For these younger participants, the overall contrast of the four current dioxin categories was not significant (p=0.144). However, the percentage of Ranch Hands in the low category with abnormally high systolic blood pressure was significantly higher than the corresponding percentage of Comparisons in the background category (Adj. RR=2.30, 95% C.I.: [1.15,4.59], p=0.018). The relative frequencies of participants with abnormally high systolic blood pressure were 11.8, 9.5, 21.6, and 17.0 percent for the background, unknown, low, and high current dioxin categories.

In the analysis of the older participants, the interaction between categorized current dioxin and differential cortisol response was significant; thus, Appendix Table K-1 presents stratified results for each differential cortisol-response stratum for the older participants. There were no significant results for older participants with a differential cortisol response of 0.6 μg/dl or less (p>0.65 for each contrast). The relative frequencies of abnormally high systolic blood pressure for the background, unknown, low, and high current dioxin categories for this stratum were 25.7, 25.0, 29.0, and 21.4 percent.

The analysis of the older participants with a differential cortisol response greater than 0.6 μg/dl but less than 4.0 μg/dl detected a significant difference in the prevalence of abnormally high systolic blood pressure among the four current dioxin categories (Appendix Table K-1: p=0.016). Specifically, the percentage of Ranch Hands with high systolic blood pressure in the unknown category was significantly lower than the corresponding percentage of Comparisons in the background category (Adj. RR=0.29, 95% C.I.: [0.10,0.79], p=0.016). Similarly, the Ranch Hands in the low category had a marginally lower percentage of abnormally high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.40, 95% C.I.: [0.15,1.07], p=0.068). For this stratum, the relative frequencies of abnormally high systolic blood pressure for the background, unknown, low, and high current dioxin categories were 27.2, 8.1, 15.0, and 31.6 percent.

For the stratum of older participants with a differential cortisol response greater than 4.0 μg/dl, the analysis detected a significant difference in the prevalence of abnormally high systolic blood pressure values among the four current dioxin categories (Appendix Table K-1: p=0.007). The Ranch Hands in the low category had a significantly lower risk of high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.08, 95% C.I.: [0.01,0.66], p=0.019). The relative frequencies of participants with abnormally high systolic blood pressure were 26.6, 27.5, 3.7 and 35.7 percent for the background, unknown, low, and high current dioxin categories.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. The adjusted analysis of discretized systolic blood pressure excluding cholesterol and percent body fat from the model detected a significant interaction between categorized current dioxin and age (Appendix Table K-2: p=0.002). In the analysis of the younger participants, the Ranch Hands in the low current dioxin category had a significantly higher risk of abnormally high systolic blood pressure than the Comparisons in the background category (Appendix Table K-3: Adj. RR=2.01, 95% C.I.: [1.04,3.91], p=0.038).

For the older participants, there was a marginally significant difference among the percentages of participants with abnormally high systolic blood pressure for the four current

dioxin categories (Appendix Table K-3: p=0.095). The Ranch Hands in the low category had a significantly lower risk of high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.53, 95% C.I.: [0.30,0.96], p=0.037). The older participants had a notably higher percentage of abnormal systolic blood pressure than younger participants in the corresponding categories, with the exception of the low category (born≥1942: background, 11.8%; unknown, 9.5%; low, 21.3%; high, 17.0%; born<1942: background, 26.5%; unknown, 20.4%; low, 16.3%; high, 29.2%).

Heart Sounds

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted and adjusted analyses revealed nonsignificant associations between initial dioxin and heart sounds under the minimal and maximal assumptions (Table 12-9 [a-d]: p>0.65 for all analyses).

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

The associations between heart sounds and current dioxin did not differ between time since tour strata in the unadjusted minimal and maximal analyses (Table 12-9 [e] and [f]: p=0.688 and p=0.159).

The adjusted analysis of heart sounds detected significant interactions among current dioxin, time since tour, and lifetime cigarette smoking history and among current dioxin, time since tour, and family history of heart disease for both the minimal (Table 12-9 [g]: p=0.007 and p=0.001, respectively) and maximal cohorts (Table 12-9 [h]: p=0.014 and p=0.006, respectively). Based on the minimal assumption, the interaction among current dioxin, time, and lifetime cigarette smoking history was not significant for Ranch Hands with a family history of heart disease. However, the analysis of these Ranch Hands revealed a marginally significant positive association between current dioxin and heart sounds for Ranch Hands with early tours (Appendix Table K-1: Adj. RR=2.66, p=0.070). Within the greater than 18.6 years time stratum, the relative frequencies of Ranch Hands with abnormal heart sounds were 12.0 and 6.3 percent for medium and high current dioxin. No Ranch Hands in this stratum with low current dioxin had an abnormal heart sound.

In the stratified analysis of Ranch Hands without a family history of heart disease in the minimal cohort, the interaction among current dioxin, time since tour, and lifetime cigarette smoking history was significant. For nonsmokers, there was a significant current dioxin-by-time interaction (p=0.014) and a nonsignificant negative association between current dioxin and heart sounds for Ranch Hands with later tours (p=0.467); for moderate smokers, there was a nonsignificant positive association for Ranch Hands with later tours (p=0.319); and for heavy smokers, there was a nonsignificant positive association for Ranch Hands with early tours (p=0.520). For both nonsmokers and moderate smokers with early tours and heavy smokers with late tours, there were no Ranch Hands with abnormal heart sounds for medium and high current dioxin.

Under the maximal assumption, the interaction among current dioxin, time since tour, and lifetime cigarette smoking history was only significant for Ranch Hands without a family history of heart disease. For Ranch Hands with a history of heart disease in their family, the

TABLE 12-9.

Analysis of Heart Sounds

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	6.4	0.93 (0.62,1.40)	0.726
	Medium	224	3.6		
	High	112	3.6		
b) Maximal (n=647)	Low	173	4.6	0.98 (0.73,1.31)	0.875
	Medium	320	3.8		
	High	154	3.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	1.03 (0.68,1.57)	0.876	AGE (p=0.016) DRKYR (p=0.109)
d) Maximal (n=647)	1.07 (0.79,1.46)	0.654	AGE (p=0.004) HRTDIS (p=0.079)

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

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

TABLE 12-9. (Continued)

Analysis of Heart Sounds

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.688[b]
(n=446)	≤18.6	6.8 (59)	0.9 (113)	4.4 (46)	0.76 (0.34,1.73)	0.515[c]
	>18.6	10.2 (49)	4.4 (115)	3.1 (64)	0.93 (0.56,1.53)	0.761[c]
f) Maximal						0.159[b]
(n=647)	≤18.6	5.8 (103)	3.0 (167)	2.9 (68)	0.73 (0.43,1.24)	0.249[c]
	>18.6	1.5 (68)	5.2 (154)	4.6 (87)	1.16 (0.79,1.69)	0.456[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			****	CURR*TIME*PACKYR (p=0.007)
(n=440)	≤18.6	****	****	CURR*TIME*HRTDIS (p=0.001)
	>18.6	****	****	AGE (p=0.036)
				DRKYR (p=0.034)
h) Maximal			****	CURR*TIME*PACKYR (p=0.014)
(n=647)	≤18.6	****	****	CURR*TIME*HRTDIS (p=0.006)
	>18.6	****	****	AGE (p=0.007)

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

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

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

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, 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 12-9. (Continued)

Analysis of Heart Sounds

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	4.3	All Categories		0.547
Unknown	320	3.1	Unknown vs. Background	0.72 (0.35,1.50)	0.384
Low	177	2.3	Low vs. Background	0.52 (0.18,1.49)	0.223
High	155	3.9	High vs. Background	0.90 (0.37,2.21)	0.824
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.438	AGE (p=0.004)
Unknown	320	Unknown vs. Background	0.69 (0.33,1.44)	0.325	PACKYR (p=0.082)
Low	177	Low vs. Background	0.53 (0.18,1.52)	0.237	HRTDIS (p=0.041)
High	155	High vs. Background	1.19 (0.48,3.00)	0.707	
Total	1,355				

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

associations between current dioxin and heart sounds were significantly different between the time strata (Appendix Table K-1: p=0.002). The analyses detected a marginally significant negative association between current dioxin and abnormal heart sounds for Ranch Hands with later tours (Adj. RR=0.21, p=0.059) and a marginally significant positive association for Ranch Hands with early tours (Adj. RR=1.90, p=0.065).

