Air Force Health Study

An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides

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SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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CHAPTER 14

RENAL ASSESSMENT

INTRODUCTION

Background

A few studies of the potential nephrotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) have been published since the literature was summarized in the report on the 1987 examinations of the Air Force Health Study (AFHS) (1). Though renal excretion of phenoxyherbicides (TCDD and 2,4,5-T) has been well established in animals (2) and in man (3, 4), recent studies indicate that it may be of secondary importance to intestinal elimination (5, 6).

In one study, rats exposed to 2,4-D by cutaneous application were noted to have an increase in renal weight but no histologic changes despite the development of a wasting syndrome (7). In contrast, in a study of TCDD toxicity in guinea pigs, a significant decrease in kidney weight was noted relative to controls, and histopathologic examination revealed focal mineralization changes in the renal parenchyma (8). A more recent report of renal function in rats exposed to 2,4-D by intraperitoneal injection revealed an increase in sodium excretion, urine volume, and blood urea nitrogen in association with a decrease in glomerular filtration, findings which point to the loop of Henle rather than the proximal tubule as the site of toxicity (9). Because the doses of phenoxyherbicides employed were extreme by any measure of reported human exposure and because routes of administration were not always comparable, the relevance of these and other animal studies to dioxin toxicity in humans is not established.

Renal and urinary tract disease have received relatively little emphasis in morbidity studies of humans exposed to phenoxyherbicides. An isolated case of hemorrhagic cystitis occurred in a child exposed to high concentrations of TCDD in soil (10); however, a causal relationship was never established and subsequent followup revealed no long-term sequelae (11). Previous reports describing medical followup of populations heavily exposed to dioxin through environmental contamination have failed to document the kidney as a target organ for TCDD toxicity (12, 13). Studies of veterans potentially exposed to Agent Orange in Southeast Asia (SEA) have produced similar results. The 1987 examination report of the AFHS (1) found no significant differences in standard indices of renal function or routine urinalysis between the Ranch Hand and Comparison cohorts. Similarly, the Vietnam Experience Study, conducted by the Centers for Disease Control, found no increased incidence of renal or urinary tract disease in veterans who served in SEA versus those who did not (14). Acute renal failure occurred in each of three recently reported cases of extreme phenoxyherbicide (not TCDD) toxicity in man; however, the mechanism appears to have been secondary to rhabdomyolysis rather than to a direct nephrotoxic effect (15, 16).

More detailed summaries of the pertinent scientific literature for the renal assessment can be found in the report of the previous analyses of the 1987 examination data (1).

Summary of Previous Analyses of the 1987 Examination Data

Without adjustments for covariates, none of the variables of reported history of kidney disease/stones, urinary protein, urinary occult blood, urinary white blood cells, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups for the 1987 examination. In general, these findings were supported by the adjusted analyses. Examination of the group-by-covariate interactions did not yield a consistent pattern to suggest renal detriment to either group. Lack of a group difference in the reported history of kidney disease/stones (consistent with the 1985 examination results) was in contrast with the Baseline findings, in which Ranch Hands reported significantly more disease. A nonsignificant difference in the percentage of participants with urinary protein also was inconsistent with the Baseline examination when the Comparisons had a marginally significant higher prevalence rate. In the longitudinal analysis of blood urea nitrogen, no difference in the change over time was detected.

Parameters of the Renal Assessment

Dependent Variables

The renal assessment was based on questionnaire and laboratory data collected at the 1987 physical examination.

Questionnaire Data

In the self-administered family and personal history questionnaire, each study participant was asked whether he had ever experienced kidney trouble or kidney stones, or had repeating occurrences of kidney infections in the year prior to the 1987 physical examination. This information was subsequently verified, and a composite variable, kidney disease, was constructed by assigning yes to any participant who was verified to have had at least one of these conditions—kidney trouble, kidney stones, or kidney infections.

Participants with a pre-SEA history of one of these conditions were excluded. No other participants were excluded for medical reasons from the analysis of this variable.

Laboratory Examination Data

Five renal variables were quantified by general laboratory procedures to assess nonspecific renal system function. The presence or absence of urine protein was determined by standard reagent strip testing. Hematuria and leukocyturia were measured by high-powered microscopic examination after centrifugation for 5 minutes. Blood urea nitrogen levels were assayed by a DuPont Automated Chemical Analyzer® model 500. Ames' Multisticks were used to measure urine specific gravity.

