/L) (Continuous)

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Mean[a]/(n) Examination 1982	1985	1987	Contrast	Difference of Examination Mean Change (95% C.I.)[e]	p-Value[f]
Background	20.7 (677)	22.8 (671)	20.5 (677)	All Categories		0.005
Unknown	17.2 (311)	19.5 (306)	19.0 (311)	Unknown vs. Background	2.0 --	<0.001
Low	21.0 (189)	22.9 (187)	20.9 (189)	Low vs. Background	0.1 --	0.890
High	22.9 (178)	24.0 (175)	23.2 (178)	High vs. Background	0.6 --	0.508
	(R^2=0.010)					

[a]Transformed from natural logarithm scale.

[e]Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 10-40.

Longitudinal Analysis of GGT (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Mean[a]/(n) Examination 1982	1985	1987	Slope (Std. Error)[b]	p-Value
a) Minimal (R^2<0.001)	Low	44.1 (124)	37.5 (121)	35.6 (124)	0.0018 (0.0174)	0.918
	Medium	42.4 (252)	35.4 (248)	36.1 (252)		
	High	44.0 (123)	34.7 (121)	36.1 (123)		
b) Maximal (R^2<0.001)	Low	33.9 (169)	27.5 (166)	28.7 (169)	-0.0065 (0.0124)	0.602
	Medium	42.4 (356)	35.7 (349)	35.6 (356)		
	High	43.2 (177)	35.1 (174)	36.1 (177)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 GGT and natural logarithm of 1982 GGT versus log_2 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.

TABLE 10-40. (Continued)

Longitudinal Analysis of GGT (U/L) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
c) Minimal (R^2<0.001)	≤18.6	1982	42.7 (69)	39.9 (123)	43.2 (50)	0.0040 (0.0285)	0.962[c] 0.889[d]
		1985	35.6 (67)	35.0 (121)	33.8 (49)		
		1987	33.3 (69)	35.8 (123)	33.4 (50)		
	>18.6	1982	48.6 (55)	43.6 (129)	44.9 (73)	0.0022 (0.0232)	0.924[d]
		1985	40.7 (54)	35.4 (127)	35.7 (72)		
		1987	39.5 (55)	36.2 (129)	37.5 (73)		
d) Maximal (R^2<0.001)	≤18.6	1982	33.5 (93)	39.9 (183)	42.4 (78)	-0.0053 (0.0195)	0.908[c] 0.785[d]
		1985	27.0 (90)	33.7 (179)	35.9 (77)		
		1987	28.4 (93)	33.0 (183)	36.7 (78)		
	>18.6	1982	34.0 (76)	45.8 (172)	43.2 (100)	-0.0083 (0.0168)	0.623[d]
		1985	27.1 (75)	38.1 (170)	35.1 (98)		
		1987	28.4 (76)	38.0 (172)	37.4 (100)		

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on difference between natural logarithm of 1987 GGT and natural logarithm of 1982 GGT versus log_2 dioxin.

[c]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[d]Test of significance for slope equal to 0 (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.

TABLE 10-40. (Continued)

Longitudinal Analysis of GGT (U/L) (Continuous)

e) Ranch Hands and Comparisons by Current Dioxin Category

Category	Mean[a]/(n) Examination 1982	1985	1987	Contrast	Difference of Examination Mean Change (95% C.I.)[e]		p-Value[f]
Background	38.1 (677)	31.8 (671)	31.6 (677)	All Categories			0.098
Unknown	32.9 (311)	27.8 (306)	29.0 (311)	Unknown vs. Background	2.6	--	0.028
Low	42.9 (189)	34.9 (187)	35.2 (189)	Low vs. Background	-1.1	--	0.804
High	42.8 (178)	35.4 (175)	37.1 (178)	High vs. Background	0.8	--	0.208
	(R^2=0.005)						

[a]Transformed from natural logarithm scale.

[e]Difference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of 1987 and 1982 examination mean changes on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

ALT (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the longitudinal analysis of ALT did not find a significant association between initial dioxin and the change in ALT between examinations (Table 10-39 [a]: p=0.684). However, under the maximal assumption, the longitudinal analysis detected a marginally significant negative association between initial dioxin and the change in ALT (Table 10-39 [b]: p=0.099). The mean level of ALT increased between 1982 and 1987 in the low (18.0 U/L to 18.8 U/L) and medium (20.9 U/L to 21.4 U/L) initial dioxin categories, but the mean level decreased in the high initial dioxin category (23.2 U/L to 22.8 U/L).

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

For both the minimal and the maximal cohorts, the longitudinal analysis of the change in ALT between the 1982 Baseline examination and the 1987 examination did not detect a significant interaction between current dioxin and time since tour (Table 10-39 [c] and [d]: p=0.797 and p=0.749, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The longitudinal analysis of categorized current dioxin detected a significant difference in the mean change in levels of ALT over time among the four current dioxin categories (Table 10-39 [e]: p=0.005). The changes in the mean ALT values for the background, unknown, low, and high categories were -0.2, 1.8, -0.1, and 0.3 U/L. The unknown versus background contrast was highly significant (Table 10-39 [e]: p<0.001); that is, the mean change in ALT values was greater for the Ranch Hands in the unknown category than for the Comparisons in the background category.

GGT (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the longitudinal analyses did not find a significant association between initial dioxin and the change in GGT between the 1982 and 1987 examinations (Table 10-40 [a] and [b]: p=0.918 and p=0.602, respectively).

