TABLE 16-8. (Continued)

Analysis of CD14 Cells (cells/mm^3)

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						0.156[c]
(n=197)	≤18.6	30.0	35.1	28.1	-0.045 (0.077)	0.559[d]
(R^2=0.662)		(22)	(49)	(23)		
	>18.6	23.4	30.3	32.7	0.111 (0.079)	0.161[d]
		(25)	(48)	(30)		
f) Maximal						0.300[c]
(n=275)	≤18.6	29.5	34.0	24.8	-0.046 (0.056)	0.415[d]
(R^2=0.573)		(39)	(70)	(31)		
	>18.6	26.4	26.8	31.3	0.039 (0.056)	0.488[d]
		(24)	(68)	(43)		

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						0.174[c]	CSMOK (p=0.018)
(n=197)	≤18.6	29.2	35.5	29.5	-0.019 (0.076)	0.801[d]	
(R^2=0.682)		(22)	(49)	(23)			
	>18.6	23.6	29.7	34.2	0.127 (0.077)	0.102[d]	
		(25)	(48)	(30)			
h) Maximal						****	CURR*TIME*PACKYR
(n=274)	≤18.6	****	****	****	****	****	(p=0.001)
(R^2=0.629)		(39)	(70)	(31)			DRKYR (p=0.085)
	>18.6	****	*****	****	****	****	
		(24)	(67)	(43)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm CD14 cells versus $\log_2$ dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 ($p \leq 0.01$); adjusted mean, adjusted slope, confidence interval, and p-value not presented.

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 16-8. (Continued)

Analysis of CD14 Cells (cells/mm^3)

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	301	32.7	All Categories		0.674
Unknown	127	32.2	Unknown vs. Background	-0.5 --	0.844
Low	73	30.4	Low vs. Background	-2.3 --	0.476
High	74	29.1	High vs. Background	-3.6 --	0.260
Total	575		(R^2=0.348)		

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	301	29.3	All Categories		0.896	AGE*CSMOK (p=0.026)
Unknown	127	28.4	Unknown vs. Background	-0.9 --	0.705	AGE*PACKYR (p=0.006)
Low	73	27.9	Low vs. Background	-1.4 --	0.612	CSMOK*PACKYR
High	74	27.4	High vs. Background	-1.9 --	0.504	(p<0.001)
Total	575		(R^2=0.423)			RACE (p=0.080)

[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 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted and adjusted analysis of CD14 cell counts, the overall contrasts of the four current dioxin categories were not significant (Table 16-8 [i] and [j]: p=0.674 and p=0.896, respectively).

CD25 Cells

The CD25 cell counts consisted of both zero and nonzero cell counts. For the minimal and maximal cohorts approximately 30 percent of the CD25 values were zero. As a preliminary analysis to the unadjusted and adjusted analyses of the nonzero CD25 cell counts, the relative frequencies of CD25 values reported as zero were compared across the three initial dioxin categories (i.e., low, medium, and high initial dioxin). Under both assumptions, the relative frequencies were not significantly different among the initial dioxin categories (minimal, p=0.279; maximal, p=0.220). Relative frequencies of CD25 values reported as zero were also compared across the six combinations of three current dioxin categories (low, medium, and high) and the two time since tour strata (≤18.6 years, >18.6 years). For both cohorts, the relative frequencies of CD25 zero values were not significantly different across the six current dioxin and time combinations (minimal, p=0.549; maximal, p=0.528). Finally, the relative frequencies of CD25 values reported as zero were compared for Ranch Hands with unknown, low, and high current dioxin and Comparisons with background current dioxin. The frequencies were not significantly different (p=0.781).

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of the nonzero CD25 cell counts, the association with initial dioxin was not significant for both the minimal and maximal assumptions (Table 16-9 [a] and [b]: p=0.339 and p=0.933, respectively).

For the nonzero CD25 cell counts, the adjusted models for both the minimal and maximal assumptions contained interactions of initial dioxin with current cigarette smoking (Table 16-9 [c]: p=0.004, Table 16-9 [d]: p=0.009), lifetime cigarette smoking history (Table 16-9 [c]: p=0.032, Table 16-9 [d]: p=0.001), and lifetime alcohol history (Table 16-9 [c]: p<0.001, Table 16-9 [d]: p=0.023).

To explore these interactions, current cigarette smoking was dichotomized into nonsmokers (never smoked and former smokers combined) and smokers, lifetime cigarette smoking history was dichotomized as 10 pack-years or less and over 10 pack-years, and lifetime alcohol history was dichotomized as 40 drink-years or less and over 40 drink-years. Under the minimal assumption, each of the eight strata combinations of current cigarette smoking, lifetime cigarette smoking, and lifetime alcohol history displayed nonsignificant associations between CD25 and initial dioxin (Appendix Table O-1). Under the maximal assumption, there was a significant positive association between CD25 and initial dioxin for smokers with 10 pack-years or less of lifetime cigarette smoking and 40 drink-years or less on lifetime alcohol history (p=0.003). A marginally significant positive association was found for smokers with 10 pack-years or less of lifetime cigarette smoking and over 40 drink-years on lifetime alcohol history (p=0.091). For the other six strata combinations, the associations were nonsignificant.

TABLE 16-9.

Analysis of CD25 Cells (cells/mm^3)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal (n=140) (R^2=0.715)	Low	28	13.3	-0.096 (0.100)	0.339
	Medium	71	10.1		
	High	41	10.1		
b) Maximal (n=191) (R^2=0.665)	Low	43	12.1	0.006 (0.070)	0.933
	Medium	92	11.3		
	High	56	11.9		

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 (n=139) (R^2=0.819)	Low	28	****	****	****	INIT*CSMOK (p=0.004) INIT*PACKYR (p=0.032) INIT*DRKYR (p<0.001) RACE (p=0.056)
	Medium	70	****			
	High	41	****			
d) Maximal (n=190) (R^2=0.735)	Low	43	****	****	****	INIT*CSMOK (p=0.009) INIT*PACKYR (p=0.001) INIT*DRKYR (p=0.023) RACE (p=0.135)
	Medium	91	****			
	High	56	****			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm CD25 cells versus log_2 dioxin.

****Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, 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.

TABLE 16-9. (Continued)

Analysis of CD25 Cells (cells/mm^3)

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						0.051[c]
(n=140)	≤18.6	22.5	9.7	5.9	-0.351 (0.155)	0.028[d]
(R^2=0.738)		(12)	(36)	(17)		
	>18.6	9.3	10.8	14.0	0.070 (0.141)	0.624[d]
		(17)	(35)	(23)		
f) Maximal						0.314[c]
(n=191)	≤18.6	10.0	12.7	9.4	-0.091 (0.110)	0.413[d]
(R^2=0.670)		(27)	(44)	(24)		
	>18.6	16.6	10.7	13.0	0.070 (0.110)	0.524[d]
		(15)	(48)	(33)		

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						0.051[c]	--
(n=140)	≤18.6	22.5	9.7	5.9	-0.351 (0.155)	0.028[d]	
(R^2=0.738)		(12)	(36)	(17)			
	>18.6	9.3	10.8	14.0	0.070 (0.141)	0.624[d]	
		(17)	(35)	(23)			
h) Maximal						0.186[c]	CSMOK*PACKYR
(n=191)	≤18.6	10.4	12.0	9.5	-0.100 (0.109)	0.361[d]	(p=0.035)
(R^2=0.689)		(27)	(44)	(24)			
	>18.6	13.7	10.7	13.5	0.114 (0.113)	0.317[d]	
		(15)	(48)	(33)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm CD25 cells versus log$_2$ dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 16-9. (Continued)

Analysis of CD25 Cells (cells/mm^3)

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	214	11.0	All Categories		0.612
Unknown	90	13.0	Unknown vs. Background	2.0 --	0.221
Low	51	10.4	Low vs. Background	-0.6 --	0.770
High	57	11.5	High vs. Background	0.5 --	0.760
Total	412		(R^2=0.538)		

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	214	10.9	All Categories		0.603	CSMOK (p=0.088) PACKYR (p=0.103)
Unknown	90	13.0	Unknown vs. Background	2.1 --	0.203	
Low	51	10.6	Low vs. Background	-0.3 --	0.839	
High	57	11.5	High vs. Background	0.6 --	0.761	
Total	412		(R^2=0.546)			

[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

In the unadjusted analysis of the nonzero CD25 cells under the minimal assumption, the interaction of current dioxin and time since tour was marginally significant (Table 16-9 [e]: p=0.051); therefore the slopes were marginally significant between the two time strata. For time less than or equal to 18.6 years, there was a significant negative association between the CD25 cell counts and current dioxin (p=0.028). For this time stratum, the unadjusted CD25 means for low, medium, and high current dioxin were 22.5, 9.7, and 5.9 cells/mm^3. For the other time stratum, there was a nonsignificant positive association (p=0.624).

Under the maximal assumption, the unadjusted analysis of nonzero CD25 cell counts had a nonsignificant interaction between current dioxin and time (Table 16-9 [f]: p=0.314); therefore, the slopes between the two time strata did not differ significantly.

In the adjusted analysis of nonzero CD25 cells under the minimal assumption, none of the covariates or interactions were retained in the model and therefore the unadjusted and adjusted results are the same for this cohort (as seen in Table 16-9 [e] and [g], respectively).

