association between current dioxin and AST for these Ranch Hands who had an early tour (time>18.6: p=0.006). The adjusted mean AST levels for this stratum were 27.06, 32.99, and 25.34 U/L. For Ranch Hands who had a later tour, there was a nonsignificant positive association (time≤18.6: p=0.647).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean levels of AST did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis of categorized current dioxin (Table 10-12 [i] and [j]: p=0.276 and p=0.374, respectively).

AST (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the prevalence of abnormally high levels of AST was not associated significantly with initial dioxin in the unadjusted analyses (Table 10-13 [a] and [b]: p=0.999 and p=0.720, respectively).

The adjusted minimal analysis detected two significant initial dioxin-by-covariate interactions (Table 10-13 [c]: initial dioxin-by-race, p=0.019 and initial dioxin-by-degreasing chemical exposure, p=0.029). To explore these interactions, separate analyses were done for Blacks and non-Blacks. The association between initial dioxin and discretized AST was significant for Blacks (Appendix Table I-1: p=0.010), even though only three Blacks had an abnormally high AST level, all in the low initial dioxin category. For non-Blacks, the initial dioxin-by-degreasing chemical exposure interaction was significant (p=0.039). The relative risk was marginally more than 1 for non-Black Ranch Hands who had never been exposed to degreasing chemicals (Adj. RR=1.97, p=0.069). By contrast, the relative risk was less than 1, but not significant, for non-Black Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.82, p=0.340). The adjusted relative risk of an abnormal level of AST was not significant (Table 10-13 [c]: Adj. RR=0.88, p=0.479) after deleting the two initial dioxin-by-covariate interactions.

In the adjusted maximal analysis, the initial dioxin-by-degreasing chemical exposure interaction was significant (Table 10-13 [d]: p=0.045). For Ranch Hands who had never been exposed to degreasing chemicals, the relative risk of an abnormal level of AST was marginally more than 1 (Appendix Table I-1: Adj. RR=1.60, p=0.086). This contrasted with a nonsignificant relative risk less than 1 for Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.85, p=0.258). After excluding the interaction, the relative risk was not significant (Table 10-13 [d]: Adj. RR=0.96, p=0.737).

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

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant for the unadjusted and adjusted analyses of discretized AST (Table 10-13 [e-h]: p>0.30 for all analyses).

TABLE 10-13.
Analysis of AST (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	6.9	1.00 (0.72,1.40)	0.999
	Medium	257	3.5		
	High	130	5.4		
b) Maximal (n=737)	Low	184	3.8	1.05 (0.82,1.33)	0.720
	Medium	368	5.7		
	High	185	4.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=514)	0.88 (0.62,1.25)**	0.479**	INIT*RACE (p=0.019) INIT*DC (p=0.029) ALC (p<0.001)
d) Maximal (n=732)	0.96 (0.75,1.23)**	0.737**	INIT*DC (p=0.045) ALC (p<0.001)

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

**Log_2 (initial 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: 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 10-13. (Continued)

Analysis of AST (Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.467[b]
(n=517)	≤18.6	5.6 (72)	3.2 (126)	1.9 (53)	0.80 (0.40,1.59)	0.520[c]
	>18.6	10.3 (58)	3.1 (131)	7.8 (77)	1.06 (0.72,1.57)	0.760[c]
f) Maximal						0.800[b]
(n=737)	≤18.6	3.8 (105)	3.2 (189)	3.7 (82)	0.96 (0.61,1.51)	0.853[c]
	>18.6	3.8 (79)	7.9 (178)	5.8 (104)	1.03 (0.77,1.37)	0.858[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.368[b]	ALC (p<0.001)
(n=514)	≤18.6	0.65 (0.30,1.39)	0.263[c]	DC (p=0.078)
	>18.6	0.95 (0.63,1.42)	0.789[c]	
h) Maximal			0.922[b]	ALC (p<0.001)
(n=732)	≤18.6	0.88 (0.54,1.44)	0.607[c]	DC (p=0.019)
	>18.6	0.90 (0.66,1.23)	0.527[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 10-13. (Continued)

Analysis of AST (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	3.6	All Categories		0.832
Unknown	341	3.5	Unknown vs. Background	0.98 (0.49,1.95)	0.950
Low	193	3.1	Low vs. Background	0.86 (0.35,2.11)	0.743
High	186	4.8	High vs. Background	1.36 (0.63,2.94)	0.429
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		0.959	ALC (p<0.001) DC (p=0.065)
Unknown	339	Unknown vs. Background	1.05 (0.51,2.15)	0.893	
Low	191	Low vs. Background	0.93 (0.38,2.30)	0.877	
High	185	High vs. Background	1.22 (0.55,2.72)	0.623	
Total	1,494				

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

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of abnormally high levels of AST did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis (Table 10-13 [i] and [j]: p=0.832 and p=0.959).

ALT (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analysis displayed a significant positive association with ALT under both the minimal and maximal assumptions (Table 10-14 [a] and [b]: p=0.039 and p<0.001). The mean levels of ALT were 21.15, 21.50, and 22.99 U/L for the low, medium, and high minimal initial dioxin categories. For the maximal cohort, the means for the low, medium, and high initial dioxin categories were 18.86, 21.47, and 22.63 U/L.

After covariate adjustment, the association between initial dioxin and ALT became nonsignificant for the minimal cohort (Table 10-14 [c]: p=0.190). This change in significance was due primarily to the adjustment for age (ALT levels decreased significantly with age; age is associated positively with dioxin, see Chapter 5, Covariate Associations). The adjusted analysis for the maximal cohort detected a significant initial dioxin-by-age interaction (Table 10-14 [d]: p=0.047). Age was dichotomized to explore the interaction. Stratified results showed a highly significant positive association between ALT and initial dioxin for younger Ranch Hands, those born in or after 1942 (Appendix Table I-1: p<0.001). For these Ranch Hands, the adjusted mean levels of ALT for the low, medium, and high initial dioxin categories were 18.29, 21.45, and 23.61 U/L. The association between ALT and initial dioxin was not significant for Ranch Hands born before 1942 (p=0.646).

After excluding the initial dioxin-by-age interaction, the adjusted results for the maximal cohort paralleled the unadjusted findings, exhibiting a significant positive association between ALT and initial dioxin (Table 10-14 [d]: p=0.005).

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

Under both the minimal and maximal assumptions, the unadjusted analysis of current dioxin and time since tour did not find a significant interaction between current dioxin and time for ALT (Table 10-14 [e] and [f]: p=0.464 and p=0.989, respectively). Although the association between current dioxin and ALT did not differ significantly between time strata, the association was significant within each stratum under the maximal assumption (time≤18.6: slope=0.0472, p=0.022; time>18.6: slope=0.0468, p=0.010). Under the minimal assumption, the association between current dioxin and ALT was marginally significant for Ranch Hands with an early tour (time≤18.6: p=0.073).

The current dioxin-by-time interaction remained nonsignificant for the adjusted minimal analysis (Table 10-14 [g]: p=0.531), but the adjusted maximal analysis detected a significant current dioxin-by-time-by-current alcohol use interaction (Table 10-14 [h]: p=0.026). Current alcohol use was dichotomized (≤1 drink/day and >1 drink/day) to explore the interaction. Appendix Table I-1 presents stratified results that show a marginally significant interaction between current dioxin and time for Ranch Hands who currently consume more than one alcoholic drink per day (p=0.068). However, for these Ranch Hands,

TABLE 10-14.
Analysis of ALT (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	21.15	0.0372 (0.0179)	0.039
(n=517)	Medium	257	21.50		
(R^2=0.008)	High	130	22.99		
b) Maximal	Low	184	18.86	0.0475 (0.0132)	<0.001
(n=737)	Medium	368	21.47		
(R^2=0.017)	High	185	22.63		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	20.20	0.0239 (0.0182)	0.190	AGE (p<0.001)
(n=514)	Medium	255	20.35			RACE*IC (p=0.007)
(R^2=0.088)	High	129	21.26			ALC*IC (p=0.004)
d) Maximal	Low	183	17.97**	0.0379 (0.0133)**	0.005**	INIT*AGE (p=0.047)
(n=732)	Medium	365	20.57**			DC (p=0.145)
(R^2=0.097)	High	184	20.82**			RACE*IC (p=0.005)
						ALC*IC (p=0.013)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm ALT versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, 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 10-14. (Continued)

Analysis of ALT (U/L) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.464[c]
(n=517)	≤18.6	20.02 (72)	21.36 (126)	22.30 (53)	0.0525 (0.0293)	0.073[d]
(R^2=0.011)	>18.6	22.65 (58)	21.68 (131)	23.37 (77)	0.0249 (0.0239)	0.298[d]
f) Maximal						0.989[c]
(n=737)	≤18.6	19.63 (105)	20.34 (189)	22.47 (82)	0.0472 (0.0205)	0.022[d]
(R^2=0.018)	>18.6	17.74 (79)	22.46 (178)	23.37 (104)	0.0468 (0.0181)	0.010[d]

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.531[c]	AGE (p<0.001)
(n=514)	≤18.6	19.04 (72)	19.80 (126)	19.83 (52)	0.0283 (0.0296)	0.339[d]	RACE*IC (p=0.006)
(R^2=0.093)							ALC*IC (p=0.005)
	>18.6	22.11 (58)	20.68 (129)	21.75 (77)	0.0053 (0.0241)	0.825[d]	
h) Maximal						0.872**[c]	CURR*TIME*ALC
(n=732)	≤18.6	18.56** (105)	19.59** (188)	20.66** (81)	0.0355 (0.0206)**	0.086**[d]	(p=0.026)
(R^2=0.091)							AGE (p=0.005)
	>18.6	17.69** (78)	21.98** (176)	22.03** (104)	0.0312 (0.0183)**	0.088**[d]	RACE*IC (p=0.007)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm ALT versus log_2 dioxin.