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

The longitudinal analysis of the change in GGT did not detect a significant current dioxin-by-time since tour interaction for either the minimal or the maximal cohorts (Table 10-40 [c] and [d]: p=0.962 and p=0.908).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The change in GGT over time differed marginally among the four current dioxin categories (Table 10-40 [e]: p=0.098). The mean levels of GGT decreased between 1982 and 1987 for each current dioxin category (mean difference: -6.5, -3.9, -7.7, and -5.7 U/L for the background, unknown, low, and high current dioxin categories). The decrease between examinations in the mean GGT was significantly less in the unknown current dioxin category than in the background category (p=0.028).

DISCUSSION

Signs and symptoms associated with the gastrointestinal system are among those most frequently encountered in ambulatory medicine. The historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice as screening tools in the outpatient investigation of digestive disorders. More definitive diagnostic studies, such as barium and endoscopic surveys of the bowel, were not included in the current study. These are rarely indicated in the initial evaluation of gastrointestinal disease except in emergency circumstances.

It is important to recognize certain limitations in relying upon data from the history and physical examination when diagnosing digestive disorders. Rather than pointing to a particular diagnosis, digestive symptoms frequently are nonspecific and intermittent. In this setting, even the best designed medical history questionnaire can be subject to error. "Ulcer" and "colitis" are diagnoses that are commonly reported but often not accurately established. In contrast, most cases of hepatitis are anicteric and escape detection. As a common target organ for situational stress, the bowel frequently gives rise to symptoms that can be severe but that are functional in nature and resolve over time. These caveats highlight the importance of the type of medical record verification conducted in the current study and, in the case of hepatitis, the need for serologic confirmation.

In contrast to some organ systems, the physical examination in gastrointestinal disease is often of limited value and can be misleading in the differential diagnosis. The ability of the examiner to detect hepatomegaly is unreliable in the obese patient. In obstructive airway disease, with hyperinflation of the lungs and flattening of the diaphragms, the liver edge may descend abnormally below the right costal margin in the absence of hepatomegaly. Even in the best circumstance, the span of the liver by palpation or percussion is often an unreliable index of liver size.

Data collected in the laboratory can provide early insight into the presence of occult liver disease even though there are limitations to the history and physical examination. The four hepatic enzymes analyzed as dependent variables (AST, ALT, GGT, and LDH) are common to most chemistry panels ordered in the outpatient setting. Present in high intracellular concentration, these enzymes are released in virtually all toxic, inflammatory, and neoplastic diseases with hepatic involvement. The hepatic enzymes are reliable laboratory markers of liver disease. GGT is considered the most sensitive and LDH, with isoenzymes derived from multiple organ systems, is the least specific.

The hepatic enzymes are used in the detection and followup of parenchymal disease. The serum alkaline phosphatase and bilirubin reflective of hepatobiliary function are used to recognize "cholestatic" or "obstructive" diseases. Though present in virtually all organ systems, the serum alkaline phosphatase in the adult population under study is of dual origin and close to a 50-50 mixture of liver- and bone-derived fractions. An elevated alkaline phosphatase is by no means diagnostic of liver disease. It may occur in a broad range of unrelated clinical conditions including drug-induced cholestasis, Paget's disease (3% of males over age 40), neoplasia with metastases to bone, and congestive heart failure.

Similarly, and pertinent to the current study, the bilirubin measurements are subject to numerous hereditary and acquired disorders unrelated to intrinsic hepatic disease. The benign hyperbilirubinemia of Gilbert's syndrome will occur in 5 percent of the population under study. Many medications, including over-the-counter preparations, have been implicated in the overproduction of bilirubin in the hemolytic reactions associated with glucose-6-phosphate dehydrogenase deficiency, which may occur in up to 15 percent of Black American males.

With reference to the current assessment, analysis of the historical and clinical examination variables revealed no evidence for any overt hepatic disease related to the current body burden of dioxin. Most of the statistically significant associations that occurred in relation to the extrapolated initial level of serum dioxin were limited to the laboratory indices. With the exceptions noted below, they were found in the continuous rather than the more clinically relevant discrete analysis. While the observed dose-response findings are not accompanied by clinical disease, they may still represent subclinical effects.

Of the historical variables analyzed, few statistically significant associations were found. There was an increased incidence of viral hepatitis related to the extrapolated initial level of serum dioxin and, in the adjusted analysis (not adjusting for occupation), the relative risk of 1.24 remained highly significant ($p<0.001$). Furthermore, Ranch Hands with the highest levels of serum dioxin (>33.3 ppt) were at significantly greater risk (Adj. RR=1.42, $p=0.047$) than Comparisons with background levels (<10 ppt).

However, these results became nonsignificant after adjustment for occupation. Pertinent to these associations are the results of testing for serologic markers for hepatitis during previous AFHS examinations. A history of hepatitis was verified in 332 of the 841 Ranch Hands (39.5%) who were fully compliant to the 1987 physical examination and had a valid dioxin result. Among the 786 Comparisons who were fully compliant to the 1987 physical examination and had a valid dioxin result less than or equal to 10 ppt, 316 (41.5%) had a verified history of hepatitis. These apparently high rates of verified hepatitis are partially the result of testing for serological markers of viral hepatitis during prior AFHS examinations. Participants found to carry markers indicating prior viral hepatitis infection were informed of their status.