In the adjusted analysis of the nonzero CD25 cells under the maximal assumption, the interaction between current dioxin and time was not significant (Table 16-9 [h]: p=0.186).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted and adjusted analysis of the nonzero CD25 cell counts, the overall contrast of the four current dioxin categories was not significant (Table 16-9 [i] and [j]: p=0.612 and p=0.603, respectively).

HLA-DR Cells

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of HLA-DR cells, the association with initial dioxin was not significant under both the minimal and maximal assumptions (Table 16-10 [a] and [b]: p=0.848 and p=0.960).

Under the minimal assumption, the adjusted analysis contained a significant interaction between initial dioxin and age (Table 16-10 [c]: p=0.002). To investigate the interaction, adjusted analyses were performed for Ranch Hands born in or after 1942 and those born before 1942. For the younger Ranch Hands, there was a significant negative association between HLA-DR cells and initial dioxin (Appendix Table O-1: p=0.020). In contrast, there was a significant positive association, for the older Ranch Hands, between HLA-DR cells and initial dioxin (p=0.050).

Under the maximal assumption, the adjusted analysis contained significant interactions between initial dioxin and age, and initial dioxin and current alcohol use (Table 16-10 [d]: p=0.025 and p=0.029, respectively). To explore the interactions, age was dichotomized for participants born in or after 1942 and those born before 1942, and current alcohol use was dichotomized for participants having one drink or less per day and over one drink per day.

TABLE 16-10.

Analysis of HLA-DR Cells (cells/mm^3)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal (n=197) (R^2=0.573)	Low	45	417.4	-0.007 (0.034)	0.848
	Medium	98	461.4		
	High	54	410.4		
b) Maximal (n=275) (R^2=0.540)	Low	65	437.0	0.001 (0.023)	0.960
	Medium	137	427.6		
	High	73	422.3		

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 (n=196) (R^2=0.674)	Low	45	****	****	****	INIT*AGE (p=0.002)
	Medium	97	****			ALC (p=0.075)
	High	54	****			DRKYR (p=0.052)
d) Maximal (n=274) (R^2=0.644)	Low	65	451.9**	0.002 (0.022)**	0.943**	INIT*AGE (p=0.025)
	Medium	136	421.1**			INIT*ALC (p=0.029)
	High	73	427.4**			CSMOK (p=0.002)
						DRKYR (p=0.015)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm HLA-DR cells 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.

****Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); adjusted mean, adjusted slope, standard error, 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.

TABLE 16-10. (Continued)

Analysis of HLA-DR Cells

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						0.198[c]
(n=197)	≤18.6	404.1	467.5	380.1	-0.058 (0.050)	0.244[d]
(R^2=0.582)		(22)	(49)	(23)		
	>18.6	390.1	475.8	440.3	0.033 (0.051)	0.516[d]
		(25)	(48)	(30)		
f) Maximal						0.131[c]
(n=275)	≤18.6	430.2	453.8	356.7	-0.043 (0.035)	0.216[d]
(R^2=0.548)		(39)	(70)	(31)		
	>18.6	406.1	424.2	469.2	0.033 (0.035)	0.336[d]
		(24)	(68)	(43)		

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						0.112[c]	CSMOK (p=0.075)
(n=196)	≤18.6	415.4	464.1	404.8	-0.049 (0.047)	0.300[d]	ALC (p=0.083)
(R^2=0.652)		(22)	(49)	(23)			DRKYR (P=0.105)
	>18.6	383.2	455.5	463.9	0.056 (0.047)	0.240[d]	
		(25)	(47)	(30)			
h) Maximal						0.136[c]	CSMOK (p<0.001)
(n=274)	≤18.6	443.2	454.4	377.2	-0.037 (0.033)	0.255[d]	AGE*DRKYR
(R^2=0.632)		(39)	(70)	(31)			(p=0.044)
	>18.6	430.1	414.4	457.5	0.032 (0.032)	0.329[d]	
		(24)	(67)	(43)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm HLA-DR cells versus log_2 dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 16-10. (Continued)

Analysis of HLA-DR Cells (cells/mm^3)

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	300	422.5	All Categories		0.520
Unknown	127	433.7	Unknown vs. Background	11.2 --	0.574
Low	73	459.5	Low vs. Background	37.0 --	0.138
High	74	433.2	High vs. Background	10.7 --	0.664
Total	574		(R^2=0.360)		

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

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	300	****	All Categories		****	DXCAT*AGE (p=0.003)
Unknown	127	****	Unknown vs. Background	****	****	CSMOK (p<0.001)
Low	73	****	Low vs. Background	****	****	
High	74	****	High vs. Background	****	****	
Total	574		(R^2=0.444)			

[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 ($p \leq 0.01$); adjusted mean, and p-value not presented.

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.

Under the maximal assumption, older Ranch Hands who had one drink or less per day displayed a significant positive association between HLA-DR cells and initial dioxin (Appendix Table O-1: p=0.019). For the other three strata combinations of age and current alcohol use, there were nonsignificant negative associations. After excluding both interactions from the model, there was a nonsignificant association between HLA-DR cells and initial dioxin (Table 16-10 [d]: p=0.943).

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

In the unadjusted analysis of HLA-DR cells, the interaction of current dioxin and time since tour was not significant for both the minimal and maximal assumptions (Table 16-10 [e] and [f]: p=0.198 and p=0.131).

Under both the minimal and maximal assumptions, the adjusted analysis also exhibited nonsignificant interactions between current dioxin and time (Table 16-10 [g] and [h]: p=0.112 and p=0.136, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis indicated that the HLA-DR cell means did not differ significantly among the Ranch Hand and Comparison current dioxin categories (Table 16-10 [i]: p=0.520).

The adjusted analysis of the HLA-DR cells contained a significant interaction between categorized current dioxin and age (Table 16-10 [j]: p=0.003). The interaction was explored separately for participants born in or after 1942 and those born prior to 1942 (Appendix Table O-1). For the younger participants, the overall contrast of the current dioxin categories was nonsignificant (p=0.157). For the older group of participants, the overall contrast of the adjusted HLA-DR cell means for the four current dioxin categories was significant (p=0.027) and the three contrasts of Ranch Hands versus Comparisons were at least marginally significant (unknown versus background, p=0.052; low versus background, p=0.058; high versus background, p=0.015).

CD4/CD8 Ratio

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted analysis of the association between the CD4/CD8 ratio and initial dioxin was not significant (Table 16-11 [a]: p=0.230). Under the maximal assumption, the unadjusted analysis of the association between CD4/CD8 and initial dioxin was marginally significant (Table 16-11 [b]: p=0.074). The mean CD4/CD8 ratios for low, medium, and high initial dioxin were 1.70, 1.91, and 1.90.

In the adjusted analysis under the minimal assumption, the association between CD4/CD8 and initial dioxin was not significant (Table 16-11 [c]: p=0.397). In the adjusted analysis under the maximal assumption, none of the covariates or interactions were retained in the model. Therefore, the unadjusted and adjusted results are the same for the maximal cohort (Table 16-11 [b] and [d]).

TABLE 16-11.

Analysis of CD4/CD8 Ratio

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	45	1.75	0.040 (0.033)	0.230
(n=193)	Medium	95	1.99		
(R^2=0.635)	High	53	2.01		
b) Maximal	Low	64	1.70	0.042 (0.023)	0.074
(n=270)	Medium	135	1.91		
(R^2=0.578)	High	71	1.90		

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	45	1.77	0.028 (0.033)	0.397	PACKYR (p=0.061)
(n=193)	Medium	95	2.01			
(R^2=0.649)	High	53	1.96			
d) Maximal	Low	64	1.70	0.042 (0.023)	0.074	- -
(n=270)	Medium	135	1.91			
(R^2=0.578)	High	71	1.90			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm CD4/CD8 ratio 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 16-11. (Continued)

Analysis of CD4/CD8 Ratio

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						0.318[c]
(n=193)	≤18.6	1.84	1.97	1.92	0.075 (0.050)	0.142[d]
(R^2=0.639)		(22)	(48)	(22)		
	>18.6	1.92	1.96	2.00	0.005 (0.048)	0.917[d]
		(24)	(47)	(30)		
f) Maximal						0.657[c]
(n=270)	≤18.6	1.75	1.88	2.18	0.062 (0.037)	0.093[d]
(R^2=0.581)		(39)	(70)	(29)		
	>18.6	1.62	1.88	1.87	0.038 (0.036)	0.283[d]
		(23)	(66)	(43)		

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						0.237[c]	PACKYR (p=0.048)
(n=193)	≤18.6	1.86	1.94	1.87	0.064 (0.050)	0.200[d]	
(R^2=0.655)		(22)	(48)	(22)			
	>18.6	2.03	1.98	1.92	-0.017 (0.048)	0.725[d]	
		(24)	(47)	(30)			
h) Maximal						0.657[c]	--
(n=270)	≤18.6	1.75	1.88	2.18	0.062 (0.037)	0.093[d]	
(R^2=0.581)		(39)	(70)	(29)			
	>18.6	1.62	1.88	1.87	0.038 (0.036)	0.283[d]	
		(23)	(66)	(43)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm CD4/CD8 ratio versus log$_2$ dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 16-11. (Continued)

Analysis of CD4/CD8 Ratio

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	301	1.89	All Categories		0.196
Unknown	126	1.71	Unknown vs. Background	-0.18 --	0.068
Low	72	1.90	Low vs. Background	0.01 --	0.969
High	72	1.98	High vs. Background	0.09 --	0.548
Total	571		(R^2=0.302)		

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	301	1.89	All Categories		0.214	CSMOK*PACKYR (p=0.002)
Unknown	126	1.72	Unknown vs. Background	-0.17 --	0.088	
Low	72	1.91	Low vs. Background	0.02 --	0.893	
High	72	1.99	High vs. Background	0.10 --	0.477	
Total	571		(R^2=0.320)			

[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 the minimal assumption, the unadjusted analysis of the CD4/CD8 ratio was not significant for the interaction of current dioxin and time since tour (Table 16-11 [e]: p=0.318). Thus, the association between the CD4/CD8 ratio and current dioxin did not differ significantly between the two time strata.