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

[d]Test of significance for slope different from 0 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

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 10-14. (Continued)

Analysis of ALT (U/L) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	20.62	All Categories		<0.001
Unknown	341	19.06	Unknown vs. Background	-1.56 --	0.011
Low	193	21.01	Low vs. Background	0.39 --	0.634
High	186	22.97	High vs. Background	2.35 --	0.006
Total	1,499		(R^2=0.012)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	777	20.34**	All Categories		0.012**	DXCAT*DRKYR (p=0.017) AGE (p<0.001)
Unknown	338	19.16**	Unknown vs. Background	-1.18 -- **	0.055**	DC (p=0.067)
Low	191	20.83**	Low vs. Background	0.49 -- **	0.531**	IC (p=0.104)
High	182	22.09**	High vs. Background	1.75 -- **	0.035**	RACE*ALC (p=0.001)
Total	1,488		(R^2=0.050)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means on natural logarithm scale.

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, 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 (categorized within group).

the association between current dioxin and ALT was not significant within either time stratum (time≤18.6: Adj. slope=0.0552, p=0.257; time>18.6: Adj. slope=-0.0603, p=0.140).

By contrast, the interaction between current dioxin and time was not significant for Ranch Hands who currently consume no more than one drink per day (p=0.388), but the association between current dioxin and ALT was significant for these Ranch Hands with an early tour (time>18.6: Adj. slope=0.0593, p=0.003; Adj. means: 16.45, 20.48, and 21.86 U/L for low, medium, and high current dioxin). After excluding the interaction, the current dioxin-by-time interaction was not significant in the adjusted maximal analysis (Table 10-14 [h]: p=0.872), but the association between current dioxin and ALT was marginally significant for each time stratum (time≤18.6: p=0.086; time>18.6: p=0.088).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin found a significant overall difference among mean levels of ALT (Table 10-14 [i]: 20.62, 19.06, 21.01, and 22.97 U/L for the background, unknown, low, and high current dioxin categories, p<0.001). The mean for the unknown category was significantly less than the background mean (p=0.011), and the mean for the high current dioxin category was significantly more than the background mean (p=0.006).

The adjusted analysis detected a significant categorized current dioxin-by-lifetime alcohol history interaction (Table 10-14 [j]: p=0.017). The lifetime alcohol history covariate was trichotomized into never (0 drink-years), moderate (>0-40 drink-years), and heavy (>40 drink-years) to explore the interaction. The mean levels of ALT did not differ significantly among current dioxin categories for participants who had never drunk alcohol (Appendix Table I-1: p=0.434). For moderate lifetime drinkers, there was a significant overall difference among category means (20.28, 18.13, 21.30, and 21.07 U/L for the background, unknown, low, and high current dioxin categories, p=0.002). In this stratum, the mean for the unknown category was significantly less than the background mean (p=0.002), but the means for the low and high categories did not differ significantly from the background mean (p=0.280 and p=0.443, respectively). The overall contrast was of borderline significance for heavy lifetime drinkers (p=0.057). The adjusted means in this stratum were 19.95, 22.78, 19.98, and 23.93 U/L for the background, unknown, low, and high current dioxin categories. The mean for the high category was significantly more than the background mean (p=0.024) and the mean for the unknown category was marginally more than the background mean (p=0.062).

After excluding the interaction, the adjusted mean levels of ALT differed significantly among the four current dioxin categories (Table 10-14 [j]: 20.34, 19.16, 20.83, and 22.09 U/L, for the background, unknown, low, and high current dioxin categories, p=0.012). The mean ALT for the unknown category was marginally less than the background mean (p=0.055), and the mean ALT for the high category was significantly more than the background mean (p=0.035).

ALT (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, discretized ALT was not associated significantly with initial dioxin in the unadjusted analysis (Table 10-15 [a]: p=0.235). However, for the maximal assumption, the unadjusted analysis revealed a significant relative risk (Table 10-15 [b]: Est. RR=1.18, p=0.031). The percentage of abnormally high ALT values increased with levels of initial dioxin (8.2%, 13.3%, and 14.6% for the low, medium, and high maximal cohort initial dioxin categories).

The adjusted analyses revealed a significant initial dioxin-by-covariate interaction for each cohort. The adjusted minimal analysis found a significant initial dioxin-by-degreasing chemical interaction (Table 10-15 [c]: p=0.011). Stratified results showed that the prevalence of abnormally high ALT levels was associated significantly with initial dioxin for Ranch Hands who had never been exposed to degreasing chemicals (Appendix Table I-1: Adj. RR=1.62, p=0.013). The relative risk was less than 1, but not significant, for Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.90, p=0.433). The initial dioxin effect was not significant (p=0.509) after excluding the interaction between initial dioxin and degreasing chemical exposure.

The adjusted maximal analysis found a significant initial dioxin-by-current alcohol use interaction (Table 10-15 [d]: p=0.035). Current alcohol use was trichotomized to explore the interaction. Appendix Table I-1 shows that the relative risk was significantly more than 1 for Ranch Hands who currently consume at most one alcoholic drink per day (Adj. RR=1.28, p=0.007; % abnormal: 6.3%, 10.3%, and 14.8% for the low, medium, and high initial dioxin categories). The relative risk was less than 1, but not significant, for the other current alcohol use strata (>1-4: Adj. RR=0.95, p=0.774; >4: Adj. RR=0.67, p=0.371). After excluding the interaction, the association between initial dioxin and ALT was marginally significant (Table 10-15 [d]: Est. RR=1.15, p=0.079).

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

The unadjusted current dioxin and time since tour analyses for discretized ALT did not find a significant current dioxin-by-time interaction for either the minimal (Table 10-15 [e]: p=0.267) or maximal (Table 10-15 [f]: p=0.338) cohorts. However, for Ranch Hands with a later tour, the estimated relative risk of an abnormally high level of ALT was marginally significant for the minimal cohort (time≤18.6: Est. RR=1.33, p=0.082; % abnormal: 6.9%, 15.1%, and 17.0% for the low, medium, and high current dioxin categories) and significant for the maximal cohort (Est. RR=1.30, p=0.028; % abnormal: 9.5%, 11.6%, and 14.6% for the low, medium, and high current dioxin categories).

After covariate adjustment, the current dioxin-by-time interaction remained nonsignificant for both cohorts (Table 10-15 [g] and [h]: p=0.230 and p=0.248 for the minimal and maximal cohorts). For Ranch Hands with a later tour, the adjusted relative risk was marginally significant in the maximal analysis (Adj. RR=1.27, p=0.062).

TABLE 10-15.