Evidence of prior Hepatitis A infection was found in the serum of 240 of 841 Ranch Hands (28.5%) and 214 of 761 Comparisons (28.1%). Heptatitis B markers were confirmed to be present in 11.1 percent (93/841) of Ranch Hands and 13.7 percent (104/761) of Comparisons. These numbers are similar to the 14 percent of Vietnam veterans found to be positive by the Centers for Disease Control in the Vietnam Experience Study.

Participants with a history of hepatitis who were not found to have serological markers for Hepatitis A or B were tested for the presence of antibodies to Hepatitis C, a recently identified cause of non-A, non-B hepatitis. None of the four Ranch Hands and none of the five Comparisons in this category were found to be positive for Hepatitis C. In these nine individuals, a specific cause of the hepatitis could not be serologically determined. These data suggest that the majority of verified episodes of hepatitis were viral in nature and not misdiagnosed dioxin-related illnesses.

Dermatologic endpoints associated with porphyria cutanea tarda following TCDD exposure have been suggested but they have been reported only in industrial accidents with levels of exposure to dioxin and other chemicals far greater than would be anticipated in the current study. By history, 31.9 percent of those with the highest levels of serum dioxin reported skin bruising or patches versus 18.4 percent for background and 27.8 percent for those with low serum levels. Although neither of the dioxin-specific skin conditions was noted on physical examination, these findings are consistent with a dose-response effect that may have resolved over time.

The laboratory data examined can be divided broadly into perenchymal (serum enzymes), hepatobiliary (serum bilirubin and alkaline phosphatase), and lipid/carbohydrate indices. It is common to find isolated elevations in some but not all of the hepatic enzymes studied when evaluating occult or low grade liver disease. Among the enzymes examined, the GGT is considered the most sensitive. By discrete and continuous analyses, it showed the strongest positive association, particularly with the extrapolated initial level of serum dioxin. In the Ranch Hand versus the Comparison analysis, GGT was the only enzyme that showed statistically significant differences in both the continuous and discrete forms. There was no apparent association between the body burden of dioxin and elevations in the urinary d-glucaric acid, which is felt by many people to be a highly sensitive marker of dioxin-induced hepatic disease.

Serum alkaline phosphatase in its continuous form was significantly associated with the extrapolated initial body burden of dioxin. By the more clinically relevant discrete analysis, however, there was no evidence of a significant dose-response effect. In contrast, both the unadjusted and adjusted analyses of total bilirubin revealed a direct opposite effect with a decreasing percentage of abnormal results in participants with higher levels of initial dioxin.

In relation to other laboratory variables, the lipid indices analyzed had the highest number of statistically significant positive associations with the body burden of dioxin. In a pattern consistent with a dose-response effect, a highly significant ($p<0.001$) association was found between the extrapolated initial serum dioxin and triglyceride levels. A significant association was noted in the discrete analysis as well. The interpretation of these results must consider the disproportionate increase in obesity in Ranch Hands with high versus those with low levels of serum dioxin (29.0% versus 12.4%; see Chapter 6, General Health Assessment).

In conclusion, the data analyzed in the current study suggest the presence of a subclinical effect on lipid metabolism, possibly related to the elevations previously seen in percent body fat. Several strongly positive associations were found between dioxin levels and triglycerides. This is not surprising since triglycerides are sensitive to weight and more specifically to percent body fat. Further longitudinal study into the pharmacokinetics of dioxin in lean versus obese individuals will be important toward understanding the clinical significance of the associations between all weight sensitive indices with serum levels of dioxin.

SUMMARY

Table 10-41 summarizes the results of the initial dioxin analyses (model 1) for the variables analyzed in the gastrointestinal assessment. Table 10-42 presents the results of the current dioxin and time since tour analyses (model 2), and Table 10-43 summarizes the categorized current dioxin analyses (model 3). Table 10-44 lists the numerous dioxin-by-covariate interactions that were encountered in the adjusted analyses of the laboratory variables.

Questionnaire Variables

Information collected at the 1987 health interview was combined with information collected at the 1982 and 1985 examinations, verified, and grouped into eight categories of liver disorders for analysis: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver, jaundice (unspecified, not of the newborn), and hepatomegaly. No Ranch Hands had necrosis of the liver or liver abscess and sequelae of chronic liver disease. Three Comparisons had necrosis of the liver and one had liver abscess and sequelae of chronic liver disease. Verified histories of ulcers and of skin bruises, patches, or sensitivity also were analyzed.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Adjusting for age and race, initial dioxin was associated significantly with an increased incidence of hepatitis under the minimal and maximal assumptions. However, this appears to be a spurious relationship that was due to the confounding effect of occupation. The incidence of hepatitis different significantly among occupations (enlisted personnel had a higher incidence than officers). The relative risk of hepatitis became nonsignificant after adjusting for occupation. Under the maximal assumption, there was a marginally significant increased risk for the category of other liver disorders. None of the other liver conditions, as well as ulcers and skin bruises, patches, or sensitivity was significantly associated with initial dioxin.

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

The current dioxin and time since tour analyses did not find a significant interaction between current dioxin and time for any of the liver conditions or for ulcers or skin bruises, patches, or sensitivity. Under the minimal and maximal assumptions, the incidence of hepatitis was associated significantly with current dioxin for Ranch Hands with a later tour when adjusting for age and race. However, these findings became nonsignificant when occupation was added to the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of hepatitis differed significantly among the four current dioxin categories when adjusting for age and race, with a significant increased risk in the high current dioxin category relative to the background category. Comparable to the hepatitis results for model 1 and model 2 analyses, these findings became nonsignificant after adjusting for the confounding effect of occupation.