Under the maximal assumption, the interaction of current dioxin and time of the unadjusted model was not significant (Table 16-11 [f]: p=0.657) for the CD4/CD8 ratio. Although the slopes for the two time strata were not significantly different, there was a marginally significant positive association for the CD4/CD8 ratio with current dioxin among the Ranch Hands with time less than or equal to 18.6 years (p=0.093). For that time stratum, the average CD4/CD8 ratios for low, medium, and high current dioxin were 1.75, 1.88, and 2.18.

In the adjusted analysis of the CD4/CD8 ratio under the minimal assumption, the adjusted slopes were not significantly different between the two time strata (Table 16-11 [g]: p=0.237). For Ranch Hands in the maximal cohort, none of the covariates was retained in the adjusted model; thus, the unadjusted and adjusted analysis results were the same (as seen in Table 16-11 [f] and [h]).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the CD4/CD8 ratio, the overall contrast of the unadjusted CD4/CD8 means was nonsignificant (Table 16-11 [i]: p=0.196) for the four current dioxin categories. The individual contrast for Ranch Hands in the unknown current dioxin category versus Comparisons in the background current dioxin category was marginally significant (p=0.068), with the Ranch Hands having the lower mean (1.71 versus 1.89).

Similar to the results of the unadjusted analysis of the CD4/CD8 ratio, the adjusted analysis also exhibited a nonsignificant overall contrast (Table 16-11 [j]: p=0.214) and the unknown versus background current dioxin category contrast was marginally significant (p=0.088).

Laboratory Examination Variables: Quantitative Studies—TLC

TLC

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted analysis exhibited a nonsignificant association between TLC and initial dioxin (Table 16-12 [a] and [b]: p=0.841 and p=0.679, respectively).

For the minimal cohort, the adjusted analysis contained a significant interaction between initial dioxin and current alcohol use (Table 16-12 [c]: p=0.018). Investigation of this interaction within dichotomized current alcohol use strata (zero to one drink per day, over one drink per day) identified a significant negative association between TLC and initial dioxin

TABLE 16-12.

Analysis of TLC (cells/mm^3)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal (n=197) (R^2<0.001)	Low	45	2,070.9	-0.004 (0.020)	0.841
	Medium	98	2,047.0		
	High	54	1,994.6		
b) Maximal (n=275) (R^2<0.001)	Low	65	2,043.4	0.006 (0.015)	0.679
	Medium	137	2,007.8		
	High	73	2,026.4		

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 (n=196) (R^2=0.140)	Low	45	2,111.0**	-0.005 (0.020)**	0.812**	INIT*ALC (p=0.018) AGE (p=0.039) CSMOK (p=0.092) PACKYR (p=0.142) DRKYR (p=0.019)
	Medium	97	2,014.2**			
	High	54	1,999.6**			
d) Maximal (n=274) (R^2=0.116)	Low	65	2,072.4	0.001 (0.014)	0.957	CSMOK (p<0.001) AGE*DRKYR (p=0.001)
	Medium	136	2,001.7			
	High	73	1,996.4			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm TLC 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 16-12. (Continued)

Analysis of TLC (cells/mm^3)

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						0.264[c]
(n=197)	≤18.6	1,996.3 (22)	2,003.9 (49)	1,934.9 (23)	-0.033 (0.031)	0.283[d]
(R^2=0.013)	>18.6	2,095.7 (25)	2,075.1 (48)	2,100.3 (30)	0.013 (0.027)	0.636[d]
f) Maximal						0.367[c]
(n=275)	≤18.6	1,974.4 (39)	2,041.5 (70)	1,871.4 (31)	-0.011 (0.022)	0.604[d]
(R^2=0.006)	>18.6	2,010.6 (24)	2,018.7 (68)	2,157.1 (43)	0.016 (0.021)	0.446[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						0.085[c]	AGE (p=0.035)
(n=196)	≤18.6	2,052.2 (22)	2,000.2 (49)	1,905.1 (23)	-0.048 (0.030)	0.110[d]	CSMOK (p=0.109)
(R^2=0.131)							PACKYR (p=0.121)
	>18.6	2,067.1 (25)	2,036.7 (47)	2,136.1 (30)	0.019 (0.027)	0.485[d]	DRKYR (p=0.027)
h) Maximal						0.216[c]	CSMOK (p<0.001)
(n=274)	≤18.6	2,185.3 (39)	2,227.3 (70)	2,018.7 (31)	-0.020 (0.021)	0.350[d]	AGE*DRKYR (p=0.002)
(R^2=0.138)							RACE*ALC (p=0.040)
	>18.6	2,273.1 (24)	2,184.1 (67)	2,324.7 (43)	0.016 (0.020)	0.442[d]	

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm TLC versus $\log_2$ dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 16-12. (Continued)

Analysis of TLC (cells/mm^3)

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	301	1,972.0	All Categories		0.817
Unknown	127	1,954.2	Unknown vs. Background	-17.8 --	0.789
Low	73	2,011.6	Low vs. Background	39.6 --	0.635
High	74	2,032.4	High vs. Background	60.4 --	0.468
Total	575		(R^2=0.002)		

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

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	300	****	All Categories		****	DXCAT*AGE (p=0.004)
Unknown	127	****	Unknown vs. Background	****	****	DXCAT*DRKYR
Low	72	****	Low vs. Background	****	****	(p=0.048)
High	74	****	High vs. Background	****	****	RACE (p=0.051)
Total	573		(R^2=0.124)			CSMOK (p<0.001)

[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 ($p \leq 0.01$); adjusted mean, and p-value not presented.

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.

for Ranch Hands who had more than one drink per day (Appendix Table O-1: p=0.013). For the other stratum, there was a nonsignificant positive association (p=0.500). Without this interaction in the model, the association between TLC and initial dioxin was not significant (Table 16-12 [c]: p=0.812).

Under the maximal assumption, the adjusted analysis displayed a nonsignificant association between TLC and initial dioxin (Table 16-12 [d]: p=0.957).

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

For both the minimal and maximal assumptions, the interaction of current dioxin and time since tour was not significant in the unadjusted analysis of TLC (Table 16-12 [e] and [f]: p=0.264 and p=0.367, respectively).

Under the minimal assumption, the adjusted analysis exhibited a marginally significant interaction between current dioxin and time; thus, the associations of the two time strata (i.e., the adjusted slopes) differed marginally between the two strata (Table 16-12 [g]: p=0.085). Covariates retained in the adjusted model were age, current and lifetime cigarette smoking, and lifetime alcohol history. Within each time stratum, the association between TLC and current dioxin was not significant. For time less than or equal to 18.6 years, there was a nonsignificant negative association (p=0.110), and for time over 18.6 years, there was a nonsignificant positive association (p=0.485).

Under the maximal assumption, the analysis indicated that the adjusted slopes for the two time strata were not significantly different (Table 16-12 [h]: p=0.216).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis indicated that TLC means among the Ranch Hand and Comparison current dioxin categories were not significantly different (Table 16-12 [i]: p=0.817).

In the adjusted analysis of TLC, there were significant interactions between categorized current dioxin and age, and between categorized current dioxin and lifetime alcohol history (Table 16-12 [j]: p=0.004 and p=0.048, respectively). To examine the interactions, age was dichotomized for participants born in or after 1942 and those born before 1942, and lifetime alcohol history was trichotomized for participants with 0 drink-years, 40 drink-years or less, and over 40 drink-years. Contrasts of Ranch Hands and Comparisons were performed for each of the six strata combinations of age and lifetime alcohol history. The analysis using nondrinking participants born in or after 1942 was based on small sample sizes. For the two younger Ranch Hands who did not drink, the contrast of the high current dioxin category versus the background current dioxin category was significant (Appendix Table O-1: p=0.021) with the Comparisons having the higher adjusted TLC mean. For younger Ranch Hands with 40 drink-years or less of alcohol history, the unknown current dioxin category differed significantly from the background current dioxin category (p=0.048) with the Comparisons again having the higher adjusted TLC mean. For older Ranch Hands with 40 drink-years or less of lifetime alcohol history, marginally significant differences were found for the unknown versus background contrast (p=0.065) and the high versus background contrast

(p=0.086). For these contrasts, the adjusted TLC mean of the Ranch Hands exceeded that of the background Comparisons.