Analysis of ALT (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	12.3	1.13 (0.93,1.38)	0.235
	Medium	257	12.8		
	High	130	16.2		
b) Maximal (n=737)	Low	184	8.2	1.18 (1.02,1.38)	0.031
	Medium	368	13.3		
	High	185	14.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=514)	1.07 (0.87,1.33)**	0.509**	INIT*DC (p=0.011) ALC (p=0.039) AGE*RACE (p=0.037)
d) Maximal (n=732)	1.15 (0.98,1.35)**	0.079**	INIT*ALC (p=0.035) RACE*AGE (p=0.018)

[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 10-15. (Continued)

Analysis of ALT (Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.267[b]
(n=517)	≤18.6	6.9 (72)	15.1 (126)	17.0 (53)	1.33 (0.96,1.84)	0.082[c]
	>18.6	15.5 (58)	12.2 (131)	15.6 (77)	1.05 (0.80,1.37)	0.729[c]
f) Maximal						0.338[b]
(n=737)	≤18.6	9.5 (105)	11.6 (189)	14.6 (82)	1.30 (1.03,1.66)	0.028[c]
	>18.6	5.1 (79)	15.2 (178)	15.4 (104)	1.12 (0.91,1.37)	0.285[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.230[b]	ALC (p=0.046)
(n=514) (p=0.022)	≤18.6	1.26 (0.89,1.78)	0.197[c]	AGE*RACE
	>18.6	0.96 (0.73,1.28)	0.799[c]	
h) Maximal			0.248[b]	ALC (p<0.001)
(n=732) (p=0.015)	≤18.6	1.27 (0.99,1.63)	0.062[c]	AGE*RACE
	>18.6	1.05 (0.85,1.30)	0.651[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 10-15. (Continued)

Analysis of ALT (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	10.9	All Categories		0.197
Unknown	341	9.4	Unknown vs. Background	0.85 (0.55,1.30)	0.442
Low	193	13.5	Low vs. Background	1.27 (0.79,2.04)	0.318
High	186	15.1	High vs. Background	1.45 (0.91,2.29)	0.116
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		0.391	AGE (p=0.002) ALC (p<0.001)
Unknown	339	Unknown vs. Background	0.89 (0.58,1.37)	0.592	
Low	191	Low vs. Background	1.32 (0.82,2.12)	0.256	
High	185	High vs. Background	1.29 (0.81,2.07)	0.282	
Total	1,494				

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

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast was not significant for either the unadjusted or adjusted categorized current dioxin analysis of discretized ALT (Table (10-15 [i] and [j]: p=0.197 and p=0.391, respectively). Also, none of the three Ranch Hand versus background contrasts was significant in either analysis.

GGT (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analysis of GGT in its continuous form was not significant for the minimal cohort (Table 10-16 [a]: p=0.357), but a highly significant positive association was evident for the maximal cohort (Table 10-16 [b]: p<0.001). The mean levels of GGT were 28.34, 35.47, and 35.90 U/L for the low, medium, and high initial dioxin categories under the maximal assumption.

The adjusted results paralleled the unadjusted findings. No significant association was found between GGT and initial dioxin for the minimal cohort (Table 10-16 [c]: p=0.338), but the association was highly significant for the adjusted maximal analysis (Table 10-16 [d]: p<0.001).

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

The unadjusted association between GGT and current dioxin did not differ significantly between time since tour strata for either the minimal or maximal cohort (Table 10-16 [e] and [f]: p=0.715 and p=0.537). However, for the maximal cohort, the unadjusted association between GGT and current dioxin was significant within each time stratum (time≤18.6: slope=0.0701, p=0.011; time>18.6: slope=0.0476, p=0.048). The mean levels of GGT for the low, medium, and high categories were 28.17, 32.77, and 36.42 U/L for Ranch Hands with a later tour, and 28.40, 37.66, and 37.13 U/L for Ranch Hands with an early tour.

For both cohorts, the interaction between current dioxin and time remained nonsignificant in the adjusted analyses (Table 10-16 [g] and [h]: p=0.718 and p=0.305 for the minimal and maximal cohorts). For the maximal cohort, the adjusted association between GGT and current dioxin was significantly positive for Ranch Hands with a later tour (time≤18.6: p=0.003) and marginally positive for Ranch Hands with an early tour (time>18.6: p=0.062).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean levels of GGT differed significantly among the four current dioxin categories for the unadjusted analysis of categorized current dioxin (Table 10-16 [i]: 32.03, 28.75, 34.99, and 36.82 U/L for the background, unknown, low, and high current dioxin categories, p<0.001). Each of the contrasts relative to the background category was significant or marginally significant. Comparable to the findings for ALT, the mean for the unknown current dioxin category was significantly less than the background mean (p=0.009) and the mean for the high category was significantly more than the background mean (p=0.007). The low current dioxin category mean was marginally more than the background category mean (p=0.083).

TABLE 10-16.

Analysis of GGT (U/L)
(Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	35.56	0.0230 (0.0249)	0.357
(n=517)	Medium	257	35.81		
(R^2=0.002)	High	130	35.94		
b) Maximal	Low	184	28.34	0.0616 (0.0175)	<0.001
(n=737)	Medium	368	35.47		
(R^2=0.017)	High	185	35.90		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	35.60	0.0232 (0.0242)	0.338	ALC*IC (p=0.021)
(n=514)	Medium	255	35.81			
(R^2=0.096)	High	129	36.60			
d) Maximal	Low	183	30.45	0.0636 (0.0169)	<0.001	RACE (p=0.092)
(n=732)	Medium	365	38.05			ALC*IC (p<0.001)
(R^2=0.121)	High	184	38.88			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm 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.

TABLE 10-16. (Continued)

Analysis of GGT (U/L) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.715[c]
(n=517)	≤18.6	33.55	35.44	33.41	0.0289 (0.0406)	0.477[d]
(R^2=0.004)		(72)	(126)	(53)		
	>18.6	39.09	36.14	37.22	0.0097 (0.0332)	0.770[d]
		(58)	(131)	(77)		
f) Maximal						0.537[c]
(n=737)	≤18.6	28.17	32.77	36.42	0.0701 (0.0273)	0.011[d]
(R^2=0.019)		(105)	(189)	(82)		
	>18.6	28.40	37.66	37.13	0.0476 (0.0240)	0.048[d]
		(79)	(178)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.718[c]	ALC*IC (p=0.024)
(n=514)	≤18.6	33.52	35.89	34.55	0.0308 (0.0392)	0.432[d]	
(R^2=0.098)		(72)	(126)	(52)			
	>18.6	38.69	35.84	37.41	0.0127 (0.0321)	0.693[d]	
		(58)	(129)	(77)			
h) Maximal						0.305[c]	RACE (p=0.092)
(n=732)	≤18.6	29.89	35.72	39.78	0.0790 (0.0263)	0.003[d]	ALC*IC (p=0.001)
(R^2=0.124)		(105)	(188)	(81)			
	>18.6	31.60	40.07	39.61	0.0434 (0.0232)	0.062[d]	
		(78)	(176)	(104)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm GGT versus log_2 dioxin.

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

[d]Test of significance for slope different from 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.

TABLE 10-16. (Continued)

Analysis of GGT (U/L) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	32.03	All Categories		<0.001
Unknown	341	28.75	Unknown vs. Background	-3.28 --	0.009
Low	193	34.99	Low vs. Background	2.96 --	0.083
High	186	36.82	High vs. Background	4.79 --	0.007
Total	1,499		(R^2=0.015)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	777	34.64	All Categories		<0.001	RACE (p=0.008) ALC*DRKYR (p<0.001)
Unknown	338	31.49	Unknown vs. Background	-3.15 --	0.017	
Low	191	38.28	Low vs. Background	3.64 --	0.043	
High	182	40.82	High vs. Background	6.18 --	0.001	
Total	1,488		(R^2=0.088)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means 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.

The results of the adjusted analysis displayed similar findings. The overall contrast remained highly significant (Table 10-16 [j]: p<0.001). The adjusted mean levels of GGT for the background, unknown, low, and high current dioxin categories were 34.64, 31.49, 38.28, and 40.82 U/L. The mean for the unknown current dioxin category was significantly less than the background mean (p=0.017) and the means for the low and high current dioxin category were significantly more than the background mean (p=0.043 and p=0.001, respectively).

GGT (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the prevalence of abnormally high levels of GGT was not associated significantly with initial dioxin based on the unadjusted analysis (Table 10-17 [a]: p=0.574). However, the unadjusted maximal analysis found a marginally significant positive association between discretized GGT and initial dioxin (Table 10-17 [b]: Est. RR=1.20, p=0.052). The percentage of abnormal GGT values increased with initial dioxin for the maximal cohort (4.9%, 9.5%, and 9.7% for the low, medium, and high initial dioxin categories).

The adjusted initial dioxin analyses of discretized GGT detected significant initial dioxin-by-covariate interactions that also were present in the adjusted analyses of discretized AST. The adjusted minimal analysis found a significant initial dioxin-by-race interaction and a significant initial dioxin-by-degreasing chemical exposure interaction (Table 10-17 [c]: p=0.043 and p=0.006, respectively). Comparable to the AST analysis, separate analyses were done for Blacks and non-Blacks to explore the interactions. Appendix Table I-1 presents stratified results. The association between initial dioxin and discretized GGT was marginally significant for Blacks (Appendix Table I-1: p=0.055). Only three Blacks had an abnormally high GGT, all in the low initial dioxin category. The initial dioxin-by-degreasing chemical interaction was significant for non-Blacks (p=0.009). The association between initial dioxin and GGT was significantly more than 1 for non-Black Ranch Hands who had never been exposed to degreasing chemicals (Adj. RR=1.65, p=0.010). The percentages of abnormal levels of GGT for these Ranch Hands were 7.3, 10.4, and 25.9 percent for the low, medium, and high initial dioxin categories. The adjusted relative risk was less than 1, but not significant, for non-Black Ranch Hands who had been exposed to degreasing chemicals (Adj. RR=0.85, p=0.336). After excluding the interactions, the adjusted relative risk was not significant for the minimal cohort (Table 10-17 [c]: Adj. RR=1.10, p=0.437).