Urinary protein (absent/present), hematuria (absent/present), and leukocyturia ($\leq$2 white blood cells per high powered field [WBC/HPF] or >2 WBC/HPF) were analzyed as dichotomous variables. Blood urea nitrogen (mg/dl) and urine specific gravity were analyzed as continuous variables. A square root transformation was applied to the blood urea nitrogen data.

The cutpoint between abnormal and normal readings for blood urea nitrogen from Scripps Clinic and Research Foundation (SCRF) is 22 mg/dl, with readings above this value considered abnormal. The SCRF cutpoint for urine specific gravity is 1.005, with readings below this value considered abnormal. Statistical analyses dichotomizing these two variables were not performed.

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

Covariates

The effects of three covariates (age, race, and diabetic class) were examined in adjusted statistical analyses of the renal data. Diabetic class was defined as diabetic (verified history of diabetes or $\geq$200 mg/dl 2-hour postprandial glucose), impaired (140 mg/dl$\leq$glucose<200 mg/dl), and normal (<140 mg/dl glucose). Age was used in its continuous form for modeling purposes for all dependent variables; occasionally, age was dichotomized for presentation purposes such as interaction summaries presented in Appendix M, Table M-1.

Relation to Baseline, 1985, and 1987 Studies

The six variables analyzed in this report were analyzed in the Baseline and 1985 studies. The kidney disease variable has been updated since the previous analyses of the 1987 examination data to reflect the addition of occurrences of kidney infections in the year prior to the 1987 physical examination, and the verification of these three kidney conditions instead of the self-reported information.

In the longitudinal analysis, changes in blood urea nitrogen from Baseline to the 1987 examination were assessed for a relationship with serum dioxin. This variable was selected because it was judged that serial blood urea nitrogen levels would be more indicative of long-term renal health than the other variables. Furthermore, both examination measurements were made by the same brand and model of high-precision automated analyzer, permitting a more valid comparison.

Statistical Methods

Chapter 4, Statistical Methods, describes the basic statistical analysis methods used in the analysis of the renal data. Table 14-1 summarizes the statistical analyses performed for the assessment of the renal data. The first part of this table describes the dependent variables and identifies the candidate covariates and the statistical methods. The second part of the table provides additional information on the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Table 14-2 provides the number of participants excluded for a pre-SEA history of kidney disease and the number of participants with missing diabetic class status.

Diabetes was shown to have a significant association with dioxin (see Chapter 15, Endocrine Assessment). Therefore, health endpoints for the renal assessment may be associated with dioxin due to the association between dioxin and diabetes. Consequently, when diabetic class was retained in the final stepwise model for a particular analysis of a dependent variable, analyses also were performed without diabetic class in the model to

TABLE 14-1.

Statistical Analysis for the Renal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Kidney Disease	Q/PE-V	D	Yes No	AGE,RACE, DIAB	U:LR A:LR
Urinary Protein	LAB	D	Present Absent	AGE,RACE, DIAB	U:LR A:LR
Urinary Occult Blood (RBC/HPF)	LAB	D	Abnormal: ≥1 Normal: Absent	AGE,RACE, DIAB	U:LR A:LR
Urinary White Blood Cell Count (WBC/HPF)	LAB	D	Abnormal: >2 Normal: ≤2	AGE,RACE, DIAB	U:LR A:LR
Blood Urea Nitrogen (BUN)(mg/dl)	LAB	C	- -	AGE,RACE, DIAB	U:GLM A:GLM L:GLM
Urine Specific Gravity	LAB	C	- -	AGE,RACE, DIAB	U:GLM A:GLM

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Diabetic Class (DIAB)	LAB/Q/PE-V	D	Diabetic: past history or ≥200 mg/dl glucose Impaired: ≥140-<200 mg/dl glucose Normal: <140 mg/dl glucose

TABLE 14-1. (Continued)

Statistical Analysis for the Renal Assessment

Abbreviations

Data Source:	LAB--1987 SCRF laboratory results MIL--Air Force military records Q/PE-V--Questionnaire and physical examination (verified)
Data Form:	C--Continuous analysis only D--Discrete analysis only D/C--Appropriate form for analysis (either discrete or continuous)
Statistical Analyses:	U--Unadjusted analyses A--Adjusted analyses L--Longitudinal analyses
Statistical Methods:	GLM--General linear models analysis LR--Logistic regression analysis

TABLE 14-2.