Laboratory Examination Data: Functional Stimulation Tests

Unstimulated PHA Response

The analyses of the unstimulated PHA responses were based on two-factor repeated measures models containing a dioxin measure, mitogen harvest day, and the dioxin-by-harvest day interaction. The unadjusted models were expanded to include the batch-to-batch and blood draw day-to-day covariates. The adjusted models also included these covariates, as well as any covariates that were retained from the stepwise modeling procedure. For the minimal and maximal assumptions, the initial dioxin-by-harvest day interaction was not significant for the model 1 analyses (minimal: p=0.792; maximal: p=0.441). Similarly, the current dioxin-by-time-by-harvest day interaction was not significant under both assumptions for the model 2 analyses (minimal: p=0.173; maximal: p=0.758). Lastly, the categorized current dioxin-by-harvest day interaction was nonsignificant for the model 3 analyses (p=0.529). Therefore, main effect associations between unstimulated PHA response and dioxin were evaluated for all models across harvest day.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

For both the minimal and maximal assumptions, the unadjusted analysis of the unstimulated PHA response was not significant for an association with initial dioxin (Table 16-13 [a] and [b]: p=0.604 and p=0.174, respectively).

For both the minimal and maximal assumptions, the adjusted analysis of the unstimulated PHA response also was nonsignificant for an association with initial dioxin (Table 16-13 [c] and [d]: p=0.464 and p=0.459, respectively).

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

For both assumptions, the unadjusted analysis indicated that the associations between unstimulated PHA and current dioxin did not differ significantly between the two time since tour strata (Table 16-13 [e] and [f]: p=0.884 and p=0.878, respectively).

Similarly, the adjusted analyses exhibited nonsignificant interactions between current dioxin and time for both cohorts (Table 16-13 [g] and [h]: p=0.553 and p=0.884, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of unstimulated PHA response indicated that the mean levels for the Ranch Hands and Comparisons did not differ significantly (Table 16-13 [i]: p=0.679).

The adjusted analysis of the unstimulated PHA response also indicated that the overall contrast of the adjusted means for Ranch Hands and Comparisons did not differ significantly (Table 16-13 [j]: p=0.765).

TABLE 16-13.

Analysis of Unstimulated PHA Response (cpm)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal (n=193) (R^2=0.660)	Low	44	2,083	0.021 (0.040)	0.604
	Medium	96	2,227		
	High	53	2,116		
b) Maximal (n=268) (R^2=0.613)	Low	63	1,871	0.035 (0.025)	0.174
	Medium	134	2,014		
	High	71	2,146		

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 (n=192) (R^2=0.737)	Low	44	2,142	0.027 (0.037)	0.464	CSMOK (p=0.015)
	Medium	95	2,154			PACKYR (p=0.046)
	High	53	2,186			ALC*DRKYR (p=0.003)
d) Maximal (n=267) (R^2=0.670)	Low	63	2,142	0.019 (0.025)	0.459	AGE (p=0.085)
	Medium	133	2,025			CSMOK (p=0.143)
	High	71	2,115			PACKYR (p=0.085)
						ALC*DRKYR (p=0.010)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm unstimulated PHA response 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 16-13. (Continued)

Analysis of Unstimulated PHA Response (cpm)

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						0.884[c]
(n=193)	≤18.6	1,946	2,418	2,215	0.038 (0.059)	0.514[d]
(R^2=0.663)		(21)	(48)	(23)		
	>18.6	2,105	2,128	2,027	0.026 (0.059)	0.656[d]
		(25)	(47)	(29)		
f) Maximal						0.878[c]
(n=268)	≤18.6	1,810	2,118	2,098	0.048 (0.040)	0.228[d]
(R^2=0.615)		(39)	(67)	(31)		
	>18.6	1,945	1,959	2,119	0.039 (0.039)	0.322[d]
		(22)	(67)	(42)		

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						0.553[c]	AGE (p=0.097)
(n=192)	≤18.6	2,276	2,343	2,200	-0.0004 (0.057)	0.994[d]	ALC*DRKYR (p=0.002)
(R^2=0.734)		(21)	(48)	(23)			
	>18.6	2,027	2,039	2,030	0.045 (0.056)	0.416[d]	
		(25)	(46)	(29)			
h) Maximal						0.884[c]	AGE (p=0.116)
(n=267)	≤18.6	1,848	2,130	2,046	0.032 (0.039)	0.414[d]	CSMOK (p=0.138)
(R^2=0.672)		(39)	(67)	(31)			PACKYR (p=0.098)
	>18.6	2,096	1,921	2,039	0.024 (0.039)	0.538[d]	ALC*DRKYR (p=0.012)
		(22)	(66)	(42)			

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm unstimulated PHA response versus log_2 dioxin.

[c]Test of significance for current dioxin-by-time interaction (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 16-13. (Continued)

Analysis of Unstimulated PHA Response (cpm)

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	297	2,003	All Categories		0.679
Unknown	123	1,962	Unknown vs. Background	-41 --	0.689
Low	71	2,129	Low vs. Background	126 --	0.332
High	73	2,064	High vs. Background	61 --	0.640
Total	564		(R^2=0.541)		

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	296	2,144	All Categories		0.765	AGE (p<0.001) RACE (p=0.074)
Unknown	123	2,137	Unknown vs. Background	-7 --	0.951	DRKYR (p=0.053)
Low	70	2,284	Low vs. Background	140 --	0.304	
High	73	2,168	High vs. Background	24 --	0.860	
Total	562		(R^2=0.565)			

[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.

PHA Net Response

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

To investigate the effects of initial dioxin on PHA net response, the analyses of the six PHA net responses (for 2 mitogen harvest days at each of 3 mitogen concentrations) were based on three-factor repeated measures models containing initial dioxin, mitogen harvest day, mitogen concentration, associated two-factor interactions, and a three-factor interaction. The unadjusted models were expanded to include the batch-to-batch and blood draw day-to-day covariates. The adjusted models also included these covariates, as well as any covariates that were retained from the stepwise modeling procedure. From the repeated measures analysis, nonsignificant interactions were found for the initial dioxin-by-harvest day effect (minimal: p=0.361; maximal: p=0.465) and the initial dioxin-by-harvest day-by-mitogen concentration effect (minimal: p=0.324; maximal: p=0.282). For both cohorts, the initial dioxin-by-mitogen concentration interaction was significant for the initial dioxin analyses (minimal: p=0.011; maximal: p=0.001). Because of those significant interactions, unadjusted and adjusted analyses were performed separately for each mitogen concentration.

Mitogen Concentration 1. The unadjusted analyses did not exhibit a significant association between PHA net response and initial dioxin under both assumptions (Table 16-14 [a1] and [b1]: minimal: p=0.418; maximal: p=0.950).

For mitogen concentration 1, the adjusted analysis had a significant initial dioxin-by-lifetime alcohol history interaction for the minimal cohort and a significant interaction between initial dioxin and lifetime cigarette smoking history for the maximal cohort (Table 16-14 [c1] and [d1]: p<0.001 and p=0.014, respectively). To investigate the former interaction, separate analyses were performed under the minimal assumption for Ranch Hands with lifetime alcohol history values of 0 drink-years, up to 40 drink-years, and over 40 drink-years. For the nondrinker stratum, there was a significant negative association between PHA net response and initial dioxin (Appendix Table O-1: p=0.014). For the over 40 drink-year stratum, there was a significant positive association between PHA net response and initial dioxin (p=0.015). The other drink-year stratum exhibited a nonsignificant positive association between PHA net response and initial dioxin (p=0.920). Separate analyses were also performed, under the maximal assumption, for Ranch Hands with lifetime cigarette smoking history values of 0 pack-years, up to 10 pack-years, and over 10 pack-years. None of the adjusted relationships between PHA net response and initial dioxin was significant within the three smoking strata (p>0.25 for all strata). Under the maximal assumption, a secondary analysis was performed without the interaction of initial dioxin and lifetime cigarette smoking history in the model. For that model, the association between PHA net response and initial dioxin was not significant (Table 16-14 [d1]: p=0.742).

Mitogen Concentration 2. The unadjusted analyses of the PHA net response exhibited significant positive associations with initial dioxin under the minimal and maximal assumptions (Table 16-14 [a2] and [b2]: p=0.016 and p=0.008). Under the minimal assumption, the mean PHA net responses for low, medium, and high initial dioxin were 153,870 cpm, 182,316 cpm, and 190,835 cpm. Under the maximal assumption, the corresponding mean PHA net responses were 170,046 cpm, 162,750 cpm, and 189,735 cpm.

TABLE 16-14.

Analysis of PHA Net Response (cpm) (Concentration 1)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a1) Minimal	Low	44	114,027	2,988 (3,671)	0.418
(n=192)	Medium	96	135,873		
(R^2=0.784)	High	52	128,374		
b1) Maximal	Low	61	130,601	137 (2,202)	0.950
(n=265)	Medium	134	124,212		
(R^2=0.786)	High	70	128,932		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c1) Minimal	Low	44	****	****	****	INIT*DRKYR (p<0.001)
(n=191)	Medium	95	****			AGE*DRKYR (p=0.005)
(R^2=0.857)	High	52	****			CSMOK*DRKYR (p=0.001)
						PACKYR*DRKYR (p<0.001)
d1) Maximal	Low	61	129,143**	-728 (2,205)**	0.742**	INIT*PACKYR (p=0.014)
(n=264)	Medium	133	125,792**			AGE (p=0.017)
(R^2=0.819)	High	70	126,836**			CSMOK (p=0.045)
						DRKYR*PACKYR (p=0.001)

[a]Slope and standard error based on PHA net response over concentration 1 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.

****Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); adjusted mean, adjusted slope, standard error, 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.