The adjusted maximal analyses for discretized GGT detected a significant initial dioxin-by-degreasing chemical interaction (Table 10-17 [d]: p=0.005), that was also noted in the adjusted maximal analysis of discretized AST. Appendix Table I-1 presents stratified results that show a significant relative risk for Ranch Hands who had never been exposed to degreasing chemicals (Est. RR=1.76, p<0.001; % abnormal: 3.5%, 8.0%, and 22.7%, for the low, medium, and high initial dioxin categories), in contrast to a nonsignificant relative risk for Ranch Hands who had been exposed to degreasing chemicals (Est. RR=1.01, p=0.930). After deleting the interaction, the adjusted maximal analysis displayed a significant increased risk of an abnormally high GGT level (Table 10-17 [d]: Adj. RR=1.24, p=0.028).

TABLE 10-17.

Analysis of GGT
(Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	10.0	1.07 (0.85,1.35)	0.574
	Medium	257	9.7		
	High	130	10.0		
b) Maximal (n=737)	Low	184	4.9	1.20 (1.00,1.43)	0.052
	Medium	368	9.5		
	High	185	9.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=514)	1.10 (0.86,1.41)***	0.437***	INIT*RACE (p=0.043) INIT*DC (p=0.006) ALC*IC (p=0.042)
d) Maximal (n=732)	1.24 (1.03,1.50)***	0.028***	INIT*DC (p=0.005) ALC*IC (p=0.012)

[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 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 10-17. (Continued)

Analysis of GGT
(Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.728[b]
(n=517)	≤18.6	5.6 (72)	11.1 (126)	7.5 (53)	1.11 (0.75,1.65)	0.599[c]
	>18.6	12.1 (58)	9.9 (131)	11.7 (77)	1.02 (0.75,1.38)	0.908[c]
f) Maximal						0.522[b]
(n=737)	≤18.6	4.8 (105)	6.9 (189)	11.0 (82)	1.27 (0.95,1.71)	0.108[c]
	>18.6	5.1 (79)	11.2 (178)	10.6 (104)	1.13 (0.89,1.42)	0.320[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.695[b]	ALC (p<0.001)
(n=514)	≤18.6	1.03 (0.68,1.57)	0.888[c]	AGE*DC (p=0.044)
	>18.6	0.93 (0.67,1.28)	0.656[c]	
h) Maximal			0.410[b]	ALC*IC (p=0.019)
(n=732)	≤18.6	1.34 (0.99,1.81)	0.061[c]	
	>18.6	1.14 (0.89,1.45)	0.308[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 10-17. (Continued)

Analysis of GGT
(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	6.0	All Categories		0.047
Unknown	341	5.6	Unknown vs. Background	0.92 (0.53,1.59)	0.763
Low	193	9.8	Low vs. Background	1.70 (0.97,2.97)	0.062
High	186	10.8	High vs. Background	1.88 (1.08,3.25)	0.025
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	777	All Categories		0.033**	DXCAT*DC (p=0.023) ALC*DRKYR (p=0.013)
Unknown	338	Unknown vs. Background	0.95 (0.54,1.65)**	0.844**	
Low	191	Low vs. Background	1.82 (1.03,3.22)**	0.039**	
High	182	High vs. Background	2.00 (1.13,3.56)**	0.018**	
Total	1,488				

**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.

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

For both cohorts, the unadjusted and adjusted discrete analyses of GGT did not find a significant interaction between current dioxin and time since tour (Table 10-17 [e-h]: p>0.40 for each analysis). The adjusted maximal analysis revealed a marginally significant association between discretized GGT and current dioxin for Ranch Hands with a later tour (time≤18.6: Adj. RR=1.34, p=0.061).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis found that the prevalence of abnormally high levels of GGT differed significantly among categories (Table 10-17 [i]: 6.0%, 5.6%, 9.8%, and 10.8% for the background, unknown, low, and high current dioxin categories, p=0.047). The estimated relative risk was marginally significant for the low versus background contrast (Est. RR=1.70, 95% C.I.: [0.97,2.97], p=0.062) and significant for the high versus background contrast (Est. RR=1.88, 95% C.I.: [1.08,3.25], p=0.025).

The adjusted analysis detected a significant interaction between current dioxin and degreasing chemical exposure (Table 10-17 [j]: p=0.023). Stratified results found a significant difference among the percentages of abnormal levels of GGT for participants who had never been exposed to degreasing chemicals (Appendix Table I-1: 6.1%, 4.8%, 8.2%, and 24.4% for the background, unknown, low, and high current dioxin categories, p=0.002). The adjusted relative risk for the high versus background contrast was highly significant (Adj. RR=5.89, 95% C.I.: [2.43,14.29], p<0.001). By contrast, the prevalence of abnormal levels of GGT did not differ significantly among current dioxin categories for participants who had been exposed to degreasing chemicals (6.0%, 6.4%, 10.8%, and 6.4% for the background, unknown, low, and high current dioxin categories, p=0.305). The low versus background contrast was marginally significant in this stratum (Adj. RR=1.93, 95% C.I.: [0.98,3.82], p=0.058).

After excluding the interaction, the results of the adjusted analysis were similar to the unadjusted analysis, except that the low versus background contrast became significant (Table 10-17 [j]: Adj. RR=1.82, 95% C.I.: [1.03,3.22], p=0.039). The overall contrast remained significant (p=0.033), as did the high versus background contrast (Adj. RR=2.00, 95% C.I.: [1.13,3.56], p=0.018).

Alkaline Phosphatase (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analyses of alkaline phosphatase treated as a continuous variable did not show a significant association with initial dioxin for the minimal cohort (Table 10-18 [a]: p=0.380), but the association with initial dioxin was significantly positive for the maximal cohort (Table 10-18 [b]: p=0.007). The mean alkaline phosphatase increased from 87.81 U/L in the low initial dioxin category to 94.31 U/L in the high initial dioxin category. The mean for the medium initial dioxin category was 94.17 U/L.

The adjusted findings supported the unadjusted results. The association between alkaline phosphatase and initial dioxin was not significant for the adjusted minimal analysis (Table 10-18 [c]: p=0.554), but the adjusted maximal analysis displayed a significant positive relationship (Table 10-18 [d]: p=0.030).

TABLE 10-18.

Analysis of Alkaline Phosphatase (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	92.58	0.0072 (0.0081)	0.380
(n=517)	Medium	257	94.55		
(R^2=0.001)	High	130	94.44		
b) Maximal	Low	184	87.81	0.0167 (0.0062)	0.007
(n=737)	Medium	368	94.17		
(R^2=0.010)	High	185	94.31		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	90.98	0.0049 (0.0083)	0.554	WINE (p=0.079)
(n=513)	Medium	254	92.66			RACE*IC (p=0.045)
(R^2=0.020)	High	129	92.30			
d) Maximal	Low	183	87.02	0.0138 (0.0063)	0.030	LWINE (p=0.004)
(n=731)	Medium	365	93.07			RACE*IC (p=0.013)
(R^2=0.036)	High	183	92.57			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm alkaline phosphatase 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.

TABLE 10-18. (Continued)

Analysis of Alkaline Phosphatase (U/L) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.715[c]
(n=517)	≤18.6	91.49	94.6	93.68	0.0027 (0.0133)	0.838[d]
(R^2=0.002)		(72)	(126)	(53)		
	>18.6	95.90	93.30	95.53	0.0090 (0.0109)	0.408[d]
		(58)	(131)	(77)		
f) Maximal						0.704[c]
(n=737)	≤18.6	87.62	93.47	93.12	0.0177 (0.0097)	0.069[d]
(R^2=0.009)		(105)	(189)	(82)		
	>18.6	88.97	94.73	94.83	0.0128 (0.0085)	0.135[d]
		(79)	(178)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.863**[c]	CURR*TIME*LWINE
(n=513)	≤18.6	89.96**	92.34**	91.56**	0.0012 (0.0135)**	0.929**[d]	(p=0.013)
(R^2=0.034)		(72)	(126)	(52)			WINE (p=0.066)
	>18.6	95.05**	91.51**	93.12**	0.0042 (0.0111)**	0.707**[d]	RACE*IC (p=0.043)
		(58)	(128)	(77)			
h) Maximal						0.551**[c]	CURR*TIME*RACE
(n=731)	≤18.6	87.09**	92.18**	92.20**	0.0169 (0.0099)**	0.090**[d]	(p=0.045)
(R^2=0.063)		(104)	(189)	(81)			CURR*TIME*WINE
	>18.6	88.30**	94.09**	93.25**	0.0092 (0.0088)**	0.297**[d]	(p=0.012)
		(78)	(176)	(103)			AGE (p=0.145)
							LWINE (p=0.034)
							RACE*IC (p=0.008)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm alkaline phosphatase versus log_2 dioxin.