For Ranch Hands without a family history of heart disease, the interaction among current dioxin, time since tour, and lifetime cigarette history was significant. In the analysis of Ranch Hands who were nonsmokers and heavy smokers, there were no significant results. However, the analysis of moderate smokers detected a marginally significant positive association between current dioxin and abnormal heart sounds for Ranch Hands with later tours (Appendix Table K-1: Adj. RR=3.11, p=0.071).

Abnormal heart sounds were rare in Ranch Hands; thus, the above interactions may have been caused or affected by the sparse number of abnormalities in the analyses.

Model 3: Ranch Hand and Comparisons by Current Dioxin Category

The prevalence of abnormal heart sounds was not significantly different among the four current dioxin categories in the unadjusted and adjusted analyses (Table 12-9 [i] and [j]: p=0.547 and p=0.438). However, relatively more Comparisons with abnormal heart sounds were found in the background category than Ranch Hands with abnormal heart sounds in any of the three other categories (4.3%, 3.1%, 2.3%, and 3.9% for the background, unknown, low, and high current dioxin categories).

Overall Electrocardiograph (ECG)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The prevalence of an abnormal overall ECG was not significantly associated with initial dioxin for either the unadjusted minimal or maximal analysis (Table 12-10 [a] and [b]: p=0.443 and p=0.712). These findings did not change after covariate adjustment (Table 12-10 [c] and [d]: p=0.671 and p=0.460 for the minimal and maximal analyses).

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

In the unadjusted analysis of the overall ECG findings, under both minimal and maximal assumptions, the interactions between current dioxin and time since tour were not significant (Table 12-10 [e] and [f]: p=0.213 and p=0.375). The associations between current dioxin and the overall ECG findings were also nonsignificant within the time strata of both minimal and maximal cohorts.

After adjusting for age and race in both the minimal and maximal analyses of the overall ECG findings, the interactions between current dioxin and time since tour remained nonsignificant (Table 12-10 [g] and [h]: p=0.105 and p=0.249). However, for Ranch Hands with 18.6 years or less since tour in the minimal cohort, there was a marginally significant positive association between current dioxin and the overall ECG findings (Table 12-10 [g]: Adj. RR=1.39, p=0.085). The percentages of Ranch Hands in this stratum with abnormal ECG findings were 13.6, 15.9, and 13.0 percent for low, medium, and high current dioxin.

TABLE 12-10.

Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	16.4	0.92 (0.74,1.15)	0.443
	Medium	224	18.3		
	High	112	13.4		
b) Maximal (n=647)	Low	173	16.2	0.97 (0.83,1.14)	0.712
	Medium	320	17.5		
	High	154	13.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	1.05 (0.83,1.33)	0.671	AGE (p<0.001) RACE (p=0.110) %BFAT (p=0.136)
d) Maximal (n=647)	1.07 (0.90,1.26)	0.460	AGE (p<0.001) RACE (p=0.093)

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

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

TABLE 12-10. (Continued)

Analysis of Overall Electrocardiograph (ECG)

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.213[b]
	≤18.6	13.6 (59)	15.9 (113)	13.0 (46)	1.06 (0.74,1.50)	0.764[c]
	>18.6	22.5 (49)	18.3 (115)	15.6 (64)	0.78 (0.58,1.06)	0.117[c]
f) Maximal (n=647)						0.375[b]
	≤18.6	15.5 (103)	14.4 (167)	13.2 (68)	1.03 (0.81,1.31)	0.821[c]
	>18.6	19.1 (68)	19.5 (154)	14.9 (87)	0.89 (0.71,1.10)	0.281[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=446)			0.105[b]	AGE (p<0.001)
	≤18.6	1.39 (0.95,2.03)	0.085[c]	RACE (p=0.117)
	>18.6	0.94 (0.69,1.28)	0.688[c]	
h) Maximal (n=647)			0.249[b]	AGE (p<0.001)
	≤18.6	1.21 (0.93,1.58)	0.152[c]	RACE (p=0.086)
	>18.6	0.99 (0.79,1.25)	0.936[c]	

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

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

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

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

TABLE 12-10. (Continued)

Analysis of Overall Electrocardiograph (ECG)

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	18.5	All Categories		0.288
Unknown	320	14.4	Unknown vs. Background	0.74 (0.51,1.07)	0.107
Low	177	18.1	Low vs. Background	0.97 (0.63,1.49)	0.899
High	155	14.2	High vs. Background	0.73 (0.45,1.19)	0.206
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.342	AGE (p<0.001)
					RACE (p=0.049)
Unknown	320	Unknown vs. Background	0.72 (0.50,1.05)	0.090	PACKYR (p=0.133)
Low	177	Low vs. Background	1.01 (0.65,1.57)	0.948	
High	155	High vs. Background	1.01 (0.61,1.67)	0.978	
Total	1,355				

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

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the overall ECG findings did not detect any significant differences among the four current dioxin categories (Table 12-10 [i]: $p>0.10$ for all contrasts).

The adjustment for age, race, and lifetime cigarette smoking history did not change the lack of significance of the simultaneous contrast of the four current dioxin categories (Table 12-10 [j]: $p=0.342$). However, the Ranch Hands in the unknown category had a marginally lower risk of abnormal ECG results than the Comparisons in the background category (Adj. RR=0.72, 95% C.I.: [0.50,1.05], $p=0.090$). The relative frequencies of abnormal ECG findings were 18.5, 14.4, 18.1, and 14.2 percent for the background, unknown, low, and high current dioxin categories.

ECG: Right Bundle Branch Block (RBBB)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between RBBB and initial dioxin was not significant for either the minimal or the maximal cohort (Table 12-11 [a] and [b]: $p=0.737$ and $p=0.985$, respectively). Adjusted analyses were not performed due to the sparse number of abnormalities.

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

Under the minimal assumption, only two Ranch Hands were diagnosed with RBBB (>18.6 years since tour, medium current dioxin). The association between current dioxin and RBBB was nonsignificant ($p=0.996$). In the maximal unadjusted analysis, there were three Ranch Hands diagnosed with RBBB. In the 18.6 years or less time stratum of the maximal cohort, only one Ranch Hand had RBBB; he was in the low current dioxin category. Thus, relative risks, confidence intervals, and p-values were not presented for this stratum. In the time greater than 18.6 years stratum, there was a nonsignificant positive association between current dioxin and RBBB (Table 12-11 [d]: $p=0.595$). Similar to the initial dioxin analyses, adjusted models were not investigated in the current dioxin and time analyses due to the sparse number of abnormalities.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Neither the unadjusted nor the adjusted analysis detected a significant difference in the prevalence of RBBB among the four current dioxin categories (Table 12-11 [e] and [f]: $p=0.467$ and $p=0.649$).

ECG: Left Bundle Branch Block (LBBB)

In both the minimal and maximal cohorts, only one Ranch Hand experienced LBBB. This Ranch Hand's serum dioxin measurement was 11.64 ppt which placed him in the low dioxin category under the minimal assumption and in the medium dioxin category under the maximal assumption in the initial dioxin and current dioxin with time since tour analyses. In the categorized current dioxin analysis, there were three Comparisons in the background category who were also diagnosed as having LBBB. However, the aforementioned Ranch Hand was not included in this analysis since his level of dioxin body burden fell between the

TABLE 12-11.

Analysis of ECG: Right Bundle Branch Block

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.0	1.21 (0.40,3.70)	0.737
	Medium	224	0.9		
	High	112	0.0		
b) Maximal (n=647)	Low	173	0.6	1.01 (0.43,2.34)	0.985
	Medium	320	0.3		
	High	154	0.7		

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=446)						--
	≤18.6	0.0 (59)	0.0 (113)	0.0 (46)	--	--
	>18.6	0.0 (49)	1.7 (115)	0.0 (64)	1.00 (0.31,3.20)	0.996[b]
d) Maximal (n=647)						--
	≤18.6	1.0 (103)	0.0 (167)	0.0 (68)	--	--
	>18.6	0.0 (68)	1.3 (154)	0.0 (87)	1.29 (0.51,3.25)	0.595[b]

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

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

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Initial Dioxin: 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.