TABLE 16-14. (Continued)

Analysis of PHA Net Response (cpm)
(Concentration 2)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a2) Minimal	Low	44	153,870	8,529 (3,475)	0.016
(n=192)	Medium	96	182,316		
(R^2=0.847)	High	52	190,835		
b2) Maximal	Low	61	170,046	6,768 (2,528)	0.008
(n=265)	Medium	134	162,750		
(R^2=0.775)	High	70	189,735		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c2) Minimal	Low	44	157,522	6,163 (3,595)	0.090	AGE (p=0.040)
(n=192)	Medium	96	181,755			
(R^2=0.854)	High	52	187,901			
d2) Maximal	Low	61	170,972	4,479 (2,525)	0.078	AGE (p=0.001)
(n=265)	Medium	134	164,724			
(R^2=0.793)	High	70	184,295			

[a]Slope and standard error based on PHA net response for concentration 2 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 16-14. (Continued)

Analysis of PHA Net Response (cpm) (Concentration 3)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a3) Minimal (n=192) (R^2=0.823)	Low	44	124,733	4,598 (3,249)	0.161
	Medium	96	148,991		
	High	52	151,319		
b3) Maximal (n=265) (R^2=0.694)	Low	61	140,798	3,352 (2,600)	0.199
	Medium	134	132,626		
	High	70	147,992		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c3) Minimal (n=192) (R^2=0.828)	Low	44	125,197	3,760 (3,263)	0.252	PACKYR (p=0.115)
	Medium	96	149,569			
	High	52	149,262			
d3) Maximal (n=264) (R^2=0.726)	Low	61	162,992**	1,824 (2,636)**	0.490**	INIT*ALC (p=0.048)
	Medium	133	156,117**			AGE (p=0.011)
	High	70	165,787**			RACE (p=0.025)

[a]Slope and standard error based on PHA net response for concentration 3 versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, 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 16-14. (Continued)

Analysis of PHA Net Response (cpm) (Across Day and Concentration)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a4) Minimal (n=192) (R^2=0.839)	Low	44	130,877	5,372 (3,010)	0.078
	Medium	96	155,727		
	High	52	156,842		
b4) Maximal (n=265) (R^2=0.785)	Low	61	147,148	3,419 (2,096)	0.105
	Medium	134	139,863		
	High	70	155,553		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c4) Minimal (n=191) (R^2=0.873)	Low	44	133,518**	3,093 (3130)**	0.326**	INIT*PACKYR (p=0.014) AGE (p=0.046) CSMOK (p=0.060) DRKYR*PACKYR (p=0.003)
	Medium	95	155,345**			
	High	52	152,978**			

[a]Slope and standard error based on PHA net response across day and concentration 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 16-14. (Continued)

Analysis of PHA Net Response (cpm)

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

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal						0.057[b]
(n=192)	≤18.6	133,816 (21)	152,504 (48)	176,224 (22)	12,371 (4,364)	0.006[c]
(R^2=0.848)	>18.6	133,168 (25)	157,289 (47)	147,659 (29)	613 (4,297)	0.887[c]
f) Maximal						0.891[b]
(n=265)	≤18.6	151,679 (38)	141,822 (67)	168,037 (30)	5,291 (3,278)	0.109[c]
(R^2=0.791)	>18.6	129,615 (21)	139,635 (67)	149,292 (42)	4,641 (3,215)	0.151[c]

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

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal						0.069**[b]	CURR*TIME*DRKYR
(n=191)	≤18.6	139,317** (21)	148,268** (48)	175,433** (22)	10,167 (4,693)**	0.033**[c]	(p=0.017)
(R^2=0.884)							AGE*DRKYR (p=0.002)
	>18.6	134,282** (25)	160,395** (46)	143,333** (29)	-959 (4,348)**	0.826**[c]	CSMOK*DRKYR (p=0.038)
h) Maximal						0.976[b]	AGE (p=0.008)
(n=264)	≤18.6	153,521 (38)	143,054 (67)	163,151 (30)	3,705 (3,235)	0.254[c]	PACKYR*DRKYR
(R^2=0.815)							(p=0.011)
	>18.6	129,873 (21)	140,630 (66)	148,487 (42)	3,565 (3,182)	0.265[c]	

[a]Slope and standard error based on PHA net response versus log_2 dioxin.

[b]Test of significance for current dioxin-by-time interaction (current dioxin continuous, time categorized).

[c]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 16-14. (Continued)

Analysis of PHA Net Response (cpm) (Concentration 1)

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

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	297	126,096	All Categories		0.810
Unknown	121	129,147	Unknown vs. Background	3,051 (-7,006, 13,108)	0.552
Low	71	130,539	Low vs. Background	4,444 (-7,650, 16,538)	0.472
High	72	130,671	High vs. Background	4,575 (-7,840, 16,990)	0.471
Total	561		(R^2=0.668)		

j1) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	297	125,477	All Categories		0.745	AGE (p<0.001) CSMOK (p=0.063)
Unknown	121	130,104	Unknown vs. Background	4,627 (-5,222, 14,477)	0.358	
Low	71	130,318	Low vs. Background	4,842 (-6,988, 16,671)	0.423	
High	72	127,162	High vs. Background	1,686 (-10,507, 13,879)	0.787	
Total	561		(R^2=0.685)			

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 16-14. (Continued)

Analysis of PHA Net Response (cpm)
(Concentration 2)

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

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	297	166,313	All Categories		0.042
Unknown	121	160,792	Unknown vs. Background	-5,521 (-15,976, 4,933)	0.301
Low	71	171,010	Low vs. Background	4,696 (-7,876, 17,269)	0.465
High	72	181,128	High vs. Background	14,815 (1,909, 27,721)	0.025
Total	561		(R^2=0.670)		

j2) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	297	165,397	All Categories		0.216	AGE (p<0.001) SMOK (p=0.040)
Unknown	121	162,332	Unknown vs. Background	-3,065 (-12,962, 6,832)	0.544	
Low	71	170,936	Low vs. Background	5,539 (-6,348, 17,426)	0.362	
High	72	175,692	High vs. Background	10,295 (-1,957, 22,547)	0.100	
Total	561		(R^2=0.707)			

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 16-14. (Continued)

Analysis of PHA Net Response (cpm)
(Concentration 3)

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

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	297	131,602	All Categories		0.223
Unknown	121	129,248	Unknown vs. Background	-2,354 (-12,762, 8,054)	0.658
Low	71	141,174	Low vs. Background	9,572 (-2,945, 22,089)	0.135
High	72	140,193	High vs. Background	8,591 (-4,258, 21,441)	0.191
Total	561		(R^2=0.577)		

j3) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	296	****	All Categories		****	DXCAT*ALC (p=0.004)
Unknown	121	****	Unknown vs. Background	****	****	AGE (p<0.001)
Low	70	****	Low vs. Background	****	****	RACE*DRKYR
High	72	****	High vs. Background	****	****	(p=0.012)
Total	559		(R^2=0.627)			

****Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, confidence interval, and p-value not presented.

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 16-14. (Continued)

Analysis of PHA Net Response (cpm) Across Day and Concentration

i4) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	297	141,337	All Categories		0.221
Unknown	121	139,729	Unknown vs. Background	-1,608 (-10,483, 7,267)	0.723
Low	71	147,574	Low vs. Background	6,237 (-4,436, 16,910)	0.253
High	72	150,664	High vs. Background	9,327 (-1,629, 20,283)	0.096
Total	561		(R^2=0.678)		

j4) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	297	146,409	All Categories		0.457	AGE (p<0.001) RACE (p=0.104)
Unknown	121	146,610	Unknown vs. Background	201 (-8,247, 8,648)	0.963	CSMOK (p=0.124)
Low	71	153,318	Low vs. Background	6,909 (-3,235, 17,053)	0.183	
High	72	152,015	High vs. Background	5,606 (-4,850, 16,062)	0.294	
Total	561		(R^2=0.712)			

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.

For mitogen concentration 2, the adjusted analyses of the PHA net response exhibited marginally significant associations with initial dioxin for the minimal and maximal assumptions (Table 16-14 [c2] and [d2]: p=0.090 and p=0.078). For both cohorts, age was the only covariate retained from the stepwise modeling strategy.

Mitogen Concentration 3. The unadjusted analyses of the PHA net response displayed a nonsignificant association with initial dioxin for both the minimal and maximal assumptions (Table 16-14 [a3] and [b3]: p=0.161 and p=0.199).

For mitogen concentration 3, the adjusted analysis based on the minimal assumption was not significant for an association with initial dioxin (Table 16-14 [c3]: p=0.252). Under the maximal assumption, there was a significant interaction between initial dioxin and current alcohol use (Table 16-14 [d3]: p=0.048). To investigate this interaction, analyses were performed for Ranch Hands with current alcohol use values of zero to one drink per day and more than one drink per day. Within these individual drinking strata, the associations between PHA net response and initial dioxin were not significant (Appendix Table O-1). Under the maximal assumption, a secondary model was used that did not include the interaction between initial dioxin and current alcohol use. For that model, the association between PHA net response and initial dioxin was not significant (Table 16-14 [d3]: p=0.490).

Across Mitogen Harvest Day and Mitogen Concentration. As noted in the introduction to the analysis of all six PHA net response variables, there was a significant interaction between initial dioxin and mitogen concentration for both assumptions (minimal: p=0.011; maximal: p=0.001). Because the p-value for the interaction of the minimal cohort was greater than 0.01, a secondary model was used that did not assume it was necessary to evaluate the association of PHA net response and initial dioxin for each individual mitogen concentration level. Unadjusted analyses were performed under both assumptions and an adjusted analysis was performed under the minimal assumption. Because the interaction of initial dioxin and mitogen concentration was highly significant (p=0.001), no adjusted analysis across mitogen harvest day and mitogen concentration was pursued under the maximal assumption.