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

[d]Test of significance for slope different from 0 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

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 10-18. (Continued)

Analysis of Alkaline Phosphatase (U/L) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	90.28	All Categories		0.064
Unknown	341	91.94	Unknown vs. Background	1.66 --	0.245
Low	193	93.92	Low vs. Background	3.64 --	0.041
High	186	94.07	High vs. Background	3.79 --	0.036
Total	1,499		(R^2=0.005)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	777	90.08	All Categories		0.098	AGE (p=0.039) CWINE (p=0.010)
Unknown	339	92.03	Unknown vs. Background	1.95 --	0.170	LWINE (p=0.049)
Low	191	93.29	Low vs. Background	3.21 --	0.070	IC (p<0.001)
High	184	93.58	High vs. Background	3.50 --	0.055	
Total	1,491		(R^2=0.027)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means 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.

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

Under both the minimal and maximal assumptions, the unadjusted analyses of current dioxin and time since tour did not detect a significant interaction between current dioxin and time for the continuous analysis of alkaline phosphatase (Table 10-18 [e] and [f]: $p>0.70$ for both cohorts). For the maximal cohort, the unadjusted association between alkaline phosphatase and current dioxin was of borderline significance for Ranch Hands with a later tour (time$\leq$18.6: $p=0.069$). The mean levels of alkaline phosphatase for low, medium, and high current dioxin were 87.62, 93.47, and 93.12 U/L.

The adjusted minimal analysis detected a significant current dioxin-by-time-by-lifetime wine history interaction (Table 10-18 [g]: $p=0.013$). The lifetime wine history covariate was dichotomized to explore the interaction. Stratified results showed that the current dioxin-by-time interaction was not significant in either lifetime wine history stratum (Appendix Table I-1: $p=0.160$ for participants who had never drunk wine, and $p=0.141$ for participants who had drunk wine). After excluding the interaction with lifetime wine history, the current dioxin-by-time interaction was not significant for the adjusted minimal analysis (Table 10-18 [g]: $p=0.863$), supporting the unadjusted findings.

The adjusted maximal analysis found two significant current dioxin-by-time-by-covariate interactions (Table 10-18 [h]: current dioxin-by-time-by-race, $p=0.045$; current dioxin-by-time-by-current wine use, $p=0.012$). Separate analyses were done for Blacks and for non-Blacks to explore the interaction with current wine use. The current dioxin-by-time interaction was not significant for Blacks (Appendix Table I-1: $p=0.205$) after deleting the current dioxin-by-time-by-current wine use interaction, which was not significant ($p=0.769$). However, for non-Blacks, there was a significant current dioxin-by-time-by-current wine use interaction ($p=0.010$). Categorizing current wine use, the current dioxin-by-time interaction was not significant within either current wine use stratum ($p=0.486$ for non-Blacks who did not currently drink wine, and $p=0.288$ for non-Blacks who currently drink wine). After excluding the interactions with race and current wine use, the current dioxin-by-time interaction was not significant in the adjusted maximal analysis (Table 10-18 [h]: $p=0.551$). As in the unadjusted analysis, the association between current dioxin and alkaline phosphatase was marginally significant for Ranch Hands with a later tour (time$\leq$18.6: $p=0.090$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Both the unadjusted and adjusted categorized current dioxin analyses for alkaline phosphatase in its continuous form found a marginally significant overall difference among current dioxin categories (Table 10-18 [i] and [j]: $p=0.064$ and $p=0.098$, respectively). The unadjusted mean levels of alkaline phosphatase were 90.28, 91.94, 93.92, and 94.07 U/L for the background, unknown, low, and high current dioxin categories. The corresponding adjusted means were 90.08, 92.02, 93.29, and 93.58 U/L. Unadjusted, the means for the low and high current dioxin categories were significantly more than the background mean ($p=0.041$ and $p=0.036$, respectively). After covariate adjustment, the low versus background contrast ($p=0.070$) and the high versus background contrast ($p=0.055$) became marginally significant.

Alkaline Phosphatase (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analysis did not show a significant relative risk of abnormally high alkaline phosphatase levels under the minimal assumption (Table 10-19 [a]: p=0.245). However, under the maximal assumption, the estimated relative risk was marginally significant (Table 10-19 [b]: Est. RR=1.25, p=0.077). For the maximal cohort, the percentage of abnormal alkaline phosphatase values increased from 2.2 percent in the low current dioxin category to 4.9 percent for both the medium and high current dioxin categories.

The adjusted initial dioxin analyses for discretized alkaline phosphatase did not find a significant relative risk for either the minimal (Table 10-19 [c]: p=0.363) or maximal (Table 10-19 [d]: p=0.179) cohort. The maximal analysis was adjusted for lifetime wine history and the interaction between current wine use and industrial chemical exposure.

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

For both cohorts, the interaction between current dioxin and time since tour was not significant in either the unadjusted or the adjusted analyses of discretized alkaline phosphatase (Table 10-19 [e-h]: p>0.25 for each analysis). However, under the maximal assumption, there was a significant increased risk of abnormally high alkaline phosphatase levels for Ranch Hands with an early tour (time>18.6: Est. RR=1.35, p=0.046). The percentages of abnormally high alkaline phosphatase levels were 1.3, 5.1, and 7.7 percent for the low, medium, and high current dioxin categories.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Both the unadjusted and adjusted categorized current dioxin analyses did not find a significant difference in the prevalence of abnormally high levels of alkaline phosphatase among current dioxin categories (Table 10-19 [i] and [j]: p>0.45 for all contrasts).

D-Glucaric Acid (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses, the association between initial dioxin and d-glucaric acid in its continuous form was not significant for the minimal cohort (Table 10-20 [a]: p=0.377), but the association was marginally positive for the maximal cohort (Table 10-20 [b]: p=0.065). The mean levels of d-glucaric acid were 12.79, 14.92, and 15.86 μM for the low, medium, and high initial dioxin categories in the maximal cohort. After adjustment for lifetime alcohol history and the age-by-current alcohol use interaction, the association became nonsignificant for the maximal cohort (Table 10-20 [d]: p=0.270).

The adjusted analysis for the minimal cohort detected a significant initial dioxin-by-race interaction (Table 10-20 [c]: p=0.044). Stratified results showed a marginally significant negative association between initial dioxin and d-glucaric acid for Blacks (Appendix Table I-1: p=0.061; Adj. means: 26.89, 13.82, and 8.67 μM for the low, medium, and high initial dioxin categories) that contrasted with a nonsignificant positive association for non-Blacks (p=0.340). After excluding the interaction, the adjusted minimal analysis was not significant (Table 10-20 [c]: p=0.580).

TABLE 10-19.

Analysis of Alkaline Phosphatase (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	3.1	1.21 (0.89,1.64)	0.245
	Medium	257	5.4		
	High	130	5.4		
b) Maximal (n=737)	Low	184	2.2	1.25 (0.98,1.59)	0.077
	Medium	368	4.9		
	High	185	4.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=512)	1.16 (0.85,1.58)	0.363	LWINE (p=0.121)
d) Maximal (n=731)	1.19 (0.93,1.52)	0.179	LWINE (p=0.111) WINE*IC (p=0.044)

[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 10-19. (Continued)

Analysis of Alkaline Phosphatase
(Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.377[b]
(n=517)	≤18.6	2.8 (72)	4.8 (126)	1.9 (53)	0.91 (0.48,1.75)	0.787[c]
	>18.6	6.9 (58)	4.6 (131)	7.8 (77)	1.27 (0.88,1.83)	0.200[c]
f) Maximal						0.281[b]
(n=737)	≤18.6	2.9 (105)	4.2 (189)	2.4 (82)	1.01 (0.65,1.58)	0.952[c]
	>18.6	1.3 (79)	5.1 (178)	7.7 (104)	1.35 (1.01,1.83)	0.046[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.407[b]	LWINE (p=0.118)
(n=512)	≤18.6	0.88 (0.46,1.71)	0.715[c]	
	>18.6	1.21 (0.83,1.75)	0.318[c]	
h) Maximal			0.281[b]	--
(n=737)	≤18.6	1.01 (0.65,1.58)	0.952[c]	
	>18.6	1.35 (1.01,1.83)	0.046[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 10-19. (Continued)

Analysis of Alkaline Phosphatase (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	4.7	All Categories		0.851
Unknown	341	3.8	Unknown vs. Background	0.79 (0.42,1.52)	0.485
Low	193	4.7	Low vs. Background	0.98 (0.47,2.07)	0.960
High	186	5.4	High vs. Background	1.14 (0.56,2.34)	0.721
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	777	All Categories		0.950	AGE (p=0.056)
					RACE (p=0.039)
Unknown	339	Unknown vs. Background	0.88 (0.46,1.69)	0.694	LWINE*IC (p<0.001)
Low	191	Low vs. Background	0.91 (0.43,1.94)	0.809	
High	183	High vs. Background	1.11 (0.53,2.32)	0.777	
Total	1,490				

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 10-20.