TABLE 10-41.

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

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Viral Hepatitis (D)	NS	NS*	+0.028	+<0.001
Viral Hepatitis[a] (D)	--	--	NS	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	ns	ns	ns
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	ns	ns	ns	ns
Other Disorders of the Liver (D)	NS	NS*	NS	NS*
Jaundice (Unspecified) (D)	NS	ns	NS	ns
Hepatomegaly (D)	ns	NS	NS	NS
Ulcer (D)	NS	NS	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	NS	NS	NS	NS
Physical Examination				
Current Hepatomegaly (D)	ns	NS	ns	NS
Laboratory				
AST (C)	NS	NS	** (ns)	NS
AST (D)	NS	NS	** (ns)	** (ns)
ALT (C)	+0.039	+<0.001	NS	** (+0.005)
ALT (D)	NS	+0.031	** (NS)	** (NS*)
GGT (C)	NS	+<0.001	NS	+<0.001
GGT (D)	NS	NS*	*** (NS)	*** (+0.028)
Alkaline Phosphatase (C)	NS	+0.007	NS	+0.030
Alkaline Phosphatase (D)	NS	NS*	NS	NS
D-Glucaric Acid (C)	NS	NS*	** (NS)	NS
D-Glucaric Acid (D)	ns	ns	--	--
Total Bilirubin (C)	ns	ns	ns	** (ns)
Total Bilirubin (D)	-0.007	-0.033	-0.001	-0.014
Direct Bilirubin (C)	NS	NS*	NS	+0.038
Direct Bilirubin (D)	ns*	ns	** (ns)	** (ns)
LDH (C)	ns	NS	ns	NS
LDH (D)	ns	ns*	--	--

TABLE 10-41. (Continued)

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

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Cholesterol (C)	NS	NS	+0.046	+0.041
Cholesterol (D)	ns	ns	ns	ns
HDL[b] (C)	ns	-<0.001	ns	*** (-<0.001)
HDL (D)	NS	NS	NS	NS
Cholesterol-HDL Ratio (C)	+0.031	+<0.001	+0.009	*** (+<0.001)
Cholesterol-HDL Ratio (D)	NS*	+<0.001	+0.004	*** (+<0.001)
Triglycerides (C)	NS*	+<0.001	+0.040	+<0.001
Triglycerides (D)	+0.021	+0.004	+0.026	+0.005
Creatine Kinase (C)	ns	ns	** (ns)	** (ns)
Creatine Kinase (D)	ns	ns	ns	ns*

[a]Adjusted for age and occupation. Appendix Table I-2 presents a detailed description of this analysis.
[b]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.
-: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.
--: Analysis not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (NS*): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (...): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.
*** (NS): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
*** (...): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

TABLE 10-42.

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

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Viral Hepatitis (D)	ns	NS	ns	ns	NS	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	NS	ns	ns	NS	ns
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	--	ns	--	--	ns	--
Other Disorders of the Liver (D)	ns	NS	NS	ns	NS	NS
Jaundice (Unspecified) (D)	NS	ns	NS	ns	NS	ns
Hepatomegaly (D)	NS	ns	ns	ns	NS	ns
Ulcer (D)	ns	NS	NS	ns	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	ns	NS	ns	ns	NS	NS
Physical Examination						
Current Hepatomegaly (D)	ns	ns	ns	ns	NS	NS
Laboratory						
AST (C)	ns	NS	ns	NS	NS	NS
AST (D)	NS	ns	NS	NS	ns	NS
ALT (C)	ns	NS*	NS	ns	+0.022	+0.010
ALT (D)	ns	NS*	NS	ns	+0.028	NS
GGT (C)	ns	NS	NS	ns	+0.011	+0.048
GGT (D)	ns	NS	NS	ns	NS	NS
Alkaline Phosphatase (C)	NS	NS	NS	ns	NS*	NS
Alkaline Phosphatase (D)	NS	ns	NS	NS	NS	+0.046
D-Glucaric Acid (C)	NS	NS	NS	ns	NS	NS
D-Glucaric Acid (D)	--	--	--	ns	ns	ns
Total Bilirubin (C)	NS	ns	NS	NS	ns	NS
Total Bilirubin (D)	ns	ns	-0.045	NS	ns	ns
Direct Bilirubin (C)	NS	NS	NS	NS	NS	NS
Direct Bilirubin (D)	NS	ns	ns	ns	ns	ns

TABLE 10-42. (Continued)

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

Unadjusted

	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
LDH (C)	NS	ns	ns	NS	ns	ns
LDH (D)	--	--	--	--	ns	--
Cholesterol (C)	NS*	ns	+0.024	NS	NS	NS
Cholesterol (D)	NS	ns	NS	NS	ns	ns
HDL[a] (C)	ns	ns	ns	NS	-0.008	-0.014
HDL (D)	ns	NS	NS	NS	ns	NS
Cholesterol-HDL Ratio (C)	NS	NS	+0.023	NS	+0.015	+0.001
Cholesterol-HDL Ratio (D)	NS	ns	+0.039	NS	NS	+0.005
Triglycerides (C)	ns	NS	NS	ns*	+<0.001	NS*
Triglycerides (D)	ns	NS	NS*	ns	+0.045	+0.044
Creatine Kinase (C)	NS	ns	NS	ns	NS	ns
Creatine Kinase (D)	NS*	ns*	NS	NS	ns	ns

[a]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: <18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.
-: <18.6 and >18.6: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.
--: Analysis not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05\leq p<0.10$).
Note: P-value given if $p\leq 0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis.