Under the minimal assumption, the unadjusted analysis indicated that there was a positive association, which was marginally significant, between PHA net response and initial dioxin across mitogen harvest day and mitogen concentration (Table 16-14 [a4]: p=0.078). The mean PHA net response at the low, medium, and high initial dioxin levels were 130,877 cpm, 155,727 cpm, and 156,842 cpm. Under the maximal assumption, the unadjusted analysis displayed a nonsignificant association (Table 16-14 [b4]: p=0.105).

Under the minimal assumption, the adjusted analysis exhibited a significant initial dioxin-by-lifetime cigarette smoking history interaction (Table 16-14 [c4]: p=0.014). This interaction was explored within each of the following three lifetime cigarette smoking history strata: 0 pack-years, up to 10 pack-years, and over 10 pack-years. For Ranch Hands with a value above 10 pack-years, there was a positive association of borderline significance between PHA net response and initial dioxin (Appendix Table O-1: p=0.075). For the nonsmokers, there was a nonsignificant negative association (p=0.596), and for the moderate

smokers, there was a nonsignificant positive association (p=0.426). A secondary model without the interaction displayed a nonsignificant association between PHA net response and initial dioxin (p=0.326).

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

To investigate the effects of current dioxin and time since tour on PHA net response, the analyses of the six PHA net responses were based on four-factor repeated measures models containing current dioxin, time, mitogen harvest day, mitogen concentration, associated two-factor and three-factor interactions, and a four-factor interaction. The unadjusted models were again expanded to include the batch-to-batch and blood draw day-to-day covariates. The adjusted models also included these covariates, as well as any covariates that were retained from the stepwise modeling procedure. Under both assumptions, the three-factor interactions of mitogen concentration-by-current dioxin-by-time and harvest day-by-current dioxin-by-time were not significant (minimal: p=0.759 and p=0.871, respectively; maximal: p=0.916 and p=0.587, respectively), as well as the four-factor interaction of harvest day-by-mitogen concentration-by-current dioxin-by-time (minimal: p=0.745; maximal: p=0.744).

In the unadjusted analysis of the PHA net response under the minimal assumption, there was a marginally significant interaction of current dioxin and time (Table 16-14 [e]: p=0.057) indicating that the associations with current dioxin differed between time strata. For time less than or equal to 18.6 years, there was a significant positive association between PHA net response and current dioxin (p=0.006). Within that time strata, the mean PHA net responses for low, medium, and high current dioxin were 133,816 cpm, 152,504 cpm, and 176,224 cpm. For time over 18.6 years, there was a nonsignificant positive association with current dioxin (p=0.887).

The unadjusted analysis under the maximal assumption did not exhibit a significant current dioxin-by-time interaction (Table 16-14 [f]: p=0.891).

Under the minimal assumption, the adjusted analysis contained a significant interaction between current dioxin, time, and lifetime alcohol history (Table 16-14 [g]: p=0.017). The interaction was investigated within the following lifetime alcohol history strata: 0 to 40 drink-years and over 40 drink-years (Appendix Table O-1). For the former alcohol history stratum, the association between PHA net response and current dioxin did not differ significantly between time strata (p=0.485). For the latter lifetime alcohol history stratum, the interaction of current dioxin and time was significant (p=0.006); there was a significant positive association between PHA net response and current dioxin for Ranch Hands with time since tour less than or equal to 18.6 years (p=0.002). For that time stratum, the adjusted PHA net response means for low, medium, and high current dioxin were 68,227 cpm, 139,403 cpm, and 196,600 cpm. For time over 18.6 years, the negative association was nonsignificant (p=0.530). Because the p-value for the significant interaction of current dioxin, time, and lifetime alcohol history was greater than 0.01, a secondary analysis was performed based on a model without the interaction. For that adjusted analysis, the interaction between current dioxin and time was marginally significant (Table 16-14 [g]: p=0.069). For time less than or equal to 18.6 years, there was a significant positive association with current dioxin (p=0.033) and for time over 18.6 years there was a nonsignificant negative association (p=0.826).

The adjusted analysis of PHA net response under the maximal assumption exhibited a nonsignificant interaction between current dioxin and time (Table 16-14 [h]: p=0.976).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

To investigate the effects of current dioxin in Ranch Hands and Comparisons on PHA net response, the analyses of the six PHA net responses (for 2 mitogen harvest days at each of 3 mitogen concentrations) were based on three-factor repeated measures models containing categorized current dioxin, mitogen harvest day, mitogen concentration, associated two-factor interactions, and a three-factor interaction. The unadjusted models were expanded to include the batch-to-batch and blood draw day-to-day covariates. The adjusted models also included these covariates, as well as any covariates that were retained from the stepwise modeling procedure. From the repeated measures analysis, nonsignificant interactions were found for the categorized current dioxin-by-harvest day effect (p=0.979) and the categorized current dioxin-by-harvest day-by-mitogen concentration effect (p=0.429). However, the categorized current dioxin-by-mitogen concentration interaction was significant for this analysis (p=0.010). Because of the significant interaction, unadjusted and adjusted analyses were performed for each mitogen concentration.

Mitogen Concentration 1. The unadjusted analysis of the PHA net responses determined at concentration 1 indicated that the unadjusted means of the four current dioxin categories were not significantly different (Table 16-14 [i1]: p=0.810). Similarly, the adjusted analysis also indicated that the adjusted means for the Ranch Hands and Comparisons did not differ significantly (Table 16-14 [j1]: p=0.745).

Mitogen Concentration 2. The unadjusted analysis of PHA net responses determined at concentration 2 displayed a significant overall contrast among the Ranch Hand and Comparison current dioxin categories (Table 16-14 [i2]: p=0.042). The unadjusted PHA net response means were 166,313 cpm, 160,792 cpm, 171,010 cpm, and 181,128 cpm for the background, unknown, low, and high current dioxin categories. The unadjusted mean for Ranch Hands with high current dioxin current dioxin was significantly greater than that of the Comparisons with background levels (p=0.025). After adjusting for age and current cigarette smoking, the analysis indicated that the overall contrast of the four current dioxin categories was nonsignificant (Table 16-14 [j2]: p=0.216). The contrast between the high versus background current dioxin categories was found to be marginally significant (p=0.100) with the high category having a larger PHA net response mean than the background category.

Mitogen Concentration 3. The unadjusted analysis of the PHA net responses determined at concentration 3 indicated that the means of the four current dioxin categories were not significantly different (Table 16-14 [i3]: p=0.223). The adjusted analysis of the PHA net responses exhibited a significant interaction between current alcohol use and the current dioxin categories (Table 16-14 [j3]: p=0.004). The interaction was examined for participants having zero to one drink per day, and for participants having more than one drink per day. For the lighter drinking participants, the overall contrast of the adjusted means of the PHA net responses determined at concentration 3 was nonsignificant (Appendix Table O-1: p=0.137). For the more frequent drinkers, the overall contrast was also found to be nonsignificant (p=0.164); however, the contrast between Ranch Hands in the unknown current dioxin category and Comparisons in the background current dioxin category was significant (p=0.030).

Across Mitogen Harvest Day and Mitogen Concentration. As noted in the introduction to the categorized current dioxin analysis, there was a significant interaction between categorized current dioxin and mitogen concentration (p=0.010). Because the p-value for the interaction fell within the interval 0.01 to 0.05, a secondary model was used that did not assume it was necessary to evaluate the association of PHA net response and categorized current dioxin at each individual mitogen concentration. Unadjusted analyses and adjusted analyses were performed across mitogen harvest day and mitogen concentration. In the unadjusted analysis of the means of the PHA net responses over mitogen harvest day and mitogen concentration, the overall contrast of the current dioxin categories was nonsignificant (Table 16-14 [i4]: p=0.221). The contrast of Ranch Hands in the high current dioxin category versus Comparisons in the background current dioxin category was marginally significant (p=0.096) with the Ranch Hands having the higher PHA mean. The corresponding adjusted analysis exhibited a nonsignificant overall contrast (Table 16-14 [j4]: p=0.457).

Maximum of Day and Concentration Level PHA Net Response

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of the maximum PHA net response (i.e., the maximum response of the six PHA net responses from 3 mitogen concentration levels and 2 mitogen harvest days), both cohorts exhibited a significant positive association with initial dioxin (Table 16-15 [a] and [b]: p=0.005 and p=0.009, respectively). Under the minimal assumption, the unadjusted means of maximum PHA net response were 184,480 cpm, 210,574 cpm, and 228,148 cpm for the low, medium, and high initial dioxin categories. Under the maximal assumption, the corresponding unadjusted means for maximum PHA net response were 205,096 cpm, 191,498 cpm, and 221,125 cpm.

In the adjusted analysis of maximum PHA net response, both the minimal and maximal cohorts also displayed a positive association with initial dioxin. However, the associations were only marginally significant (Table 16-15 [c] and [d]: p=0.054 and p=0.072, respectively). For both adjusted analyses, age and lifetime cigarette smoking history were covariates retained in the adjusted models.