Current Dioxin: 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 12-11. (Continued)

Analysis of ECG: Right Bundle Branch Block

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.7	All Categories		0.467
Unknown	320	0.6	Unknown vs. Background	0.88 (0.17,4.55)	0.999
Low	177	1.1	Low vs. Background	1.60 (0.31,8.29)	0.854
High	155	0.0	High vs. Background	–	0.736
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.649	AGE (p=0.002)
Unknown	320	Unknown vs. Background	0.79 (0.14,4.38)	0.791	RACE (p=0.027)
Low	177	Low vs. Background	1.97 (0.37,10.60)	0.429	%BFAT (p=0.069)
High	155	High vs. Background	–	–	
Total	1,355				

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

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

cutpoints of the unknown and low current dioxin categories. Due to the sparse number of abnormalities, relative risks, confidence intervals, and p-values are not presented (Table 12-12 [a-e]).

ECG: Nonspecific ST- and T-Wave Changes

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The analysis of the prevalence of nonspecific ST- and T-wave changes did not reveal a significant association with initial dioxin for the unadjusted minimal or maximal analyses (Table 12-13 [a] and [b]: p=0.347 and p=0.694). These nonsignificant results did not change after adjusting for significant covariates (Table 12-13 [c] and [d]: minimal, p=0.948; maximal, p=0.542).

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

In the unadjusted analysis of nonspecific ST- and T-wave changes, the interactions between current dioxin and time since tour were nonsignificant for both the minimal and maximal cohorts (Table 12-13 [e] and [f]: p=0.587 and p=0.848). The associations between current dioxin and the prevalence of nonspecific ST- and T-wave changes were also nonsignificant within the time strata under both minimal and maximal assumptions.

The adjusted minimal analysis of nonspecific ST- and T-wave changes displayed similar nonsignificant results (Table 12-13 [g]: p>0.40 for interaction and time-specific strata). Under the maximal assumption, the adjusted analysis of nonspecific ST- and T-wave changes revealed a significant interaction among current dioxin, time since tour, and age (Table 12-13 [h]: p=0.029). Appendix Table K-1 presents separate analyses for younger and older Ranch Hands in order to examine this interaction. The stratified analyses did not detect any significant results in either age stratum (p>0.15 for each interaction and time-specific stratum). The analysis of the younger Ranch Hands displayed nonsignificant negative associations between current dioxin and nonspecific ST- and T-waves within each time stratum. In contrast, the analysis of the older Ranch Hands exhibited nonsignificant positive associations within each time stratum.

The results of the maximal adjusted analyses of nonspecific ST- and T-wave changes were nonsignificant after the deletion of the current dioxin-by-time-by-age interaction (Table 12-13 [h]: p>0.60 for each analysis).

Results of Analyses Without Adjustment for Percent Body Fat. After excluding percent body fat from the maximal adjusted analysis of nonspecific ST- and T-wave changes, the interaction among current dioxin, time since tour, and age remained significant (Appendix Table K-2: p=0.015). Stratified analyses also changed very little (Appendix Table K-3). The analysis of older Ranch Hands with later tours became significant (Adj. RR=1.63, p=0.032).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In both the unadjusted and adjusted analyses, the prevalence of nonspecific ST- and T-wave changes did not differ significantly among the four current dioxin categories (Table

TABLE 12-12.

Analysis of ECG: Left Bundle Branch Block

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	n	Percent Abnormal
a) Minimal (n=446)	Low	110	0.9
	Medium	224	0.0
	High	112	0.0
b) Maximal (n=647)	Low	173	0.0
	Medium	320	0.3
	High	154	0.0

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin		
		Low	Medium	High
c) Minimal (n=446)	≤18.6	0.0 (59)	0.0 (113)	0.0 (46)
	>18.6	2.0 (49)	0.0 (115)	0.0 (64)
d) Maximal (n=647)	≤18.6	0.0 (103)	0.0 (167)	0.0 (68)
	>18.6	0.0 (68)	0.7 (154)	0.0 (87)

Note: Initial Dioxin: 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.

Current Dioxin: 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 12-12. (Continued)

Analysis of ECG: Left Bundle Branch Block

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	n	Percent Yes
Background	703	0.4
Unknown	320	0.0
Low	177	0.0
High	155	0.0
Total	1,355	

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 12-13.

Analysis of ECG: Nonspecific ST- and T-Wave Changes

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	11.8	0.89 (0.69,1.14)	0.347
	Medium	224	14.3		
	High	112	8.9		
b) Maximal (n=647)	Low	173	8.7	1.04 (0.87,1.24)	0.694
	Medium	320	12.8		
	High	154	9.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.99 (0.76,1.30)	0.948	AGE (p<0.001) RACE (p=0.010) PACKYR (p=0.013) %BFAT (p=0.003)
d) Maximal (n=647)	1.06 (0.87,1.30)	0.542	AGE (p<0.001) RACE (p=0.024) PACKYR (p=0.005) %BFAT (p=0.002)

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

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

TABLE 12-13. (Continued)

Analysis of ECG: Nonspecific ST- and T-Wave Changes

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.587[b]
(n=446)	≤18.6	10.2 (59)	9.7 (113)	6.5 (46)	0.92 (0.58,1.45)	0.721[c]
	>18.6	18.4 (49)	14.8 (115)	14.1 (64)	0.79 (0.57,1.09)	0.153[c]
f) Maximal						0.848[b]
(n=647)	≤18.6	8.7 (103)	8.4 (167)	8.8 (68)	1.02 (0.75,1.39)	0.893[c]
	>18.6	10.3 (68)	14.9 (154)	13.8 (87)	0.98 (0.78,1.25)	0.889[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.428[b]	AGE (p=0.001)
(n=446)	≤18.6	1.12 (0.70,1.81)	0.636[c]	RACE (p=0.012)
	>18.6	0.89 (0.63,1.25)	0.499[c]	PACKYR (p=0.015)
				%BFAT (p=0.003)
h) Maximal			0.823**[b]	CURR*TIME*AGE (p=0.029)
(n=647)	≤18.6	1.08 (0.77,1.52)**	0.645**[c]	RACE (p=0.042)
	>18.6	1.03 (0.80,1.33)**	0.799**[c]	PACKYR (p=0.007)
				%BFAT (p=0.004)

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

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

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

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

Note: Minimal--Low: >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 12-13. (Continued)

Analysis of ECG: Nonspecific ST- and T-Wave Changes

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	10.8	All Categories		0.308
Unknown	320	7.8	Unknown vs. Background	0.70 (0.44,1.12)	0.138
Low	177	12.4	Low vs. Background	1.17 (0.71,1.94)	0.541
High	155	11.6	High vs. Background	1.08 (0.63,1.87)	0.772
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.297	AGE (p<0.001)
					RACE (p=0.047)
Unknown	320	Unknown vs. Background	0.75 (0.46,1.22)	0.246	PACKYR (p=0.019)
Low	177	Low vs. Background	1.20 (0.71,2.01)	0.492	%BFAT (p=0.010)
High	155	High vs. Background	1.35 (0.76,2.39)	0.299	
Total	1,355				

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.

12-13 [i] and [j]: p>0.10 for each contrast). The percentages of nonspecific ST- and T-wave changes were higher for Ranch Hands in the low and high current dioxin categories than for Comparisons in the background category (background, 10.8%; unknown, 7.8%; low, 12.4%; high, 11.6%).

ECG: Bradycardia

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the prevalence of bradycardia was not related significantly to initial dioxin (Table 12-14 [a]: p=0.298) in the unadjusted analysis. The maximal unadjusted analysis detected a marginally significant negative association between initial dioxin and bradycardia (Table 12-14 [b]: Adj. RR=0.75, p=0.092). The relative frequencies of Ranch Hands diagnosed with bradycardia were 5.8, 3.4, and 2.0 percent for the low, medium, and high initial dioxin categories in the maximal cohort.

The minimal analysis of bradycardia remained nonsignificant after adjustment for percent body fat (Table 12-14 [c]: p=0.393). Similarly, after adjustment for covariate information, the maximal analysis again displayed a marginally significant negative association between initial dioxin and bradycardia (Table 12-14 [d]: Adj. RR=0.75, p=0.096).

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

Under the minimal assumption, the unadjusted analysis of bradycardia displayed a nonsignificant interaction between current dioxin and time since tour (Table 12-14 [e]: p=0.363). In contrast, the maximal unadjusted analysis revealed a marginally significant current dioxin-by-time interaction (Table 12-14 [f]: p=0.067). The analysis of Ranch Hands with 18.6 years or less since tour displayed a nonsignificant positive association between current dioxin and bradycardia (Adj. RR=1.02, p=0.905), while for those with more than 18.6 years since tour, there was a marginally significant negative association (Adj. RR=0.46, p=0.076). For the maximal cohort, the relative frequencies of Ranch Hands with early tours who were diagnosed with bradycardia were 5.9 percent and 2.0 percent for low and medium current dioxin; there were no Ranch Hands with bradycardia for high current dioxin in this stratum.