TABLE 10-42. (Continued)

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

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Viral Hepatitis (D)	ns	+0.046	NS	ns	+0.002	NS*
Viral Hepatitis[a] (D)	ns	NS	ns	ns	NS	ns
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	ns	NS	ns*	ns	NS	ns*
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	--	--	--	--	--	--
Other Disorders of the Liver (D)	ns	NS	NS	ns	NS	NS
Jaundice (Unspecified) (D)	NS	NS	NS	ns	NS	ns
Hepatomegaly (D)	ns	NS	NS	ns	NS*	NS
Ulcer (D)	ns	NS	NS	ns	NS	NS
Skin Bruises, Patches, or Sensitivity (D)	ns	NS	NS	ns	NS	NS
Physical Examination						
Current Hepatomegaly (D)	ns	NS	NS	ns	NS	NS
Laboratory						
AST (C)	ns	ns	ns	****	****	****
AST (D)	NS	ns	ns	NS	ns	ns
ALT (C)	ns	NS	NS	** (ns)	** (NS*)	** (NS*)
ALT (D)	ns	NS	ns	ns	NS*	NS
GGT (C)	ns	NS	NS	ns	+0.003	NS*
GGT (D)	ns	NS	ns	ns	NS*	NS
Alkaline Phosphatase (C)	** (NS)	** (NS)	** (NS)	** (ns)	** (NS*)	** (NS)
Alkaline Phosphatase (D)	NS	ns	NS	NS	NS	+0.046
D-Glucaric Acid (C)	NS	NS	NS	ns	NS	NS
D-Glucaric Acid (D)	--	--	--	--	--	--
Total Bilirubin (C)	NS	ns	NS	NS	ns	NS
Total Bilirubin (D)	ns	ns	-0.008	ns	ns	ns*
Direct Bilirubin (C)	NS	NS	NS	ns	NS	NS
Direct Bilirubin (D)	** (NS)	** (ns)	** (ns)	ns	NS	ns

TABLE 10-42. (Continued)

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

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
LDH (C)	NS	ns	ns	NS	ns	ns
LDH (D)	--	--	--	--	--	--
Cholesterol (C)	+0.049	NS	+0.002	** (NS)	** (NS)	** (+0.030)
Cholesterol (D)	****	****	****	NS	ns	ns
HDL[b] (C)	** (ns)	**(ns)	** (ns)	NS	-0.027	-0.042
HDL (D)	ns	NS	NS	NS	ns	NS
Cholesterol-HDL Ratio (C)	** (NS)	**(NS)	** (+0.009)	NS	+0.008	+<0.001
Cholesterol-HDL Ratio (D)	** (NS)	**(NS)	** (+0.003)	NS	NS	+0.001
Triglycerides (C)	ns	NS	NS	ns	+<0.001	+0.045
Triglycerides (D)	NS	NS	NS*	ns	+0.050	NS*
Creatine Kinase (C)	NS	ns	NS	ns	NS	ns
Creatine Kinase (D)	NS	ns*	ns	NS	ns	ns

[a]Adjusted for age and occupation. Appendix Table I-1 presents a detailed description of this analysis.
[b]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: C*T: Slope for ≤18.6 category less than slope for >18.6 category.
≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.
-: ≤18.6 and >18.6: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.
--: Analysis not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.05<p\leq0.10$); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (NS*): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.05<p\leq0.10$); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (...): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.05<p\leq0.10$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.
****: Log_2 (current dioxin)-by-time-by-covariate interaction ($p\leq0.01$); refer to Appendix Table I-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis.

TABLE 10-43.

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

Variable	Unadjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Viral Hepatitis (D)	NS	ns*	ns	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	NS	ns	NS	ns
Other Disorders of the Liver (D)	NS*	ns	NS	+0.036
Jaundice (D)	NS*	NS	-0.042	ns
Hepatomegaly (D)	NS	ns	ns	NS
Ulcer (D)	NS	NS	ns	NS
Skin Bruises, Patches, or Sensitivity (D)	<0.001	+0.005	+0.004	+<0.001
Physical Examination				
Current Hepatomegaly (D)	NS*	-0.036	NS	NS
Laboratory				
AST (C)	NS	ns	ns	NS
AST (D)	NS	ns	ns	NS
ALT (C)	<0.001	-0.011	NS	+0.006
ALT (D)	NS	ns	NS	NS
GGT (C)	<0.001	-0.009	NS*	+0.007
GGT (D)	0.047	ns	NS*	+0.025
Alkaline Phosphatase (C)	NS*	NS	+0.041	+0.036
Alkaline Phosphatase (D)	NS	ns	ns	NS
D-Glucaric Acid (C)	NS	ns	NS	NS
D-Glucaric Acid (D)	NS	NS	ns	NS
Total Bilirubin (C)	NS	ns	ns	ns
Total Bilirubin (D)	0.048	ns	NS	-0.050
Direct Bilirubin (C)	NS	ns	NS	+0.025
Direct Bilirubin (D)	NS	ns	NS	ns

TABLE 10-43. (Continued)