Number of Participants Excluded and With Missing Data for the Renal Assessment

Variable	Variable Use	Assumption (Ranch Hands Only)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
Diabetic Class	COV	2	2	3	2
Pre-SEA Kidney Disease	EXC	18	24	23	28

COV--Covariate (missing data).
EXC--Exclusion.

investigate whether conclusions regarding the association between the health endpoint and dioxin differed. Summaries of these analyses are presented in Appendix Tables M-2 and M-3.

Three statistical models were used to examine the association between a dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour of duty in SEA. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (1). All three models were implemented with and without covariate adjustment. Chapter 4, Statistical Methods, provides a more detailed discussion of the models.

Appendix M-1 contains graphic displays of individual dependent variables versus initial dioxin for the minimal and maximal cohorts, and individual variables versus current dioxin for Ranch Hands and Comparisons. Appendix M-2 presents graphics for dioxin-by-covariate interactions as determined by various statistical models. Chapter 4 provides a guide to interpret the graphics.

RESULTS

Exposure Analysis

Questionnaire Variable

Kidney Disease

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analysis indicated that the relative frequency of Ranch Hands with a history of kidney disease was not associated significantly with initial dioxin (Table 14-3 [a] and [b]: p=0.942 and p=0.927, respectively).

In the adjusted analysis relating the history of kidney disease to initial dioxin, none of the covariates was retained; therefore, the unadjusted and adjusted results were the same.

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

Under both assumptions, the interaction of current dioxin and time since tour was not significant for the unadjusted analysis of history of kidney disease (Table 14-3 [e] and [f]: p=0.375 and p=0.910, respectively).

TABLE 14-3.

Analysis of Kidney Disease

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=503)	Low	123	11.4	0.99 (0.78,1.26)	0.942
	Medium	253	9.5		
	High	127	10.2		
b) Maximal (n=718)	Low	180	9.4	1.01 (0.85,1.20)	0.927
	Medium	356	10.7		
	High	182	9.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=503)	0.99 (0.78,1.26)	0.942	- -
d) Maximal (n=718)	1.01 (0.85,1.20)	0.927	- -

[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 14-3. (Continued)

Analysis of Kidney Disease

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

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.375[b]
(n=503)	≤18.6	15.2 (66)	8.9 (123)	9.4 (53)	0.89 (0.60,1.33)	0.572[c]
	>18.6	10.5 (57)	7.7 (130)	12.2 (74)	1.12 (0.82,1.53)	0.479[c]
f) Maximal						0.910[b]
(n=718)	≤18.6	8.7 (103)	11.8 (178)	8.5 (82)	1.01 (0.77,1.32)	0.961[c]
	>18.6	8.9 (79)	9.7 (175)	11.9 (101)	1.03 (0.81,1.31)	0.823[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*DIAB (p=0.004)
(n=501)	≤18.6	****	****	
	>18.6	****	****	
h) Maximal			0.910[b]	- -
(n=718)	≤18.6	1.01 (0.77,1.32)	0.961[c]	
	>18.6	1.03 (0.81,1.31)	0.823[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).

****Log_2 (current dioxin)-by-time-by-covariate interaction (p≤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.
CURR: Log_2 (current dioxin).
TIME: Time since tour.

TABLE 14-3. (Continued)

Analysis of Kidney Disease

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

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	758	9.2	All Categories		
					0.883
Unknown	333	10.2	Unknown vs. Background	1.12 (0.73,1.72)	0.614
Low	189	8.5	Low vs. Background	0.91 (0.52,1.60)	0.742
High	183	10.4	High vs. Background	1.14 (0.67,1.94)	0.634
Total	1,463				

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	758	All Categories			
				0.820	AGE (p=0.070)
Unknown	333	Unknown vs. Background	1.10 (0.72,1.70)	0.660	
Low	189	Low vs. Background	0.91 (0.52,1.61)	0.748	
High	183	High vs. Background	1.23 (0.72,2.12)	0.450	
Total	1,463				

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 kidney disease, there was a significant interaction among current dioxin, time, and diabetic class (Table 14-3 [g]: p=0.004). To investigate the interaction, the data were examined within each of the following diabetic class stratum: normal, impaired, and diabetic. For the impaired stratum, there was a marginally significant current dioxin-by-time interaction (Table M-1: p=0.063). The impaired stratum displayed a nonsignificant positive association (p=0.128) between history of kidney disease and current dioxin for time of 18.6 years or less and a nonsignificant negative association (p=0.252) for time more than 18.6 years. For the normal stratum and the diabetic stratum, the interactions of current dioxin and time were not significant (p=0.412 and p=0.113, respectively).