After adjusting the minimal analysis of bradycardia for percent body fat, the results remained nonsignificant (Table 12-14 [g]: p>0.35 for each analysis). Similarly, the adjustment for race and lifetime alcohol history did not change the marginal significance of the current dioxin-by-time since tour interaction under the maximal assumption (Table 12-14 [h]: p=0.051). The positive association between current dioxin and bradycardia remained nonsignificant for Ranch Hands with later tours (Adj. RR=1.05, p=0.829); the negative association for Ranch Hands with early tours also remained marginally significant (Adj. RR=0.44, p=0.063).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis did not detect any significant differences in the prevalence of bradycardia among the four current dioxin categories (Table 12-14 [i]: p=0.184).

TABLE 12-14.

Analysis of ECG: Bradycardia

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	3.6	0.77 (0.46,1.29)	0.298
	Medium	224	3.6		
	High	112	1.8		
b) Maximal (n=647)	Low	173	5.8	0.75 (0.53,1.07)	0.092
	Medium	320	3.4		
	High	154	2.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.80 (0.47,1.36)	0.393	%BFAT (p=0.109)
d) Maximal (n=638)	0.75 (0.53,1.07)	0.096	RACE (p=0.107) DRKYR (p=0.096)

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

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

TABLE 12-14. (Continued)

Analysis of ECG: Bradycardia

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.363[b]
(n=446)	≤18.6	6.8 (59)	4.4 (113)	4.4 (46)	1.03 (0.58,1.83)	0.930[c]
	>18.6	0.0 (49)	2.6 (115)	0.0 (64)	0.56 (0.15,2.05)	0.379[c]
f) Maximal						0.067[b]
(n=647)	≤18.6	5.8 (103)	4.2 (167)	5.9 (68)	1.02 (0.69,1.52)	0.905[c]
	>18.6	5.9 (68)	2.0 (154)	0.0 (87)	0.46 (0.20,1.08)	0.076[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.361[b]	%BFAT (p=0.102)
(n=446)	≤18.6	1.08 (0.60,1.95)	0.802[c]	
	>18.6	0.58 (0.15,2.17)	0.417[c]	
h) Maximal			0.051[b]	RACE (p=0.076)
(n=638)	≤18.6	1.05 (0.70,1.56)	0.829[c]	DRKYR (p=0.118)
	>18.6	0.44 (0.19,1.05)	0.063[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-14. (Continued)

Analysis of ECG: Bradycardia

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	5.8	All Categories		0.184
Unknown	320	5.9	Unknown vs. Background	1.02 (0.58,1.79)	0.947
Low	177	3.4	Low vs. Background	0.57 (0.24,1.36)	0.202
High	155	2.6	High vs. Background	0.43 (0.15,1.21)	0.110
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.256**	DXCAT*RACE (p=0.029)
Unknown	303	Unknown vs. Background	1.01 (0.56,1.81)**	0.986**	PACKYR (p=0.006)
Low	174	Low vs. Background	0.57 (0.24,1.39)**	0.217**	%BFAT (p=0.064)
High	150	High vs. Background	0.45 (0.16,1.30)**	0.141**	DIFCORT (p=0.018)
Total	1,294				HRTDIS (p=0.045)

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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

The adjusted analysis of bradycardia revealed a significant interaction between categorized current dioxin and race (Table 12-14 [j]: p=0.029). Stratified analyses were performed to investigate this interaction (Appendix Table K-1). Within the Black stratum, there were only three Ranch Hands with bradycardia (two in the unknown category and one in the low category) and no Comparisons. Due to this sparse number of abnormalities, adjusted relative risks and confidence intervals were not presented. However, in an unadjusted analysis of the Black stratum, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category was marginally significant (p=0.080). The analysis of the non-Black stratum did not detect any significant differences in the prevalence of bradycardia among the four current dioxin categories (p>0.10 for each contrast). However, the percentages of Ranch Hands with bradycardia in the unknown (5.5%), low (3.0%), and high (2.8%) categories were all lower than the corresponding percentage of Comparisons in the background category (6.2%).

After deletion of the categorized current dioxin-by-race interaction from the adjusted model, the analysis of bradycardia did not find any significant differences among the four current dioxin categories (Table 12-14 [j]: p>0.10 for each contrast).

Results of Analyses Without Adjustment for Percent Body Fat. The exclusion of percent body fat from the adjusted analysis of bradycardia did not change the significance of the categorized current dioxin-by-race interaction (Appendix Table K-2: p=0.025). The stratified analyses of this interaction also changed very little. However, within the non-Black stratum, the contrast of Ranch Hands in the high current dioxin category versus Comparisons in the background category became marginally significant with the Ranch Hands having a lower risk of bradycardia relative to the Comparisons (Appendix Table K-3: Adj. RR=0.40, 95% C.I.: [0.14,1.14], p=0.087).

Similarly, after deletion of percent body fat and the categorized current dioxin-by-race interaction from the adjusted model, the contrast of the prevalence of bradycardia in Ranch Hands in the high category versus Comparisons in the background category became marginally significant (Appendix Table K-2: Adj. RR=0.51, 95% C.I.: [0.14,1.17], p=0.095). The other contrasts in the analysis remained nonsignificant.

ECG: Arrhythmia

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis of the prevalence of arrhythmia did not detect a significant association with initial dioxin under either assumption (Table 12-15 [a] and [b]: minimal, p=0.270; maximal, p=0.601).

The minimal adjusted analysis of arrhythmia revealed a significant interaction between initial dioxin and personality type (Table 12-15 [c]: p=0.036). Stratified analyses detected a significant positive association between initial dioxin and arrhythmia for type A Ranch Hands (Appendix Table K-1: Adj. RR=2.54, p=0.005) and a nonsignificant positive association for type B Ranch Hands (Adj. RR=1.06, p=0.837). The relative frequencies of type A Ranch Hands diagnosed with arrhythmia were 1.9, 1.1, and 9.1 percent for the low, medium, and high initial dioxin categories.

TABLE 12-15.

Analysis of ECG: Arrhythmia

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	1.8	1.25 (0.85,1.84)	0.270
	Medium	224	4.5		
	High	112	4.5		
b) Maximal (n=647)	Low	173	4.6	1.08 (0.81,1.43)	0.601
	Medium	320	3.1		
	High	154	5.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=433)	1.43 (0.96,2.13)**	0.092**	INIT*PERS (p=0.036) AGE (p<0.001) PACKYR (p=0.093)
d) Maximal (n=617)	1.23 (0.91,1.66)	0.186	AGE (p=0.003) DRKYR (p=0.109) DIFCORT (p=0.051)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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

TABLE 12-15. (Continued)

Analysis of ECG: Arrhythmia

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.339[b]
(n=446)	≤18.6	1.7 (59)	2.7 (113)	8.7 (46)	1.55 (0.85,2.83)	0.149[c]
	>18.6	2.0 (49)	5.2 (115)	3.1 (64)	1.05 (0.61,1.81)	0.867[c]
f) Maximal						0.032[b]
(n=647)	≤18.6	1.9 (103)	1.8 (167)	7.4 (68)	1.51 (0.96,2.37)	0.074[c]
	>18.6	10.3 (68)	3.9 (154)	3.5 (87)	0.78 (0.51,1.17)	0.230[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.201[b]	AGE (p<0.001)
(n=446)	≤18.6	2.18 (1.15,4.15)	0.017[c]	
	>18.6	1.28 (0.75,2.21)	0.366[c]	
h) Maximal			0.034**[b]	CURR*TIME*DIFCORT
(n=617)	≤18.6	1.79 (1.11,2.90)**	0.018**[c]	(p=0.033)
	>18.6	0.90 (0.58,1.40)**	0.648**[c]	AGE (p=0.008)
				DRKYR (p=0.062)

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

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

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

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

Note: Minimal--Low: >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 12-15. (Continued)

Analysis of ECG: Arrhythmia

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	3.7	All Categories		0.626
Unknown	320	4.7	Unknown vs. Background	1.28 (0.67,2.45)	0.456
Low	177	2.8	Low vs. Background	0.76 (0.29,2.00)	0.574
High	155	5.2	High vs. Background	1.42 (0.63,3.19)	0.400
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.238	AGE (p<0.001) DIFCORT (p=0.048)
Unknown	303	Unknown vs. Background	1.33 (0.68,2.58)	0.404	
Low	174	Low vs. Background	0.83 (0.31,2.23)	0.712	
High	150	High vs. Background	2.34 (1.00,5.51)	0.051	
Total	1,294				

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.