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

	Unadjusted			
Variable	All	Unknown versus Background	Low versus Background	High versus Background
LDH (C)	NS	ns	ns	NS
LDH (D)	NS	ns	ns	ns
Cholesterol (C)	NS	NS	NS	NS*
Cholesterol (D)	NS	+0.022	NS	NS
HDL[a] (C)	<0.001	+<0.001	ns	-0.031
HDL (D)	NS	ns	NS	NS
Cholesterol-HDL Ratio (C)	<0.001	-0.002	NS*	+0.003
Cholesterol-HDL Ratio (D)	0.021	ns*	NS	NS
Triglycerides (C)	<0.001	-0.005	+<0.001	+0.004
Triglycerides (D)	<0.001	ns	+0.045	+0.002
Creatine Kinase (C)	NS	ns	ns	NS
Creatine Kinase (D)	NS*	ns	ns	ns*

[a]Negative difference considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.
-: Relative risk less than 1.00 for discrete analysis; difference in means negative for continuous analysis.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

TABLE 10-43. (Continued)

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

Variable	Adjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Viral Hepatitis (D)	0.022	ns*	ns	+0.047
Viral Hepatitis[a] (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Alcohol-Related) (D)	NS	NS	ns	NS
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related) (D)	NS	NS	NS	- -
Other Disorders of the Liver (D)	NS*	ns	NS	+0.038
Jaundice (D)	0.014	NS	- -	ns
Hepatomegaly (D)	NS	ns	ns	NS
Ulcer (D)	NS	NS	ns	NS
Skin Bruises, Patches, or Sensitivity (D)	<0.001	+0.005	+0.004	+<0.001
Physical Examination				
Current Hepatomegaly (D)	0.006	- -	NS	NS
Laboratory				
AST (C)	NS	ns	ns	NS
AST (D)	NS	NS	ns	NS
ALT (C)	** (0.012)	** (ns*)	** (NS)	** (+0.035)
ALT (D)	NS	ns	NS	NS
GGT (C)	<0.001	-0.017	+0.043	+0.001
GGT (D)	** (0.033)	** (ns)	** (+0.039)	** (+0.018)
Alkaline Phosphatase (C)	NS*	NS	NS*	+0.044
Alkaline Phosphatase (D)	NS	ns	ns	NS
D-Glucaric Acid (C)	NS	ns	NS	NS
D-Glucaric Acid (D)	- -	- -	- -	- -
Total Bilirubin (C)	NS	ns	ns	ns
Total Bilirubin (D)	0.018	ns	NS	-0.030
Direct Bilirubin (C)	*** (NS*)	*** (ns)	*** (NS)	*** (+0.018)
Direct Bilirubin (D)	NS	ns	NS	ns

TABLE 10-43. (Continued)

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

Variable	Adjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
LDH (C)	NS	ns	ns	NS
LDH (D)	--	--	--	--
Cholesterol (C)	NS	NS	NS	+0.038
Cholesterol (D)	NS	+0.018	NS	NS
HDL[b] (C)	** (<0.001)	** (+<0.001)	** (ns)	** (ns)
HDL (D)	** (NS)	** (NS)	** (NS)	** (NS)
Cholesterol-HDL Ratio (C)	<0.001	-<0.001	NS	+0.003
Cholesterol-HDL Ratio (D)	0.023	ns*	NS	NS*
Triglycerides (C)	** (<0.001)	** (-0.004)	** (+<0.001)	** (+0.002)
Triglycerides (D)	** (<0.001)	** (ns*)	** (+0.045)	** (+0.001)
Creatine Kinase (C)	** (NS)	** (ns)	** (ns)	** (NS)
Creatine Kinase (D)	** (NS)	** (ns)	** (ns)	** (ns*)

[a]Adjusted for age and occupation. Appendix Table I-2 presents a detailed description of this analysis.
[b]Negative difference considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.
-: Relative risk less than 1.00 for discrete analysis; difference in means negative for continuous analysis.
--: Analysis not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (ns*): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
** (...): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.
*** (NS)/*** (ns): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); not significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
*** (NS*): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); marginally significant when interaction is deleted; refer to Appendix Table I-1 for a detailed description of this interaction.
*** (...): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table I-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

TABLE 10-44.

Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Gastrointestinal Variables

Variable	Assumption	Covariate
Model 1: Log_2 (Initial Dioxin)		
AST (C)	Minimal	DC
AST (D)	Minimal	RACE, DC
AST (D)	Maximal	DC
ALT (C)	Maximal	AGE
ALT (D)	Minimal	DC
ALT (D)	Maximal	ALC
GGT (D)	Minimal	RACE, DC
GGT (D)	Maximal	DC
D-Glucaric Acid (C)	Minimal	RACE
Total Bilirubin (C)	Maximal	RACE
Direct Bilirubin (D)	Minimal	IC
Direct Bilirubin (D)	Maximal	IC
HDL (C)	Maximal	DC
Cholesterol-HDL Ratio (C)	Maximal	DC
Cholesterol-HDL Ratio (D)	Maximal	AGE, DC
Creatine Kinase (C)	Minimal	AGE
Creatine Kinase (C)	Maximal	AGE
Model 2: Log_2 (Current Dioxin) and Time		
AST (C)	Maximal	ALC
ALT (C)	Maximal	ALC
Alkaline Phosphatase (C)	Minimal	LWINE
Alkaline Phosphatase (C)	Maximal	RACE, WINE
Direct Bilirubin (D)	Minimal	DC
Cholesterol (C)	Maximal	DRKYR
Cholesterol (D)	Minimal	IC
HDL (C)	Minimal	IC
Cholesterol-HDL Ratio (C)	Minimal	IC
Cholesterol-HDL Ratio (D)	Minimal	IC
Model 3: Ranch Hands and Comparisons by Current Dioxin Category		
ALT (C)	--	DRKYR
GGT (D)	--	DC
Direct Bilirubin (C)	--	RACE
HDL (C)	--	DRKYR
HDL (D)	--	DC
Triglycerides (C)	--	ALC
Triglycerides (D)	--	ALC
Creatine Kinase (C)	--	RACE
Creatine Kinase (D)	--	RACE

C: Continuous analysis.
D: Discrete analysis.