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

In the unadjusted analysis of maximum PHA net response, the interaction of current dioxin and time since tour was not significant under both the minimal and maximal assumptions (Table 16-15 [e] and [f]: p=0.145 and p=0.662). However, for the minimal cohort, there was a significant positive association between maximum PHA net response and current dioxin for time less than or equal to 18.6 years (p=0.002). The unadjusted means for this time stratum for low, medium, and high current dioxin were 190,138 cpm, 205,695 cpm, and 245,112 cpm. For the maximal cohort, both time strata contained significant positive associations (time≤18.6 years, p=0.049; time>18.6 years, p=0.008). For time less than or equal to 18.6 years, the unadjusted means for low, medium, and high current dioxin were 210,389 cpm, 193,570 cpm, and 238,122 cpm. For time over 18.6 years, the corresponding unadjusted means were 180,289 cpm, 190,555 cpm, and 215,787 cpm.

In the adjusted analysis of the maximum PHA net response under the minimal assumption, the interaction of current dioxin and time was not significant (Table 16-15 [g]: p=0.136); however, similar to the corresponding unadjusted analysis, there was a significant

TABLE 16-15.

Analysis of Maximum PHA Net Response (cpm)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	44	184,480	10,112 (3,490)	0.005
(n=192)	Medium	96	210,574		
(R^2=0.861)	High	52	228,148		
b) Maximal	Low	61	205,096	6,606 (2,499)	0.009
(n=265)	Medium	134	191,498		
(R^2=0.804)	High	70	221,125		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal	Low	44	188,163	6,990 (3,574)	0.054	AGE (p=0.070)
(n=192)	Medium	96	210,808			PACKYR (p=0.070)
(R^2=0.873)	High	52	223,115			
d) Maximal	Low	61	204,191	4,501 (2,483)	0.072	AGE (p=0.004)
(n=265)	Medium	134	193,964			PACKYR (p=0.072)
(R^2=0.823)	High	70	215,003			

[a]Slope and standard error based on maximum PHA net response 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 16-15. (Continued)

Analysis of Maximum PHA Net Response (cpm)

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

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal						0.145[b]
(n=192)	≤18.6	190,138 (21)	205,695 (48)	245,112 (22)	16,692 (5,095)	0.002[c]
(R^2=0.867)	>18.6	186,440 (25)	212,728 (47)	223,015 (29)	6,241 (5,018)	0.217[c]
f) Maximal						0.662[b]
(n=265)	≤18.6	210,389 (38)	193,570 (67)	238,122 (30)	7,706 (3,880)	0.049[c]
(R^2=0.812)	>18.6	180,289 (21)	190,555 (67)	215,787 (42)	10,170 (3,805)	0.008[c]

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

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal						0.136[b]	AGE (p=0.123)
(n=192)	≤18.6	194,871 (21)	203,365 (48)	238,874 (22)	13,263 (5,213)	0.013[c]	PACKYR (p=0.062)
(R^2=0.877)	>18.6	193,326 (25)	213,510 (47)	216,867 (29)	2,760 (5,041)	0.585[c]	
h) Maximal						0.685[b]	AGE (p=0.008)
(n=265)	≤18.6	210,758 (38)	194,477 (67)	229,611 (30)	5,179 (3,853)	0.181[c]	PACKYR (p=0.137)
(R^2=0.827)	>18.6	182,766 (21)	193,442 (67)	213,111 (42)	7,398 (3,773)	0.052[c]	

[a]Slope and standard error based on maximum PHA net response versus log_2 dioxin.

[b]Test of significance for current dioxin-by-time interaction (current dioxin continuous, time categorized).

[c]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 16-15. (Continued)

Analysis of Maximum PHA Net Response (cpm)

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

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	297	200,475	All Categories		0.037
Unknown	121	194,152	Unknown vs. Background	-6,323 (-17,188, 4,541)	0.255
Low	71	201,590	Low vs. Background	1,115 (-11,951, 14,180)	0.867
High	72	216,159	High vs. Background	15,684 (2,272, 29,097)	0.022
Total	561		(R^2=0.699)		

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

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	297	199,500	All Categories		0.221	AGE (p<0.001)
Unknown	121	195,650	Unknown vs. Background	-3,850 (-14,177, 6,477)	0.465	CSMOK (p=0.005)
Low	71	201,223	Low vs. Background	1,723 (-10,681, 14,126)	0.786	
High	72	210,652	High vs. Background	11,152 (-1,632, 23,936)	0.088	
Total	561		(R^2=0.730)			

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.

positive association between maximum PHA net response and current dioxin for time less than or equal to 18.6 years (p=0.013). In the adjusted analysis of the maximal cohort, the current dioxin-by-time interaction was not significant (Table 16-15 [h]: p=0.685). For this cohort, Ranch Hands with more than 18.6 years since their tour exhibited a marginally significant positive association (p=0.052). For both adjusted models, age and lifetime cigarette smoking history were covariates retained in the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the maximum PHA net response indicated that the average maximum PHA net response differed significantly among current dioxin categories in Ranch Hands and Comparisons (Table 16-15 [i]: p=0.037). The averages for maximum PHA net response within the background, unknown, low, and high categories were 200,475 cpm, 194,152 cpm, 201,590 cpm, and 216,159 cpm. The contrast of Ranch Hands in the high current dioxin category versus Comparisons in the background current dioxin category was significant (p=0.022).

After adjusting for the covariates of age and current cigarette smoking, the adjusted analysis of the maximum PHA net response no longer indicated there was a significant difference among the four categories (Table 16-15 [j]: p=0.221). The covariate adjustment also affected the high versus background contrast in that it was now marginally significant (p=0.088).

Unstimulated MLC Response

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of the unstimulated MLC response, the association with initial dioxin was not significant under the minimal assumption (Table 16-16 [a]: p=0.238). Under the maximal assumption, the association of unstimulated MLC response and initial dioxin was marginally significant (Table 16-16 [b]: p=0.069). The unadjusted means for unstimulated MLC response were 3,668 cpm, 3,887 cpm, and 4,618 cpm for the low, medium, and high initial dioxin categories under the maximal assumption.

In the adjusted analysis of unstimulated MLC, both the minimal and maximal cohorts exhibited nonsignificant associations between unstimulated MLC and initial dioxin (Table 16-16 [c] and [d]: p=0.850 and p=0.388, respectively). Age, race, and the interaction of the alcohol covariates were retained in the adjusted model under the maximal assumption. Age and the cited interaction were retained under the minimal assumption.

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

In the unadjusted analysis of unstimulated MLC response, the interaction of current dioxin and time since tour was not significant under the minimal assumption (Table 16-16 [e]: p=0.881).

The current dioxin-by-time interaction also was not significant in the unadjusted analysis under the maximal assumption (Table 16-16 [f]: p=0.621); however, for Ranch Hands with time over 18.6 years, there was a marginally significant positive association between unstimulated MLC response and current dioxin (p=0.075).

TABLE 16-16.

Analysis of Unstimulated MLC Response (cpm)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	45	3,923	0.065 (0.055)	0.238
(n=193)	Medium	97	4,431		
(R^2=0.742)	High	51	5,014		
b) Maximal	Low	63	3,668	0.074 (0.040)	0.069
(n=269)	Medium	137	3,887		
(R^2=0.645)	High	69	4,618		

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	45	4,494	0.010 (0.055)	0.850	AGE (p=0.005)
(n=192)	Medium	96	4,148			ALC*DRKYR (p=0.022)
(R^2=0.788)	High	51	4,716			
d) Maximal	Low	63	4,796	0.035 (0.041)	0.388	AGE (p=0.005)
(n=268)	Medium	136	4,962			RACE (p=0.095)
(R^2=0.691)	High	69	5,305			ALC*DRKYR (p=0.022)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm unstimulated MLC response 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 16-16. (Continued)

Analysis of Unstimulated MLC Response (cpm)

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						0.881[c]
(n=193)	≤18.6	3,561	4,717	5,056	0.082 (0.079)	0.300[d]
(R^2=0.743)		(22)	(49)	(23)		
	>18.6	4,231	4,327	4,824	0.065 (0.081)	0.424[d]
		(25)	(46)	(28)		
f) Maximal						0.621[c]
(n=269)	≤18.6	3,497	4,284	4,342	0.066 (0.061)	0.283[d]
(R^2=0.648)		(37)	(70)	(31)		
	>18.6	2,981	4,038	4,690	0.109 (0.061)	0.075[d]
		(24)	(67)	(40)		

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						****	CURR*TIME*DRKYR
(n=192)	≤18.6	****	****	****	****	****	(p=0.004)
(R^2=0.797)		(22)	(49)	(23)			AGE (p=0.014)
	>18.6	****	****	****	****	****	
		(25)	(45)	(28)			
h) Maximal						0.391**[c]	CURR*TIME*PACKYR
(n=268)	≤18.6	4,637**	5,633**	5,044**	0.014 (0.061)**	0.823**[d]	(p=0.016)
(R^2=0.709)		(37)	(70)	(31)			AGE (p=0.009)
	>18.6	4,165**	5,143**	5,638**	0.087 (0.060)**	0.153**[d]	RACE (p=0.044)
		(24)	(66)	(40)			ALC*DRKYR (p=0.005)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm unstimulated MLC response versus log_2 dioxin.

[c]Test of significance for current dioxin-by-time interaction (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.

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p<0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented.