After deletion of the initial dioxin-by-personality type interaction and adjusting only for age, lifetime cigarette smoking history, and personality type, the minimal analysis displayed a marginally significant positive association between initial dioxin and the prevalence of arrhythmia in Ranch Hands (Table 12-15 [c]: Adj. RR=1.43, p=0.092). The percentages of Ranch Hands in the minimal cohort with arrhythmia were 1.8, 4.5, and 4.5 percent for the low, medium, and high initial dioxin categories.

The findings of the maximal adjusted analysis concurred with the unadjusted results in the lack of significance of the relationship between initial dioxin and the prevalence of arrhythmia (Table 12-15 [d]: p=0.186).

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

In the unadjusted analysis of arrhythmia under the minimal assumption, the interaction between current dioxin and time since tour was not significant (Table 12-15 [e]: p=0.339). Based on the maximal assumption, the associations between current dioxin and arrhythmia differed significantly for the two time strata in the unadjusted analysis (Table 12-15 [f]: p=0.032). For Ranch Hands with 18.6 years or less since tour, there was a marginally significant positive relationship between current dioxin and arrhythmia (Adj. RR=1.51, p=0.074). Within the time greater than 18.6 years stratum, there was a nonsignificant negative association between current dioxin and arrhythmia (Adj. RR=0.78, p=0.230). The relative frequencies of Ranch Hands with later tours who were diagnosed with arrhythmia were 1.9, 1.8, and 7.4 percent for low, medium, and high current dioxin.

After adjusting for age in the minimal analysis of arrhythmia, the interaction between current dioxin and time since tour remained nonsignificant (Table 12-15 [g]: p=0.201). However, for Ranch Hands with later tours, the positive association between current dioxin and the prevalence of arrhythmia became significant (Adj. RR=2.18, p=0.017). In the stratum of Ranch Hands with early tours, the positive association remained nonsignificant (p=0.366). For the Ranch Hands with 18.6 years or less since tour, the percentages of arrhythmia in the low, medium, and high current dioxin categories were 1.7, 2.7, and 8.7 percent.

The adjusted maximal analysis revealed a significant interaction among current dioxin, time since tour, and differential cortisol response (Table 12-15 [h]: p=0.033). To examine this interaction, analyses were performed separately for each differential cortisol-response stratum (Appendix Table K-1). For Ranch Hands with a differential cortisol response of 0.6 µg/dl or less, the interaction between current dioxin and time was not significant (p=0.314). However, there was a marginally significant positive association between current dioxin and arrhythmia for Ranch Hands with late tours (Adj. RR=1.97, p=0.086) and a nonsignificant positive association for Ranch Hands with early tours (Adj. RR=1.08, p=0.888). Within the 18.6 years or less time stratum, there were no Ranch Hands with arrhythmia for the low current dioxin classification; the relative frequencies of arrhythmia for the medium and high classifications were 5.7 and 10.0 percent.

In the stratified analysis of Ranch Hands with a differential cortisol response between 0.6 µg/dl and 4.0 µg/dl, there was only one Ranch Hand diagnosed with arrhythmia (high current dioxin) in the 18.6 years or less time stratum. In the greater than 18.6 years time stratum, there was a marginally significant negative association between current dioxin and

arrhythmia (Adj. RR=0.36, p=0.077). The percentages of Ranch Hands diagnosed with arrhythmia in this time stratum were 12.0 and 5.8 percent for low and medium current dioxin; there were no Ranch Hands in the high current dioxin classification with arrhythmia.

For Ranch Hands with a differential cortisol response greater than 4.0 μg/dl, the analysis displayed nonsignificant positive relationships between current dioxin and arrhythmia for the two time strata, which were not significantly different (Appendix Table K-1: p>0.15 for the interaction and time-specific strata).

After deletion of the interaction and adjustment for only age, lifetime alcohol history, and differential cortisol response, the maximal analysis detected a significant interaction between current dioxin and time (Table 12-15 [h]: p=0.034). The analysis also revealed a significant positive association between current dioxin and arrhythmia for Ranch Hands with later tours (Adj. RR=1.79, p=0.018) and a nonsignificant negative association for Ranch Hands with early tours (Adj. RR=0.90, p=0.648).

Longitudinal analyses of the overall ECG displayed significant negative associations with dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the prevalence of arrhythmia did not detect any significant differences among the four current dioxin categories (Table 12-15 [i]: p>0.35 for each contrast).

In the analysis of arrhythmia, the adjustment for age and differential cortisol response did not change the lack of significance of the overall contrast of the four current dioxin categories (Table 12-15 [j]: p=0.238). However, the contrast of the Ranch Hands in the high category versus the Comparisons in the background category became marginally significant with the Ranch Hands having a higher risk of arrhythmia than the Comparisons (Adj. RR=2.34, 95% C.I.: [1.00,5.51], p=0.051). The relative frequencies of participants diagnosed with arrhythmia were 3.7, 4.7, 2.8, and 5.2 percent for the background, unknown, low, and high current dioxin categories.

ECG: Other Diagnoses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted nor the adjusted analysis detected significant associations between initial dioxin and other ECG diagnoses under the minimal and maximal assumptions (Table 12-16 [a-d]: p>0.10 for each analysis).

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

Based on the minimal assumption, the unadjusted analysis of other ECG diagnoses did not detect a significant current dioxin-by-time since tour interaction (Table 12-16 [e]: p=0.129). However, for Ranch Hands with greater than 18.6 years since tour, there was a significant negative association between current dioxin and other abnormal ECG diagnoses

TABLE 12-16.

Analysis of ECG: Other Diagnoses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	17.3	0.85 (0.67,1.07)	0.146
	Medium	224	18.3		
	High	112	10.7		
b) Maximal (n=647)	Low	173	19.1	0.88 (0.75,1.04)	0.122
	Medium	320	19.1		
	High	154	11.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.90 (0.71,1.15)	0.396	AGE (p=0.019)
d) Maximal (n=638)	0.93 (0.78,1.09)	0.365	AGE (p=0.002) DRKYR (p=0.143)

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

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

TABLE 12-16. (Continued)

Analysis of ECG: Other Diagnoses

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.129[b]
(n=446)	≤18.6	13.6 (59)	22.1 (113)	13.0 (46)	1.01 (0.73,1.41)	0.942[c]
	>18.6	24.5 (49)	13.9 (115)	7.8 (64)	0.70 (0.49,1.00)	0.048[c]
f) Maximal						0.040[b]
(n=647)	≤18.6	16.5 (103)	19.8 (167)	13.2 (68)	1.03 (0.82,1.29)	0.814[c]
	>18.6	22.1 (68)	20.1 (154)	6.9 (87)	0.72 (0.56,0.93)	0.011[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.120[b]	AGE (p=0.013)
(n=440)	≤18.6	1.15 (0.81,1.63)	0.428[c]	DRKYR (p=0.141)
	>18.6	0.78 (0.55,1.12)	0.185[c]	
h) Maximal			0.026[b]	AGE (p=0.002)
(n=638)	≤18.6	1.13 (0.89,1.44)	0.305[c]	DRKYR (p=0.109)
	>18.6	0.77 (0.59,1.00)	0.046[c]	

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

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

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

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

TABLE 12-16. (Continued)

Analysis of ECG: Other Diagnoses

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	18.9	All Categories		0.024
Unknown	320	19.1	Unknown vs. Background	1.01 (0.72,1.41)	0.957
Low	177	19.8	Low vs. Background	1.06 (0.70,1.60)	0.796
High	155	9.7	High vs. Background	0.46 (0.26,0.81)	0.007
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	664	All Categories		0.140	AGE (p<0.001) CHOL (p=0.042)
Unknown	302	Unknown vs. Background	0.95 (0.67,1.35)	0.776	PERS (p=0.081)
Low	172	Low vs. Background	1.07 (0.70,1.64)	0.751	
High	149	High vs. Background	0.53 (0.29,0.96)	0.036	
Total	1,287				

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.