The overall contrast was marginally significant for the category of other liver disorders in the adjusted analysis. For this variable, the relative risk for Ranch Hands with the highest current levels of dioxin (>33.3 ppt) was significantly greater than 1.

For jaundice, the unadjusted analyses found that the incidence of jaundice differed marginally among the current dioxin categories, but this was due to a significantly decreased incidence in the low current dioxin category, relative to the background category. Although the model 1 and model 2 analyses for skin bruises, patches, or sensitivity were not significant, the categorized current dioxin analyses found a highly significant increase in the incidence of skin bruises, patches, or sensitivity in each of the three Ranch Hand current dioxin categories relative to the background incidence. The categorized current dioxin analyses were not significant for the other questionnaire variables.

Physical Examination Variable

The initial dioxin analyses and the current dioxin and time since tour analyses did not reveal any significant findings in hepatomegaly diagnosed at the 1987 physical examination. The unadjusted categorized current dioxin analysis showed a marginally significant difference in the prevalence of hepatomegaly among current dioxin categories, but the only significant Ranch Hand versus background contrast was a decreased risk in the unknown category.

Laboratory Variables

The gastrointestinal assessment analyzed 13 laboratory variables (AST, ALT, GGT, alkaline phosphatase, d-glucaric acid, total bilirubin, direct bilirubin, LDH, cholesterol, HDL, cholesterol-HDL ratio, triglycerides, and creatine kinase). The only significant laboratory finding from the previous results of the 1987 examination was that the Ranch Hands had a higher mean alkaline phosphatase than the Comparisons.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the adjusted initial dioxin analyses detected significant positive associations with cholesterol (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete). They also found a significant decreased risk of abnormally high levels of total bilirubin. In addition to these significant findings, the adjusted maximal analyses also found significant positive associations between initial dioxin and ALT (continuous), GGT (continuous and discrete), alkaline phosphatase (continuous), and direct bilirubin (continuous). The adjusted maximal analyses also showed a significant negative relationship between initial dioxin and HDL (continuous) and a marginally significant decreased risk of abnormally high levels of creatine kinase.

The adjusted analyses frequently revealed initial dioxin-by-covariate interactions. In most instances, the covariate was either age, race, or degreasing chemical exposure. With degreasing chemical exposure, stratified analyses found significant or marginally significant increased risks of abnormally high levels of AST (minimal and maximal), ALT (minimal), GGT (minimal and maximal), and the cholesterol-HDL ratio (maximal) for Ranch Hands who had never been exposed to degreasing chemicals. In addition, the association between initial dioxin and the cholesterol-HDL ratio in its continuous form was significant for these Ranch Hands. This pattern is puzzling since it is counter to any hypothesized synergistic effort of dioxin and degreasing chemicals. Degreasing chemicals are associated with occupation

(officers were generally not exposed to degreasing chemicals). However, additional analyses adjusting for occupation still detected significant dioxin-by-degreasing chemical interactions. The initial dioxin-by-race interactions for AST and GGT were affected by sparse data. No consistent pattern emerged from exploration of the other interactions.

Initial dioxin levels were not associated significantly with the change in levels of AST, ALT, and GGT in the longitudinal analyses.

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

The association between current dioxin and the laboratory variables generally did not differ significantly between time since tour strata. The adjusted minimal analyses found a significant current dioxin-by-time interaction for cholesterol (continuous). For this analysis, the association with current dioxin was significant for Ranch Hands with an early tour, but the association was not significant for those with a later tour. The current dioxin-by-time interaction was not significant for any of the adjusted maximal analyses, although it was marginally significant in the unadjusted maximal analysis of triglycerides (continuous). Many of the adjusted analyses exhibited current dioxin-by-time-by-covariate interactions, but no consistent pattern emerged suggestive of a dioxin effect. The longitudinal analyses were not significant for AST, ALT, and GGT.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The adjusted categorized current dioxin analyses found significant overall contrasts for ALT (continuous), GGT (continuous and discrete), total bilirubin (discrete), HDL (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete). There was a marginally significant overall contrast for alkaline phosphatase (continuous) and direct bilirubin (continuous). The adjusted mean levels of ALT, GGT, alkaline phosphatase, direct bilirubin, cholesterol, the cholesterol-HDL ratio, and triglycerides in the high current dioxin category were significantly more than the respective adjusted means in the background category. Relative to the background category, the adjusted analyses found that Ranch Hands in the high current dioxin category had a significant increased risk of abnormally high levels of GGT and triglycerides and a significant decreased risk of abnormally high levels of total bilirubin. The high versus background contrast also showed a marginally significant increased risk of an abnormally high cholesterol-HDL ratio and a marginally significant decreased risk of an abnormally high level of creatine kinase.

In the adjusted analyses, the low versus background contrast exhibited significant positive differences for GGT (continuous and discrete) and triglycerides (continuous and discrete). The low current dioxin category also had a marginally higher adjusted mean alkaline phosphatase than the background category. The unknown versus background contrast often displayed differences that were in the opposite direction of the high versus background contrast. For this contrast, the adjusted analyses showed significant or marginally significant negative differences for ALT (continuous), GGT (continuous), the cholesterol-HDL ratio (continuous and discrete), and triglycerides (continuous and discrete), along with significant positive differences for cholesterol (discrete) and HDL (continuous).