Analysis of D-Glucaric Acid (μM) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	124	15.78	0.0585 (0.0662)	0.377
(n=503)	Medium	252	14.75		
(R^2=0.002)	High	127	15.54		
b) Maximal	Low	176	12.79	0.0907 (0.0492)	0.065
(n=714)	Medium	357	14.92		
(R^2=0.005)	High	181	15.86		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	124	17.20**	0.0379 (0.0684)**	0.580**	INIT*RACE (p=0.044)
(n=503)	Medium	252	15.92**			AGE (p=0.147)
(R^2=0.018)	High	127	16.37**			
d) Maximal	Low	170	12.76	0.0564 (0.0511)	0.270	DRKYR85 (p=0.108)
(n=684)	Medium	341	14.77			AGE*ALC85 (p=0.007)
(R^2=0.028)	High	173	15.13			

[a]Transformed from square root scale.

[b]Slope and standard error based on square root d-glucaric acid versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, 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.
DRKYR85 and ALC85 refer to lifetime alcohol history and current alcohol use, based on information from the 1985 examination.

TABLE 10-20. (Continued)

Analysis of D-Glucaric Acid (μM) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.846[c]
(n=503)	≤18.6	14.76	15.75	14.74	0.0462 (0.1095)	0.673[d]
(R^2=0.002)		(68)	(124)	(51)		
	>18.6	15.18	15.06	15.29	0.0735 (0.0875)	0.402[d]
		(56)	(128)	(76)		
f) Maximal						0.993[c]
(n=714)	≤18.6	13.14	14.61	16.32	0.0900 (0.0773)	0.245[d]
(R^2=0.004)		(100)	(182)	(80)		
	>18.6	12.84	15.03	15.48	0.0890 (0.0670)	0.185[d]
		(76)	(174)	(102)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.792[c]	AGE (p=0.084)
(n=503)	≤18.6	15.06	15.54	13.87	0.0001 (0.1124)	0.999[d]	
(R^2=0.008)		(68)	(124)	(51)			
	>18.6	15.93	15.26	15.07	0.0371 (0.0898)	0.680[d]	
		(56)	(128)	(76)			
h) Maximal						0.984[c]	DRKYR85
(n=684)	≤18.6	12.96	14.42	14.84	0.0447 (0.0801)	0.577[d]	(p=0.102)
(R^2=0.027)		(97)	(175)	(75)			AGE*ALC85
	>18.6	13.23	15.27	14.57	0.0426 (0.0694)	0.540[d]	(p=0.008)
		(74)	(165)	(98)			

[a]Transformed from square root scale.

[b]Slope and standard error based on square root d-glucaric acid 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.

TABLE 10-20. (Continued)

Analysis of D-Glucaric Acid (μM) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	746	14.14	All Categories		0.504
Unknown	328	14.09	Unknown vs. Background	-0.05 --	0.953
Low	190	14.62	Low vs. Background	0.48 --	0.672
High	182	15.85	High vs. Background	1.71 --	0.147
Total	1,446		(R^2=0.002)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	727	14.11	All Categories		0.781	DRKYR85 (p=0.100) RACE*IC85 (p=0.003)
Unknown	317	13.99	Unknown vs. Background	-0.12 --	0.894	
Low	180	14.43	Low vs. Background	0.32 --	0.778	
High	173	15.22	High vs. Background	1.11 --	0.339	
Total	1,397		(R^2=0.013)			

[a]Transformed from square root scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on square root scale.

[f]P-value is based on difference of means on square root 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.
IC85 refers to degreasing chemical exposure based on information from the 1985 examination.

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

Both the unadjusted and adjusted current dioxin and time since tour analyses of d-glucaric acid did not find a significant interaction between current dioxin and time (Table 10-20 [c]: p>0.75 for analyses under the minimal and maximal assumptions).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean levels of d-glucaric acid did not differ significantly among the current dioxin categories in either the unadjusted (Table 10-20 [i]: p=0.504) or adjusted (Table 10-20 [j]: p=0.781) categorized current dioxin analyses.

D-Glucaric Acid (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

There were only two abnormally high levels of d-glucaric acid in the minimal cohort and four in the maximal cohort. All were in either the low or medium current dioxin category. The unadjusted initial dioxin analyses were not significant for both cohorts (Table 10-21 [a] and [b]: p=0.631 and p=0.430 for the minimal and maximal cohorts). No adjusted analyses were done because of the sparseness of the data.

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

The current dioxin-by-time since tour interaction was not analyzed under the minimal assumption because there was only one abnormally high level of d-glucaric acid within each time stratum. Under the maximal assumption, the interaction was not significant in the unadjusted analysis (Table 10-21 [c]: p=0.394). No adjusted analyses were done due to sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis did not find a significant overall difference in the prevalences of abnormally high levels of d-glucaric acid (Table 10-21 [e]: 0.4%, 1.5%, 0.0%, and 0.5% for the background, unknown, low, and high categories, p=0.107). No adjusted analysis was done because there were so few abnormalities.

Total Bilirubin (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses did not find a significant association with total bilirubin for both the minimal (Table 10-22 [a]: p=0.934) and maximal (Table 10-22 [b]: p=0.828) cohorts. The adjusted minimal analysis was identical to the unadjusted analysis because no covariates were associated with total bilirubin. The adjusted maximal analysis detected a significant initial dioxin-by-race interaction (Table 10-22 [d]: p=0.031). Stratified results showed a significant negative association between total bilirubin and initial dioxin for Blacks (Appendix Table I-1: p=0.031). The adjusted mean levels of total bilirubin decreased with levels of initial dioxin (1.212, 0.803, and 0.732 mg/dl, for the low, medium, and high initial dioxin categories). The association for non-Blacks was positive, but not significant (p=0.885). After excluding the interaction, the adjusted maximal analysis was not significant (Table 10-22 [d]: p=0.840).

TABLE 10-21.

Analysis of D-Glucaric Acid (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=503)	Low	124	0.8	0.73 (0.18,2.88)	0.631
	Medium	252	0.4		
	High	127	0.0		
b) Maximal (n=714)	Low	176	0.6	0.72 (0.30,1.71)	0.430
	Medium	357	0.8		
	High	181	0.0		

[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 10-21. (Continued)

Analysis of D-Glucaric Acid
(Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=503)	≤18.6	0.0 (68)	0.8 (124)	0.0 (51)	--	--
	>18.6	1.8 (56)	0.0 (128)	0.0 (76)	--	--
d) Maximal (n=714)	≤18.6	1.0 (100)	0.0 (182)	1.3 (80)	0.93 (0.29,3.00)	0.394[b] 0.899[c]
	>18.6	1.3 (76)	0.6 (174)	0.0 (102)	0.39 (0.07,2.27)	0.292[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 10-21. (Continued)

Analysis of D-Glucaric Acid (Discrete)

e) 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	746	0.4	All Categories		0.106
Unknown	328	1.5	Unknown vs. Background	3.83 (0.91,16.14)	0.067
Low	190	0.0	Low vs. Background	--	--
High	182	0.5	High vs. Background	1.37 (0.14,13.23)	0.787
Total	1,446				

--: Relative risk, confidence interval, and p-value not given due to absence of abnormalities.

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 10-22.