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 16-16. (Continued)

Analysis of Unstimulated MLC Response (cpm)

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	294	3,619	All Categories		0.070
Unknown	124	3,691	Unknown vs. Background	72 --	0.820
Low	72	4,065	Low vs. Background	446 --	0.269
High	71	4,773	High vs. Background	1,154 --	0.011
Total	561		(R^2=0.443)		

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	293	3,862	All Categories		0.160	AGE*DRKYR (p=0.031) RACE*PACKYR (p=0.049)
Unknown	124	4,160	Unknown vs. Background	298 --	0.376	
Low	71	4,420	Low vs. Background	558 --	0.179	
High	71	4,797	High vs. Background	935 --	0.038	
Total	559		(R^2=0.503)			

[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.

In the adjusted analysis of unstimulated MLC under the minimal assumption, there was a significant interaction of current dioxin, time since tour, and lifetime alcohol history (Table 16-16 [g]: p=0.004). To investigate the interaction, adjusted analyses were performed for Ranch Hands with lifetime alcohol values of at most 40 drink-years and over 40 drink-years. For both subgroups of Ranch Hands, the interaction of current dioxin and time was nonsignificant (Appendix Table O-1: p=0.279 and p=0.159, respectively). However, for Ranch Hands with more than 40 drink-years, there was a marginally significant positive association (p=0.059) between unstimulated MLC response and current dioxin for time less than or equal to 18.6 years.

Under the maximal assumption, the adjusted analysis of unstimulated MLC contained a significant interaction for current dioxin, time, and lifetime cigarette smoking history (Table 16-16 [h]: p=0.016). To examine the interaction, adjusted analyses were performed for Ranch Hands with lifetime smoking values of 0 pack-years, 10 pack-years or less, and over 10 pack-years. For the nonsmokers, the interaction between current dioxin and time was significant (Appendix Table O-1: p=0.041). For this subgroup of Ranch Hands, there was a nonsignificant negative association between unstimulated MLC response and current dioxin for time of 18.6 years or less (p=0.750) but a significant positive association for time over 18.6 years (p=0.008). The interactions for the other two lifetime cigarette smoking history strata were nonsignificant (p=0.781 and p=0.312, respectively). A followup model without the interaction of current dioxin, time, and lifetime cigarette smoking history displayed a nonsignificant current dioxin-by-time interaction (Table 16-16 [h]: p=0.391).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of unstimulated MLC exhibited a marginally significant overall contrast among the Ranch Hand and Comparison current dioxin categories (Table 16-16 [i]: p=0.070). The unadjusted means of unstimulated MLC for the background, unknown, low, and high categories were 3,619 cpm, 3,691 cpm, 4,065 cpm, and 4,773 cpm. The contrast for Ranch Hands in the high current dioxin category versus Comparisons in the background current dioxin category was significant (p=0.011).

The adjusted analysis of unstimulated MLC displayed a nonsignificant overall contrast for the four current dioxin categories (Table 16-16 [j]: p=0.160). The contrast of the high versus background current dioxin categories remained significant (p=0.038).

MLC Net Response

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of MLC net response, the association with initial dioxin was nonsignificant under both the minimal and maximal assumptions (Table 16-17 [a] and [b]: p=0.977 and p=0.922).

Under both the minimal and maximal assumptions, the adjusted analysis of the association between MLC net response and initial dioxin was also not significant (Table 16-17 [c] and [d]: p=0.649 and p=0.779, respectively).

TABLE 16-17.

Analysis of MLC Net Response (cpm)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal (n=193) (R^2=0.714)	Low	45	84,357	96 (3,382)	0.977
	Medium	97	98,647		
	High	51	90,587		
b) Maximal (n=269) (R^2=0.665)	Low	63	92,445	215 (2,193)	0.922
	Medium	137	91,511		
	High	69	90,007		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal (n=192) (R^2=0.743)	Low	45	83,597	1,549 (3,395)	0.649	DRKYR*PACKYR (p=0.022)
	Medium	96	97,312			
	High	51	92,884			
d) Maximal (n=268) (R^2=0.696)	Low	63	92,393	597 (2,124)	0.779	ALC*PACKYR (p=0.003)
	Medium	136	93,429			
	High	69	91,892			

[a]Slope and standard error based on MLC net response 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 16-17. (Continued)

Analysis of MLC Net Response (cpm)

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

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal						0.537[b]
(n=193)	≤18.6	77,912 (22)	97,893 (49)	87,102 (23)	1,066 (4,824)	0.826[c]
(R^2=0.717)	>18.6	98,313 (25)	95,852 (46)	93,045 (28)	-3,186 (4,976)	0.524[c]
f) Maximal						0.826[b]
(n=269)	≤18.6	92,142 (37)	91,847 (70)	89,781 (31)	-778 (3,329)	0.816[c]
(R^2=0.665)	>18.6	79,549 (24)	99,662 (67)	86,117 (40)	286 (3,337)	0.932[c]

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

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal						0.936[b]	ALC*PACKYR
(n=192)	≤18.6	82,939 (22)	98,003 (49)	85,843 (23)	-753 (4,657)	0.872[c]	(p=0.008)
(R^2=0.755)	>18.6	92,046 (25)	97,181 (45)	97,402 (28)	-1,291 (4,873)	0.792[c]	
h) Maximal						0.487[b]	ALC*PACKYR
(n=268)	≤18.6	94,073 (37)	94,606 (70)	90,730 (31)	-1,356 (3,210)	0.673[c]	(p=0.003)
(R^2=0.697)	>18.6	77,114 (24)	101,149 (66)	88,714 (40)	1,914 (3,270)	0.559[c]	

[a]Slope and standard error based on MLC net response versus log_2 dioxin.

[b]Test of significance for current dioxin-by-time interaction (current dioxin continuous, time categorized).

[c]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 16-17. (Continued)

Analysis of MLC Net Response (cpm)

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

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	294	88,293	All Categories		0.582
Unknown	124	89,021	Unknown vs. Background	728 (-8,397, 9,853)	0.876
Low	72	91,936	Low vs. Background	3,643 (-7,347, 14,632)	0.516
High	71	82,307	High vs. Background	-5,986 (-17,381, 5,409)	0.304
Total	561		(R^2=0.558)		

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

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	294	95,904	All Categories		0.528	RACE (p=0.040)
						CSMOK (p=0.115)
Unknown	124	97,140	Unknown vs. Background	1,236 (-7,848, 10,320)	0.790	PACKYR (p=0.149)
Low	71	100,908	Low vs. Background	5,004 (-5,950, 15,958)	0.371	ALC (p=0.066)
High	71	90,642	High vs. Background	-5,263 (-16,549, 6,024)	0.361	
Total	560		(R^2=0.572)			

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 assumptions, the unadjusted and adjusted analyses of MLC net response contained nonsignificant interactions between current dioxin and time since tour (Table 16-17 [e-h]: p >0.400 for all). Analyses within time strata were not significant.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted and adjusted analysis of the MLC net response, the overall contrasts of the four current dioxin categories were not significant (Table 16-17 [i] and [j]: p=0.582 and p=0.528, respectively). All other analyses between individual Ranch Hand versus Comparison dioxin categories were also nonsignificant.

NKCA 50/1 Net Response

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis of NKCA 50/1 net response, the association with initial dioxin was nonsignificant under both the minimal and maximal assumptions (Table 16-18 [a] and [b]: p=0.946 and p=0.629).

Under both the minimal and maximal assumptions, the adjusted analyses were nonsignificant for an association between NKCA 50/1 net response and initial dioxin (Table 16-18 [c] and [d]: p=0.970 and p=0.526, respectively).

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

In the unadjusted analysis of NKCA 50/1 net response, the interactions of current dioxin and time since tour were nonsignificant under both assumptions (Table 16-18 [e] and [f]: p=0.480 and p=0.277, respectively).

In the adjusted analysis of NKCA 50/1 net response, the interaction of current dioxin and time was nonsignificant (Table 16-18 [g]: p=0.253) under the minimal assumption.

Under the maximal assumption, the current dioxin-by-time interaction was marginally significant in the adjusted analysis of NKCA 50/1 net response (Table 16-18 [h]: p=0.060). For this model, current alcohol use and an interaction between current cigarette smoking and lifetime cigarette smoking history were retained in the adjusted model. For Ranch Hands with time of 18.6 years or less, there was a nonsignificant positive association with current dioxin (p=0.394). For time over 18.6 years, there was a marginally significant negative association between NKCA 50/1 net response and current dioxin (p=0.067). For the latter time stratum, the NKCA 50/1 net response adjusted means for low, medium, and high current dioxin were 437.7, 411.4, and 387.5 cpm.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted and adjusted analysis of the NKCA 50/1 net response, the overall contrasts of the four current dioxin categories were not significant (Table 16-18 [i] and [j]: p=0.266 and p=0.299, respectively).

TABLE 16-18.

Analysis of NKCA 50/1 Net Response (cpm)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	44	428.0	1.0 (15.4)	0.946
(n=191)	Medium	95	374.9		
(R^2=0.342)	High	52	428.6		
b) Maximal	Low	64	432.0	-4.8 (9.9)	0.629
(n=268)	Medium	133	396.1		
(R^2=0.380)	High	71	409.4		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal	Low	44	495.0	0.5 (14.2)	0.970	RACE (p=0.062)
(n=190)	Medium	94	465.0			PACKYR (p=0.064)
(R^2=0.457)	High	52	502.8			ALC (p<0.001)
d) Maximal	Low	64	430.1	-6.0 (9.4)	0.526	PACKYR (p=0.021)
(n=267)	Medium	132	401.5			ALC (p<0.001)
(R^2=0.445)	High	71	405.4			

[a]Slope and standard error based on NKCA 50/1 net response 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.