(Est. RR=0.70, p=0.048). Within this stratum, the percentages of Ranch Hands with other abnormal ECG diagnoses decreased as current dioxin increased (low, 24.5%; medium, 13.9%; high, 7.8%).

The maximal unadjusted analysis revealed that the association between current dioxin and other ECG diagnoses differed significantly between the time strata (Table 12-16 [f]: p=0.040). For Ranch Hands with later tours, there was a nonsignificant positive relationship between current dioxin and other ECG diagnoses (Adj. RR=1.03, p=0.814). In contrast, there was a significant negative association for Ranch Hands with early tours (Adj. RR=0.72, p=0.011). Similar to the minimal unadjusted analysis, within the time greater than 18.6 years stratum of the maximal cohort, the percentages of Ranch Hands with other abnormal ECG diagnoses decreased with increasing levels of dioxin (low, 22.1%; medium, 20.1%; high, 6.9%).

After adjusting for age and lifetime alcohol history, the minimal analysis of other ECG diagnoses did not detect any significant results (Table 12-16 [g]: p>0.10 for interaction and time-specific analyses). Under the maximal assumption, the current dioxin-by-time since tour interaction remained significant after including the same covariates (Table 12-16 [h]: p=0.026). Also, the negative association between current dioxin and the prevalence of other ECG diagnoses remained nonsignificant for Ranch Hands with more than 18.6 years since tour (Adj. RR=0.77, p=0.046).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the prevalence of other abnormal ECG diagnoses, the simultaneous contrast of the four current dioxin categories was significant (Table 12-16 [i]: p=0.024). The percentages of participants with other abnormal ECG diagnoses were nearly equivalent for the background, unknown, and low current dioxin categories (18.9%, 19.1%, and 19.8%), but the percentage of the Ranch Hands in the high category was much lower (9.7%). In fact, the Ranch Hands in the high category had a significantly lower risk of other abnormal ECG diagnoses relative to the Comparisons in the background category (Est. RR=0.46, 95% C.I.: [0.26,0.81], p=0.007).

After adjusting for age, cholesterol, and personality type, the analysis of other ECG diagnoses did not detect a significant overall difference among the four current dioxin categories (Table 12-16 [j]: p=0.140). However, the Ranch Hands in the high current dioxin category had a significantly lower risk of other abnormal ECG diagnoses relative to the Comparisons in the background category (Adj. RR=0.53, 95% C.I.: [0.29,0.96], p=0.036).

Physical Examination: Peripheral Vascular Function Variables

Diastolic Blood Pressure (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analyses of diastolic blood pressure in its continuous form did not detect a significant association with initial dioxin (Table 12-17 [a] and [b]: p=0.640 and p=0.176).

TABLE 12-17.

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	110	75.02	0.172 (0.367)	0.640
(n=446)	Medium	224	76.48		
(R^2<0.001)	High	112	75.62		
b) Maximal	Low	173	74.61	0.359 (0.265)	0.176
(n=647)	Medium	320	75.79		
(R^2=0.003)	High	154	76.09		

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	107	77.74	0.119 (0.369)	0.748	RACE (p=0.013)
(n=431)	Medium	217	79.59			CHOL (p=0.008)
(R^2=0.068)	High	107	78.28			%BFAT (p=0.005)
						PERS (p=0.026)
						HRTDIS (p=0.019)
d) Maximal	Low	163	****	****	****	INIT*PERS (p=0.002)
(n=621)	Medium	310	****			RACE (p=0.013)
(R^2=0.069)	High	148	****			CHOL (p=0.003)
						%BFAT (p<0.001)

[a]Slope and standard error based on diastolic blood pressure 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 12-17. (Continued)

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

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						0.884[b]
(n=446)	≤18.6	74.19	76.18	74.67	0.188 (0.583)	0.747[c]
(R^2=0.004)		(59)	(113)	(46)		
	>18.6	75.65	77.12	75.89	0.077 (0.494)	0.877[c]
		(49)	(115)	(64)		
f) Maximal						0.680[b]
(n=647)	≤18.6	74.85	75.45	74.82	0.180 (0.402)	0.655[c]
(R^2=0.004)		(103)	(167)	(68)		
	>18.6	74.87	75.81	77.18	0.406 (0.373)	0.277[c]
		(68)	(154)	(87)		

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						0.543[b]	RACE (p=0.015)
(n=431)	≤18.6	76.91	78.99	78.04	0.370 (0.599)	0.537[c]	CHOL (p=0.008)
(R^2=0.072)		(56)	(109)	(42)			%BFAT (p=0.005)
	>18.6	78.54	79.99	78.16	-0.098 (0.489)	0.842[c]	PERS (p=0.030)
		(48)	(113)	(63)			HRTDIS (p=0.019)
h) Maximal						0.692[b]	RACE (p=0.017)
(n=643)	≤18.6	77.26	77.18	76.60	-0.026 (0.401)	0.949[c]	CHOL (p=0.003)
(R^2=0.054)		(102)	(165)	(67)			%BFAT (p<0.001)
	>18.6	76.97	77.56	78.36	0.188 (0.368)	0.610[c]	
		(68)	(154)	(87)			

[a]Slope and standard error based on diastolic blood pressure versus log_2 dioxin.

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

[c]Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

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

TABLE 12-17. (Continued)

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

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	703	74.54	All Categories		0.017
Unknown	320	74.04	Unknown vs. Background	-0.50 (-1.72,0.73)	0.429
Low	177	76.25	Low vs. Background	1.71 (0.18,3.24)	0.028
High	155	76.15	High vs. Background	1.61 (0.00,3.23)	0.051
Total	1,355		(R^2=0.008)		

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	659	74.54***	All Categories		0.062***	DXCAT*PERS (p=0.007)
Unknown	297	74.36***	Unknown vs. Background	-0.19 (-1.45,1.07)***	0.772***	DXCAT*HRTDIS
Low	170	76.22***	Low vs. Background	1.68 (0.15,3.20)***	0.032***	(p=0.014)
High	143	75.96***	High vs. Background	1.42 (-0.26,3.09)***	0.098***	AGE (p=0.035)
Total	1,269		(R^2=0.089)			DRKYR (p=0.022) CHOL (p=0.001) %BFAT (p<0.001) DIFCORT (p=0.018)

***Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of these interactions.

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.

After adjustment for covariate information, the association between diastolic blood pressure and initial dioxin in its continuous form remained nonsignificant in the minimal analysis (Table 12-17 [c]: p=0.748). The adjusted maximal analysis revealed a significant interaction between initial dioxin and personality type (Table 12-17 [d]: p=0.002). Stratified analyses detected a marginally significant negative association between initial dioxin and diastolic blood pressure for type A Ranch Hands (Appendix Table K-1: p=0.060) and a significant positive association for type B Ranch Hands (p=0.015). The adjusted mean diastolic blood pressure values for type A Ranch Hands were 77.99, 77.21, and 75.85 mm Hg for the low, medium, and high initial dioxin categories. The corresponding means for type B Ranch Hands were 75.97, 77.96, and 79.30 mm Hg, respectively.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. The maximal analysis of diastolic blood pressure in its continuous form without cholesterol and percent body fat in the model also revealed a significant initial dioxin-by-personality type interaction (Appendix Table K-2: p=0.005). In the stratified analyses of this interaction, the decreasing association between initial dioxin and diastolic blood pressure for type A Ranch Hands became nonsignificant (Appendix Table K-3: p=0.263) after the exclusion of cholesterol and percent body fat from the model. The positive association between initial dioxin and diastolic blood pressure remained significant for type B Ranch Hands (p=0.003).

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

Under the minimal and the maximal assumptions, the association between current dioxin and diastolic blood pressure did not differ significantly between time since tour strata for the unadjusted or adjusted analyses (Table 12-17 [e-h]: p>0.50 for each analysis). The associations between current dioxin and diastolic blood pressure also were nonsignificant within the time strata in the minimal and maximal unadjusted and adjusted analyses.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of diastolic blood pressure in its continuous form detected a significant difference among the four current dioxin categories (Table 12-17 [i]: p=0.017). Specifically, the unadjusted mean diastolic blood pressure of the Ranch Hands in the low category was significantly higher than the corresponding mean of the Comparisons in the background category (p=0.028). Also, the unadjusted mean diastolic blood pressure of the Ranch Hands in the high category was marginally higher than the corresponding mean of the Comparisons (p=0.051). The unadjusted mean diastolic blood pressures for participants in the background, unknown, low, and high current dioxin categories were 74.54, 74.04, 76.25, and 76.15 mm Hg.