Analysis of Total Bilirubin (mg/dl) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	0.814	-0.0009 (0.0111)	0.934
(n=517)	Medium	257	0.768		
(R^2<0.001)	High	130	0.784		
b) Maximal	Low	184	0.788	-0.0018 (0.0081)	0.828
(n=737)	Medium	368	0.777		
(R^2<0.001)	High	185	0.784		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	0.814	-0.0009 (0.0111)	0.934	--
(n=517)	Medium	257	0.768			
(R^2<0.001)	High	130	0.784			
d) Maximal	Low	184	0.812**	-0.0016 (0.0081)**	0.840**	INIT*RACE (p=0.031)
(n=737)	Medium	368	0.798**			
(R^2=0.008)	High	185	0.806**			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm total bilirubin versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from 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 10-22. (Continued)

Analysis of Total Bilirubin (mg/dl) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.607[c]
(n=517)	≤18.6	0.796	0.789	0.772	-0.0068 (0.0181)	0.707[d]
(R^2<0.001)		(72)	(126)	(53)		
	>18.6	0.779	0.771	0.794	0.0052 (0.0148)	0.724[d]
		(58)	(131)	(77)		
f) Maximal						0.346[c]
(n=737)	≤18.6	0.812	0.772	0.798	-0.0082 (0.0126)	0.516[d]
(R^2=0.002)		(105)	(189)	(82)		
	>18.6	0.766	0.778	0.777	0.0076 (0.0111)	0.491[d]
		(79)	(178)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.607[c]	--
(n=517)	≤18.6	0.796	0.789	0.772	-0.0068 (0.0181)	0.707[d]	
(R^2<0.001)		(72)	(126)	(53)			
	>18.6	0.779	0.771	0.794	0.0052 (0.0148)	0.724[d]	
		(58)	(131)	(77)			
h) Maximal						0.346[c]	--
(n=737)	≤18.6	0.812	0.772	0.798	-0.0082 (0.0126)	0.516[d]	
(R^2=0.002)		(105)	(189)	(82)			
	>18.6	0.766	0.778	0.777	0.0076 (0.0111)	0.491[d]	
		(79)	(178)	(104)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm total bilirubin versus log_2 dioxin.

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

[d]Test of significance for slope different from 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.

TABLE 10-22. (Continued)

Analysis of Total Bilirubin (mg/dl)
(Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	0.793	All Categories		0.466
Unknown	341	0.773	Unknown vs. Background	-0.020 --	0.191
Low	193	0.770	Low vs. Background	-0.023 --	0.229
High	186	0.786	High vs. Background	-0.007 --	0.715
Total	1,499		(R^2=0.002)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	779	0.779	All Categories		0.409	ALC (p=0.116) AGE*RACE (p=0.023)
Unknown	339	0.755	Unknown vs. Background	-0.024 --	0.121	AGE*IC (p=0.008)
Low	191	0.760	Low vs. Background	-0.019 --	0.332	AGE*DC (p=0.040)
High	185	0.776	High vs. Background	-0.003 --	0.904	
Total	1,494		(R^2=0.016)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means 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.

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

The unadjusted current dioxin and time since tour analyses for total bilirubin did not find a significant interaction between current dioxin and time for both the minimal (Table 10-22 [e]: p=0.607) and maximal (Table 10-22 [f]: p=0.346) analyses. The adjusted analyses were identical to the unadjusted analyses because no covariates were retained in the final models.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean levels of total bilirubin did not differ significantly among the four current dioxin categories for either the unadjusted or adjusted analysis (Table 10-22 [i] and [j]: p=0.466 and p=0.409).

Total Bilirubin (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of discretized total bilirubin found that the relative risk of abnormally high total bilirubin levels was significantly less than 1 for both the minimal (Table 10-23 [a]: Est. RR=0.46, p=0.007) and maximal (Table 10-23 [b]: Est. RR=0.68, p=0.033) cohorts. The percentage of abnormally high total bilirubin values decreased with initial dioxin for the minimal cohort (5.4%, 3.1%, and 0.0% for the low, medium, and high initial dioxin categories). The corresponding percentages for the maximal cohort categories were 2.7, 4.3, and 0.5 percent.

The relative risk remained significantly less than 1 for each cohort after covariate adjustment (Table 10-23 [c] and [d]: Adj. RR=0.37, p=0.001 for the minimal cohort; Adj. RR=0.63, p=0.014 for the maximal cohort).

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

Under both the minimal and maximal assumptions, the association between discretized total bilirubin and current dioxin did not differ significantly between time since tour strata for either the unadjusted or adjusted analyses (Table 10-23 [e-h]: p>0.20 for each analysis). Both the unadjusted and adjusted analyses for the minimal cohort found that the prevalence of abnormally high total bilirubin levels significantly decreased with current dioxin for Ranch Hands with an early tour (time>18.6: Est. RR=0.34, p=0.045; Adj. RR=0.18, p=0.008). For these Ranch Hands, the percentages of abnormally high total bilirubin levels for the low, medium, and high current dioxin categories were 5.2, 3.8, and 0.0 percent. For the maximal cohort, the adjusted association between discretized total bilirubin and current dioxin was of borderline significance for Ranch Hands with an early tour (Adj. RR=0.60, p=0.076).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis displayed a significant overall difference among the percentages of abnormally high levels of total bilirubin (Table 10-23 [i]: 3.9%, 3.2%, 4.1%, and 0.5% for the background, unknown, low, and high current dioxin categories, p=0.048). The prevalence rate in the high current dioxin category was significantly less than the prevalence rate in the background category (Est. RR=0.13, 95% C.I.: [0.02,1.00], p=0.050).

TABLE 10-23.
Analysis of Total Bilirubin
(Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	5.4	0.46 (0.24,0.89)	0.007
	Medium	257	3.1		
	High	130	0.0		
b) Maximal (n=737)	Low	184	2.7	0.68 (0.46,1.00)	0.033
	Medium	368	4.3		
	High	185	0.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=511)	0.37 (0.18,0.77)	0.001	AGE (p=0.070) ALC (p=0.113) IC (p=0.040) DRKYR*DC (p=0.023)
d) Maximal (n=728)	0.63 (0.42,0.94)	0.014	ALC*IC (p=0.041) DRKYR*DC (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 10-23. (Continued)

Analysis of Total Bilirubin (Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin: Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.517[b]
(n=517)	≤18.6	2.8 (72)	4.0 (126)	0.0 (53)	0.55 (0.21,1.43)	0.221[c]
	>18.6	5.2 (58)	3.8 (131)	0.0 (77)	0.34 (0.12,0.98)	0.045[c]
f) Maximal						0.820[b]
(n=737)	≤18.6	3.8 (105)	3.7 (189)	1.2 (82)	0.64 (0.35,1.16)	0.141[c]
	>18.6	1.3 (79)	5.1 (178)	0.0 (104)	0.70 (0.41,1.21)	0.204[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.227[b]	AGE (p=0.019)
(n=511)	≤18.6	0.48 (0.17,1.34)	0.159[c]	DRKYR (p=0.109)
	>18.6	0.18 (0.05,0.64)	0.008[c]	IC (p=0.019) DC (p=0.019)
h) Maximal			0.934[b]	ALC*IC (p=0.044)
(n=728)	≤18.6	0.62 (0.33,1.17)	0.139[c]	DRKYR*DC (p=0.015)
	>18.6	0.60 (0.34,1.06)	0.076[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 10-23. (Continued)

Analysis of Total Bilirubin (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	3.9	All Categories		0.048
Unknown	341	3.2	Unknown vs. Background	0.83 (0.41,1.68)	0.609
Low	193	4.1	Low vs. Background	1.08 (0.49,2.39)	0.850
High	186	0.5	High vs. Background	0.13 (0.02,1.00)	0.050
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		0.018	AGE (p=0.004)
					RACE*ALC (p=0.030)
Unknown	339	Unknown vs. Background	0.77 (0.37,1.61)	0.486	IC*DC (p=0.047)
Low	191	Low vs. Background	1.05 (0.47,2.36)	0.900	
High	185	High vs. Background	0.11 (0.01,0.81)	0.030	
Total	1,494				

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.

The adjusted results paralleled the unadjusted findings. The overall contrast was significant (Table 10-23 [j]: p=0.018) and the high versus background relative risk was significantly less than 1 (Adj. RR=0.11, 95% C.I.: [0.01,0.81], p=0.030).

Direct Bilirubin (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted initial dioxin analysis was not significant for direct bilirubin (Table 10-24 [a]: p=0.522), but the association between initial dioxin and direct bilirubin was marginally significant under the maximal assumption (Table 10-24 [b]: p=0.097). The unadjusted mean levels of direct bilirubin for the maximal cohort were 0.142, 0.158, and 0.170 mg/dl for the low, medium, and high initial dioxin categories.

After covariate adjustment, the association between initial dioxin and direct bilirubin remained nonsignificant under the minimal assumption (Table 10-24 [c]: p=0.317), but the association became significant for the maximal assumption (Table 10-24 [d]: p=0.038). The maximal analysis was adjusted for current alcohol use, degreasing chemical exposure, and the race-by-industrial chemical exposure interaction. Adjusted mean levels of direct bilirubin increased with initial dioxin (0.161, 0.178, and 0.195 mg/dl for the low, medium, and high maximal initial dioxin categories).