In many instances, the means displayed a dose-response relationship for the unknown, low, and high current dioxin categories, with the background mean falling between the unknown and high categories. A possible explanation for this consistent trend was that it was due to an occupational difference among Ranch Hand categories (most officers were in the unknown category). However, the pattern persisted after performing additional analyses adjusting for occupation.

The adjusted analyses detected several categorized current dioxin-by-covariate interactions. However, no consistent pattern was noted except that both the continuous and discrete adjusted analyses of triglycerides found significant categorized current dioxin-by-current alcohol use interactions and that both the continuous and discrete adjusted analyses of creatine kinase revealed significant categorized current dioxin-by-race interactions.

The high versus background contrasts were not significant in the longitudinal analyses for AST, ALT, and GGT. The overall contrast in the longitudinal analyses was significant for ALT and marginally significant for GGT, but these findings were due to a significant unknown versus background contrast.

CONCLUSION

The gastrointestinal assessment found statistically significant associations between dioxin and skin bruises, patches, or sensitivity, and several laboratory variables (primarily lipid related). In conjunction with findings in other chapters, these observations may represent a dioxin mediated alteration of biochemical processes.

CHAPTER 10

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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 transglutamase 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 proliferentiation 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 angiomata, 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: ≥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_2 (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_2 (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 (time$\leq$18.6 years) there was a significant positive association (Est. RR=1.21, p=0.025). In the earlier tour stratum (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.

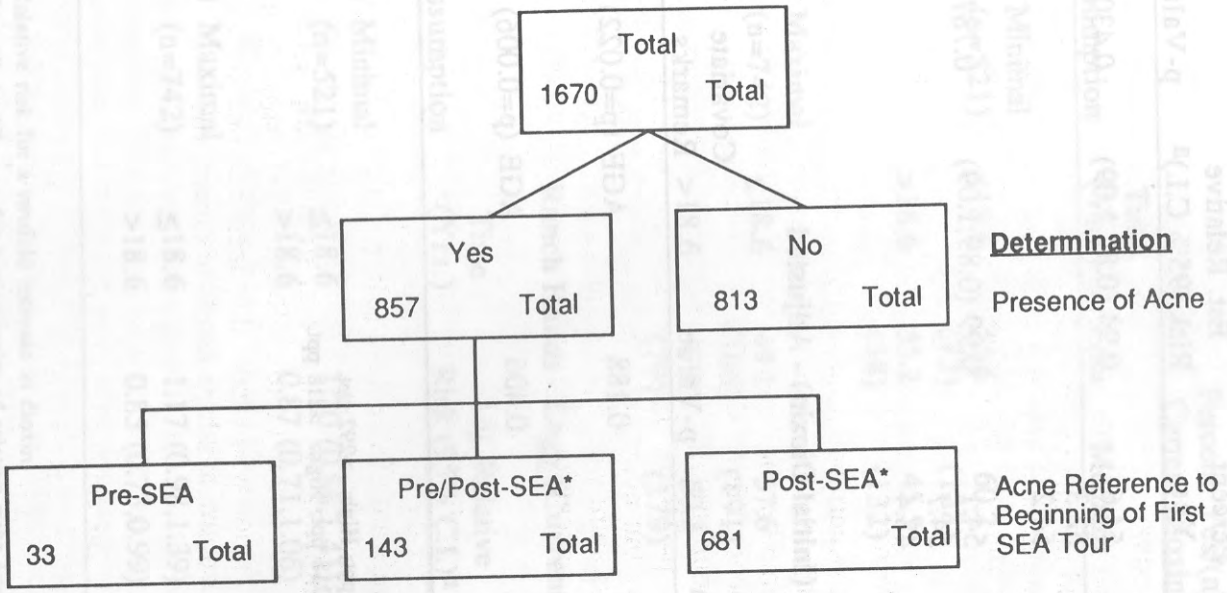
In the adjusted minimal analysis, the current dioxin-by-time interaction remained nonsignificant (Table 11-2 [g]: p=0.131). Under the maximal assumption, the interaction between current dioxin and time remained significant (Table 11-2 [h]: p=0.006). However, after the model had been adjusted for age, 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)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=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		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
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)

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

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

TABLE 11-2. (Continued)

Analysis of Occurrence of Acne (Lifetime)

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

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

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=521)			0.131[b]	AGE (p=0.096)
	≤18.6	1.10 (0.86,1.41)	0.447[c]	
	>18.6	0.87 (0.71,1.06)	0.171[c]	
h) Maximal (n=742)			0.006[b]	AGE (p=0.017)
	≤18.6	1.17 (0.98,1.39)	0.078[c]	
	>18.6	0.85 (0.73,0.99)	0.040[c]	

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

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

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

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

TABLE 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 ≤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.

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_2 (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)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Pre/Post-SEA Post-SEA	Est. Relative Risk (95% C.I.)[a]	p-Value
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		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
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)

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

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

TABLE 11-3. (Continued)

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

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Post-SEA	Est. Relative Risk (95% C.I.)[a]	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		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	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)

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 11-3. (Continued)

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

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Pre/Post-SEA	Est. Relative Risk (95% C.I.)[a]	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		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

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)

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

****Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); 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_2 (initial dioxin).