The adjusted analysis of diastolic blood pressure revealed significant interactions between categorized current dioxin and personality type and between categorized current dioxin and family history of heart disease (Table 12-17 [j]: p=0.007 and p=0.014). In order to investigate these interactions, separate analyses were performed for each stratum combination of family history of heart disease and personality type (Appendix Table K-1). For type A participants with and without a family history of heart disease, there were no significant differences in the mean diastolic blood pressures of the four current dioxin categories (p>0.25 for each contrast).

The stratified analysis of type B participants with a family history of heart disease detected a significant difference among the mean diastolic blood pressures of the four current dioxin categories (Appendix Table K-1: $p<0.001$). Specifically, the mean diastolic blood pressure of the Ranch Hands in the low category was significantly higher than the corresponding mean of the Comparisons in the background category ($p<0.001$). Also, the mean of the Ranch Hands in the high category was marginally greater than the mean of the Comparisons in the background category ($p=0.061$). The adjusted mean diastolic blood pressures of the background, unknown, low, and high current dioxin categories were 74.10, 71.73, 81.02, and 78.39 mm Hg.

For type B participants without a family history of heart disease, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories was marginally significant (Appendix Table K-1: $p=0.065$). The Ranch Hands in the high current dioxin category had a significantly higher mean diastolic blood pressure than the Comparisons in the background category ($p=0.016$). The adjusted mean diastolic blood pressures of the participants in the background, unknown, low, and high current dioxin categories were 74.22, 73.58, 74.94, and 77.28 mm Hg.

After deletion of the categorized current dioxin-by-covariate interactions from the model, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories was marginally significant (Table 12-17 [j]: $p=0.062$). Similar to the unadjusted analysis, the Ranch Hands in the low category had a significantly higher mean diastolic blood pressure than the Comparisons in the background category ($p=0.032$), and the Ranch Hands in the high current dioxin category had a marginally greater mean diastolic blood pressure than the Comparisons ($p=0.098$).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After removing cholesterol and percent body fat from the adjusted analysis of diastolic blood pressure in its continuous form, the interactions between categorized current dioxin and personality type and between categorized current dioxin and family history of heart disease remained significant (Appendix Table K-2: $p=0.012$ and $p=0.011$, respectively). In the stratified analyses excluding cholesterol and percent body fat for type A participants with a family history of heart disease, the contrast of the Comparisons in the background category and the Ranch Hands in the low category became marginally significant (Appendix Table K-3: $p=0.083$) with the Ranch Hands having a higher mean diastolic blood pressure. The adjusted mean diastolic blood pressures for this stratum were 74.79, 73.76, 79.60, and 75.50 mm Hg for the background, unknown, low, and high current dioxin categories. The results remained nonsignificant for the type A participants with no family history of heart disease.

For type B participants with a family history of heart disease, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category became marginally significant (Appendix Table K-3: $p=0.087$) with the Ranch Hands having a lower mean diastolic blood pressure. However, the contrast of the Ranch Hands versus the Comparisons in the high category became nonsignificant ($p=0.187$). Also, for type B participants with no history of heart disease in the family, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories became significant ($p=0.002$) with Ranch Hands in the high current dioxin category having a significantly higher mean than the Comparisons ($p=0.002$).

In the model without the categorized current dioxin-by-covariate interactions, the exclusion of cholesterol and percent body fat increased the significance of the contrast of the mean diastolic blood pressure of the Ranch Hands in the high category versus the corresponding mean of the Comparisons in the background category (Appendix Table K-2: p=0.017).

Diastolic Blood Pressure (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted minimal nor maximal analysis detected a significant association between initial dioxin and discretized diastolic blood pressure (Table 12-18: [a] and [b]: p=0.784 and p=0.728, respectively).

After adjusting for covariate information, the minimal and maximal analyses also displayed nonsignificant results (Table 12-18 [c] and [d]: p=0.394 and p=0.751, respectively).

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

The associations between current dioxin and the prevalence of abnormally high diastolic blood pressure did not differ significantly with time since tour for either the unadjusted or adjusted minimal and maximal analyses (Table 12-18 [e-h]: p>0.35 for each interaction).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted and adjusted analyses of discretized diastolic blood pressure, the simultaneous contrast of the four current dioxin categories was nonsignificant (Table 12-18 [i] and [j]: p=0.301 and p=0.413, respectively). The Ranch Hands versus Comparisons contrasts were also nonsignificant.

Funduscopic Examination

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between the frequency of abnormalities in small blood vessels detected by the funduscopic examination and initial dioxin was not significant for either the minimal or the maximal cohort (Table 12-19 [a] and [b]: p=0.727 and p=0.868). Adjusted analyses were not performed due to the sparse number of abnormalities.

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

Similar to the initial dioxin analyses, the unadjusted current dioxin and time since tour analyses of the prevalence of abnormal funduscopic examinations displayed nonsignificant results for Ranch Hands with later tours in the minimal and maximal cohorts (Table 12-19 [c] and [d]: p=0.458 and p=0.749). Due to the sparse number of abnormalities, adjusted analyses were not conducted.

TABLE 12-18.

Analysis of Diastolic Blood Pressure (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	4.6	0.95 (0.67,1.36)	0.784
	Medium	224	7.1		
	High	112	3.6		
b) Maximal (n=647)	Low	173	4.1	1.05 (0.81,1.36)	0.728
	Medium	320	5.3		
	High	154	5.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=443)	0.85 (0.58,1.25)	0.394	AGE (p=0.033) CHOL (p=0.005) HRTDIS (p=0.045)
d) Maximal (n=643)	1.04 (0.80,1.35)	0.751	CHOL (p=0.075)

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

TABLE 12-18. (Continued)

Analysis of Diastolic Blood Pressure (Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.963[b]
	≤18.6	3.4 (59)	6.2 (113)	2.2 (46)	0.94 (0.50,1.75)	0.835[c]
	>18.6	6.1 (49)	7.8 (115)	4.7 (64)	0.95 (0.61,1.49)	0.832[c]
f) Maximal (n=647)						0.547[b]
	≤18.6	4.9 (103)	4.2 (167)	4.4 (68)	0.95 (0.62,1.47)	0.829[c]
	>18.6	2.9 (68)	6.5 (154)	5.8 (87)	1.13 (0.80,1.58)	0.488[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=443)			0.978[b]	AGE (p=0.018)
	≤18.6	0.79 (0.40,1.56)	0.502[c]	CHOL (p=0.004)
	>18.6	0.80 (0.49,1.31)	0.381[c]	HRTDIS (p=0.048)
h) Maximal (n=643)			0.556[b]	CHOL (p=0.078)
	≤18.6	0.95 (0.62,1.48)	0.832[c]	
	>18.6	1.12 (0.80,1.57)	0.495[c]	

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

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

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

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

TABLE 12-18. (Continued)

Analysis of Diastolic Blood Pressure (Discrete)

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	4.3	All Categories		0.301
Unknown	320	3.1	Unknown vs. Background	0.72 (0.35,1.50)	0.384
Low	177	6.8	Low vs. Background	1.63 (0.82,3.26)	0.165
High	155	5.2	High vs. Background	1.22 (0.55,2.72)	0.625
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.413	PACKYR (p=0.078) %BFAT (p=0.078)
Unknown	320	Unknown vs. Background	0.78 (0.37,1.62)	0.501	
Low	177	Low vs. Background	1.61 (0.80,3.22)	0.180	
High	155	High vs. Background	1.17 (0.52,2.63)	0.701	
Total	1,355				

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 12-19.

Analysis of Funduscopic Examination

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.0	1.22 (0.40,3.72)	0.727
	Medium	224	0.9		
	High	112	0.0		
b) Maximal (n=647)	Low	173	1.2	0.94 (0.44,1.99)	0.868
	Medium	320	0.3		
	High	154	0.7		

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=446)						--
	≤18.6	0.0 (59)	0.9 (113)	2.2 (46)	1.58 (0.49,5.06)	0.458[b]
	>18.6	0.0 (49)	0.0 (115)	0.0 (64)	--	--
d) Maximal (n=647)						--
	≤18.6	1.0 (103)	1.2 (167)	1.5 (68)	1.13 (0.53,2.43)	0.749[b]
	>18.6	0.0 (68)	0.0 (154)	0.0 (87)	--	--

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

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

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Initial Dioxin: 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.