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

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant for either the unadjusted or adjusted analyses (Table 10-24 [e-h]: p>0.60 for each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin found that the mean direct bilirubin for the high current dioxin category was significantly more than the background mean (Table 10-24 [i]: 0.171 mg/dl versus 0.149 mg/dl, p=0.025), although the overall category contrast was not significant (p=0.120). The mean levels of direct bilirubin for the unknown and low categories were 0.148 mg/dl and 0.157 mg/dl.

The adjusted analysis detected a significant interaction between categorized current dioxin and race (Table 10-24 [j]: p=0.006). Stratified results showed that the mean levels of direct bilirubin differed significantly among current dioxin categories for Blacks (Appendix Table I-1: 0.119, 0.261, 0.162, and 0.175 mg/dl for the background, unknown, low, and high current dioxin categories, p=0.008) and that the overall difference among categories was marginally significant for non-Blacks (0.153, 0.145, 0.159, and 0.175 mg/dl for the background, unknown, low, and high current dioxin categories, p=0.061). For Blacks, the mean direct bilirubin in the unknown category was significantly more than the background mean (p<0.001). For non-Blacks, the mean for the high current dioxin category was significantly more than the background mean (p=0.033). The interaction occurred because the unknown current dioxin category had the largest mean for Blacks, but it had the smallest mean of the four current dioxin categories for non-Blacks. After deleting the interaction, the overall difference in adjusted mean levels of direct bilirubin among current dioxin categories was marginally significant (Table 10-24 [j]: 0.148, 0.146, 0.156, and 0.172 mg/dl for the

TABLE 10-24.

Analysis of Direct Bilirubin (mg/dl) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	0.169	0.0105 (0.0164)	0.522
(n=517)	Medium	257	0.157		
(R^2<0.001)	High	130	0.165		
b) Maximal	Low	184	0.142	0.0200 (0.0120)	0.097
(n=737)	Medium	368	0.158		
(R^2=0.004)	High	185	0.170		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	0.171	0.0165 (0.0165)	0.317	DC (p=0.015)
(n=517)	Medium	257	0.161			
(R^2=0.012)	High	130	0.173			
d) Maximal	Low	183	0.161	0.0255 (0.0123)	0.038	ALC (p=0.094)
(n=732)	Medium	365	0.178			DC (p=0.034)
(R^2=0.027)	High	184	0.195			RACE*IC (p=0.038)

[a]Transformed from natural logarithm (X + 0.1) scale.

[b]Slope and standard error based on natural logarithm (direct bilirubin + 0.1) 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.

TABLE 10-24. (Continued)

Analysis of Direct Bilirubin (mg/dl) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.760[c]
(n=517)	≤18.6	0.158	0.160	0.167	0.0042 (0.0268)	0.876[d]
(R^2=0.001)		(72)	(126)	(53)		
	>18.6	0.159	0.162	0.168	0.0148 (0.0218)	0.500[d]
		(58)	(131)	(77)		
f) Maximal						0.915[c]
(n=737)	≤18.6	0.145	0.150	0.183	0.0183 (0.0189)	0.331[d]
(R^2=0.004)		(105)	(189)	(82)		
	>18.6	0.146	0.162	0.163	0.0210 (0.0165)	0.205[d]
		(79)	(178)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.646[c]	DC (p=0.013)
(n=517)	≤18.6	0.167	0.173	0.183	0.0103 (0.0277)	0.710[d]	AGE*ALC (p=0.049)
(R^2=0.035)		(72)	(126)	(53)			RACE*IC (p=0.033)
	>18.6	0.163	0.174	0.187	0.0261 (0.0227)	0.251[d]	
		(58)	(131)	(77)			
h) Maximal						0.982[c]	ALC (p=0.095)
(n=732)	≤18.6	0.163	0.171	0.210	0.0258 (0.0190)	0.176[d]	DC (p=0.035)
(R^2=0.026)		(105)	(188)	(81)			RACE*IC (p=0.039)
	>18.6	0.167	0.183	0.187	0.0252 (0.0167)	0.131[d]	
		(78)	(176)	(104)			

[a]Transformed from natural logarithm (X + 0.1) scale.

[b]Slope and standard error based on natural logarithm (direct bilirubin + 0.1) versus log_2 dioxin.

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

[d]Test of significance for slope different from 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.

TABLE 10-24. (Continued)

Analysis of Direct Bilirubin (mg/dl) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	0.149	All Categories		0.120
Unknown	341	0.148	Unknown vs. Background	-0.001 --	0.846
Low	193	0.157	Low vs. Background	0.008 --	0.444
High	186	0.171	High vs. Background	0.022 --	0.025
Total	1,499		(R^2=0.004)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	779	0.148***	All Categories		0.079***	DXCAT*RACE (p=0.006)
Unknown	341	0.146***	Unknown vs. Background	-0.002 -- ***	0.708***	AGE*DC (p=0.027)
Low	193	0.156***	Low vs. Background	0.008 -- ***	0.400***	AGE*IC (p=0.014)
High	186	0.172***	High vs. Background	0.024 -- ***	0.018***	
Total	1,499		(R^2=0.020)			

[a]Transformed from natural logarithm (X + 0.1) scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm (X + 0.1) scale.

[f]P-value is based on difference of means on natural logarithm (X + 0.1) scale.

***Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean 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.

background, unknown, low, and high current dioxin categories, p=0.079). Comparable to the unadjusted analysis, the high current dioxin category mean was significantly more than the background mean (p=0.018).

Direct Bilirubin (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses for direct bilirubin in its discrete form found that the relative risk of an abnormally high level of direct bilirubin was marginally less than 1 under the minimal assumption (Table 10-25 [a]: Est. RR=0.68, p=0.064). The percentages of abnormal levels of direct bilirubin decreased with initial dioxin for the minimal cohort (7.7%, 3.5%, and 1.5% for the low, medium, and high initial dioxin categories). The relative risk was less than 1, but not significant, under the maximal assumption (Table 10-25 [b]: Est. RR=0.90, p=0.473).

Under both the minimal and maximal assumptions, the adjusted analyses detected a significant initial dioxin-by-industrial chemical exposure interaction (Table 10-25 [c] and [d]: p=0.014 and p=0.019, respectively). Appendix Table I-1 presents stratified results. Under the minimal assumption, the adjusted relative risk was significantly less than 1 for Ranch Hands who had been exposed to industrial chemicals (Adj. RR=0.42, p=0.018; % abnormal: 12.3%, 2.7%, and 1.1% for the low, medium, and high initial dioxin categories). Under the maximal assumption, the adjusted relative risk was marginally less than 1 for these Ranch Hands (Adj. RR=0.68, p=0.081; % abnormal: 2.3%, 6.1%, and 1.6% for the low, medium, and high initial dioxin categories). Under both assumptions, the adjusted relative risk was greater than 1, but not significant, for Ranch Hands who had never been exposed to industrial chemicals. After excluding the interaction, the adjusted relative risks were not significant for both cohorts (Table 10-25 [c]: Adj. RR=0.73, p=0.137 for the minimal cohort; Table 10-25 [d]: Adj. RR=0.92, p=0.579 for the maximal cohort).

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

Under both the minimal and maximal assumptions, the unadjusted current dioxin and time since tour analyses for discretized direct bilirubin did not find a significant interaction between current dioxin and time (Table 10-25 [e] and [f]: p=0.961 and p=0.893 for the minimal and maximal cohorts). The current dioxin-by-time interaction also was not significant in the adjusted maximal analysis (Table 10-25 [h]: p=0.656), but the adjusted minimal analysis detected a significant current dioxin-by-time-by-degreasing chemical exposure interaction (Table 10-25 [g]: p=0.040). Stratified results showed a marginally significant interaction between current dioxin and time for Ranch Hands who had been exposed to degreasing chemicals (Appendix Table I-1: p=0.095), although the association between current dioxin and direct bilirubin was not significant within either time stratum (time≤18.6: Adj. RR=0.86, p=0.722; time>18.6: Adj. RR=0.15, p=0.116). The current dioxin-by-time interaction was not significant for Ranch Hands who had never been exposed to degreasing chemicals (p=0.232). After excluding the current dioxin-by-time-by-degreasing chemical interaction, the adjusted minimal analysis did not find a significant interaction between current dioxin and time (Table 10-25 [g]: p=0.980).

TABLE 10-25.

Analysis of Direct Bilirubin (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	130	7.7	0.68 (0.43,1.06)	0.064
	Medium	257	3.5		
	High	130	1.5		
b) Maximal (n=737)	Low	184	2.2	0.90 (0.66,1.21)	0.473
	Medium	368	4.6		
	High	185	2.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=517)	0.73 (0.47,1.14)**	0.137**	INIT*IC (p=0.014) DC (p=0.008)
d) Maximal (n=737)	0.92 (0.68,1.25)**	0.579**	INIT*IC (p=0.019) DC (p=0.003)

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

**Log_2 (initial 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: 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.