Current Dioxin: 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 12-19. (Continued)

Analysis of Funduscopic Examination

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.6	All Categories		0.922
Unknown	320	0.9	Unknown vs. Background	1.65 (0.37,7.43)	0.764
Low	177	0.6	Low vs. Background	0.99 (0.11,8.94)	0.999
High	155	0.7	High vs. Background	1.14 (0.13,10.22)	0.999
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.892**	DXCAT*DIFCORT (p=0.024)
Unknown	303	Unknown vs. Background	1.70 (0.37,7.85)**	0.496**	AGE (p=0.028)
Low	174	Low vs. Background	0.94 (0.10,8.57)**	0.953**	HRTDIS (p=0.117)
High	150	High vs. Background	1.72 (0.18,16.74)**	0.639**	
Total	1,294				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis, there were no significant differences in the prevalence of abnormal findings in the funduscopic examinations among the four current dioxin categories (Table 12-19 [e]: $p>0.75$ for each contrast).

The adjusted analysis of the results of the funduscopic examination revealed a significant interaction between categorized current dioxin and differential cortisol response (Table 12-19 [f]: $p=0.024$). The stratified analyses showed very few participants with abnormal funduscopic examinations for each differential cortisol response classification (Appendix Table K-1). For participants with a differential cortisol response of 0.6 µg/dl or less, only four Comparisons in the background category and one Ranch Hand in the unknown category had abnormal funduscopic examination findings. Thus, the overall contrast of the four current dioxin categories was not significant ($p=0.476$), nor was the individual contrast of the unknown versus background category ($p=0.600$).

Similarly, in the greater than 0.6 to 4.0 µg/dl differential cortisol-response stratum, there were only two Ranch Hands with abnormalities: one in the low current dioxin category and one in the high current dioxin category. Among the participants with a differential cortisol response greater then 4.0 µg/dl, there were only two Ranch Hands in the unknown category with abnormal results of the funduscopic examination. Due to the sparse number of abnormalities in these strata, relative risks, confidence intervals, and most p-values were not presented.

After deletion of the categorized current dioxin-by-differential cortisol response interaction, the results of the adjusted analysis of the funduscopic examination were nonsignificant (Table 12-19 [f]: $p>0.45$ for each contrast).

Carotid Bruits

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted and adjusted analyses revealed nonsignificant negative associations between initial dioxin and carotid bruits (Table 12-20 [a-d]: $p>0.35$ for each analysis).

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

In the unadjusted analysis of carotid bruits under both assumptions, only one Ranch Hand with 18.6 years or less since tour was diagnosed with carotid bruits (minimal: low current dioxin; maximal: medium current dioxin). The negative associations between current dioxin and carotid bruits were nonsignificant within the greater than 18.6 years time stratum of both the minimal and maximal cohorts (Table 12-20 [e] and [f]: $p=0.315$ and $p=0.240$). Due to the rarity of carotid bruits, adjusted analyses were not performed.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the prevalence of carotid bruits did not detect a significant overall difference among the four current dioxin categories (Table 12-20 [g]: $p=0.236$).

TABLE 12-20.

Analysis of Carotid Bruits

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.9	0.63 (0.21,1.85)	0.357
	Medium	224	1.3		
	High	112	0.0		
b) Maximal (n=647)	Low	173	0.6	0.81 (0.42,1.58)	0.517
	Medium	320	1.6		
	High	154	0.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	0.62 (0.16,2.45)	0.446	AGE (p=0.017) DRKYR (p=0.034) HRTDIS (p=0.091)
d) Maximal (n=638)	0.86 (0.39,1.86)	0.686	AGE (p=0.001) DRKYR (p=0.040)

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

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

TABLE 12-20. (Continued)

Analysis of Carotid Bruits

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						--
	≤18.6	1.7 (59)	0.0 (113)	0.0 (46)	--	--
	>18.6	2.0 (49)	1.7 (115)	0.0 (64)	0.48 (0.12,2.00)	0.315[b]
f) Maximal (n=647)						--
	≤18.6	0.0 (103)	0.6 (167)	0.0 (68)	--	--
	>18.6	2.9 (68)	2.0 (154)	0.0 (87)	0.60 (0.25,1.41)	0.240[b]

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

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

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

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 12-20. (Continued)

Analysis of Carotid Bruits

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.6	All Categories		0.236
Unknown	320	1.6	Unknown vs. Background	2.77 (0.74,10.39)	0.228
Low	177	1.1	Low vs. Background	2.00 (0.36,10.99)	0.694
High	155	0.0	High vs. Background	–	0.900
Total	1,355				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.234	AGE (p=0.062)
Unknown	320	Unknown vs. Background	2.75 (0.73,10.36)	0.134	
Low	177	Low vs. Background	2.12 (0.38,11.74)	0.389	
High	155	High vs. Background	–	–	
Total	1,355				

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

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

Adjustment for age did not change the lack of significance of the unadjusted analysis (Table 12-20 [h]: p=0.234).

Radial Pulses

In the minimal cohort, only one Ranch Hand had an abnormal (absent) radial pulse; he was in the low initial dioxin category. In the maximal cohort, there were two Ranch Hands with absent radial pulses: one in the low initial dioxin category and the other in the medium category. Due to this sparse number of abnormalities, relative risks, confidence intervals, and p-values were not presented for the initial dioxin or current dioxin and time since tour analyses. Similarly, only four Comparisons in the background category and one Ranch Hand in the unknown category had absent radial pulses. Thus, relative risks, confidence intervals, and p-values were not displayed for the analysis of categorized current dioxin. Table 12-21 presents the sample sizes and relative frequencies for all three analyses.

Femoral Pulses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between initial dioxin and femoral pulses was not significant under the minimal or the maximal assumption (Table 12-22 [a] and [b]: p=0.703 and p=0.922).

The adjusted analysis of the minimal and the maximal cohorts revealed significant interactions between initial dioxin and personality type (Table 12-22 [c] and [d]: p=0.027 and p=0.032, respectively). Stratified analyses of these interactions displayed a significant positive association between initial dioxin and absent femoral pulses for type A Ranch Hands (Appendix Table K-1: minimal assumption, Adj. RR=3.28, p=0.045; maximal assumption, Adj. RR=3.09, p=0.038). In contrast, the analyses of type B Ranch Hands exhibited nonsignificant negative associations between initial dioxin and abnormal femoral pulses (minimal assumption, Adj. RR=0.65, p=0.319; maximal assumption, Adj. RR=0.86, p=0.604). However, of the type A Ranch Hands in both the minimal and maximal cohorts, only two (both in the high initial dioxin category) had absent femoral pulses. Thus, the stratified analyses may have been affected by this sparse number of abnormalities.

After deletion of the initial dioxin-by-personality type interactions, neither the minimal nor the maximal adjusted analysis detected a significant association between initial dioxin and the frequency of Ranch Hands with abnormal femoral pulses (Table 12-22 [c] and [d]: p=0.984 and p=0.683, respectively).

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

Under the minimal and the maximal assumptions, the unadjusted analyses of femoral pulses did not detect a significant interaction between current dioxin and time since tour (Table 12-22 [e] and [f]: p=0.562 and p=0.656, respectively). The associations between current dioxin and the femoral pulses were also nonsignificant within each time stratum for the minimal and maximal cohorts.

TABLE 12-21.

Analysis of Radial Pulses

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	n	Percent Abnormal
a) Minimal (n=442)	Low	109	0.9
	Medium	223	0.0
	High	110	0.0
b) Maximal (n=641)	Low	172	0.6
	Medium	318	0.3
	High	151	0.0

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal (n=442)	≤18.6	0.0 (58)	0.0 (113)	0.0 (46)
	>18.6	2.0 (49)	0.0 (114)	0.0 (62)
d) Maximal (n=641)	≤18.6	1.0 (102)	0.0 (166)	0.0 (68)
	>18.6	0.0 (68)	0.7 (152)	0.0 (85)

Note: Initial Dioxin: 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.

Current Dioxin: 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 12-21. (Continued)

Analysis of Radial Pulses

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	n	Percent Yes
Background	694	0.6
Unknown	317	0.3
Low	176	0.0
High	153	0.0
Total	1,340	

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.