Under the maximal assumption, the adjusted analysis for presence of kidney disease did not retain any of the covariates in evaluating the current dioxin-by-time interaction. Therefore, the unadjusted and the adjusted analyses were the same.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted analyses comparing the relative frequencies of Ranch Hands and Comparisons with a history of kidney disease using the four current dioxin categories were not significant (Table 14-3 [i] and [j]: p=0.883 and p=0.820, respectively).

Laboratory Examination Variables

Urinary Protein

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analysis of the relative frequency of Ranch Hands with urinary protein present was not associated significantly with initial dioxin (Table 14-4 [a] and [b]: p=0.840 and p=0.984, respectively). For the minimal and the maximal cohorts, the adjusted analysis exhibited a nonsignificant association between the presence of urinary protein and initial dioxin (Table 14-4 [c] and [d]: p=0.664 and p=0.709, respectively). For both adjusted models, diabetic class was the only covariate that remained in the model after the stepwise procedure was implemented.

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

Under the minimal and maximal assumptions, the interaction of current dioxin and time since tour was not significant (Table 14-4 [e] and [f]: p=0.174 and p=0.625, respectively) for the unadjusted analysis of the presence of urinary protein. Under both assumptions, the adjusted analysis of the presence of urinary protein displayed nonsignificant interactions between current dioxin and time (Table 14-4 [g] and [h]: p=0.204 and p=0.657, respectively). Again, diabetic class was the only covariate retained in the adjusted models after the stepwise procedure was implemented.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted analysis of the relative frequency of Ranch Hands and Comparisons with urinary protein present, the simultaneous contrast of the four current dioxin categories was not significant (Table 14-4 [i]: p=0.889). In the adjusted analysis of the presence of urinary protein, the four current dioxin categories did not differ significantly (Table 14-4 [j]: p=0.930). The covariates of age, race, and diabetic class were included in the adjusted model.

TABLE 14-4.

Analysis of Urinary Protein

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Present	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	5.4	0.96 (0.68,1.36)	0.840
	Medium	260	4.6		
	High	131	3.8		
b) Maximal (n=742)	Low	185	5.4	1.00 (0.78,1.29)	0.984
	Medium	371	4.9		
	High	186	3.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	0.93 (0.66,1.31)	0.664	DIAB (p=0.084)
d) Maximal (n=740)	0.95 (0.74,1.23)	0.709	DIAB (p=0.035)

[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 14-4. (Continued)

Analysis of Urinary Protein

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

Assumption	Time (Yrs.)	Percent Present/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.174[b]
(n=521)	≤18.6	9.7 (72)	3.9 (128)	5.6 (54)	0.81 (0.47,1.39)	0.440[c]
	>18.6	1.7 (58)	3.8 (132)	3.9 (77)	1.32 (0.83,2.12)	0.245[c]
f) Maximal						0.625[b]
(n=742)	≤18.6	2.8 (106)	5.2 (191)	6.0 (83)	1.09 (0.75,1.58)	0.640[c]
	>18.6	5.1 (79)	5.0 (179)	2.9 (104)	0.96 (0.67,1.37)	0.826[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			0.204[b]	DIAB (p=0.089)
(n=519)	≤18.6	0.80 (0.47,1.35)	0.400[c]	
	>18.6	1.25 (0.79,1.98)	0.344[c]	
h) Maximal			0.657[b]	DIAB (p=0.036)
(n=740)	≤18.6	1.05 (0.72,1.52)	0.818[c]	
	>18.6	0.93 (0.65,1.32)	0.674[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 14-4. (Continued)

Analysis of Urinary Protein

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

Current Dioxin Category	n	Percent Present	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	5.0	All Categories		0.889
Unknown	345	4.1	Unknown vs. Background	0.81 (0.43,1.51)	0.509
Low	196	4.1	Low vs. Background	0.82 (0.37,1.77)	0.606
High	187	4.3	High vs. Background	0.86 (0.39,1.86)	0.695
Total	1,514				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.930	AGE (p=0.073)
Unknown	344	Unknown vs. Background	0.87 (0.46,1.63)	0.654	RACE (p=0.003)
Low	194	Low vs. Background	0.80 (0.37,1.76)	0.585	DIAB (p=0.066)
High	187	High vs. Background	0.88 (0.39,1.96)	0.748	
Total	1,509				

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.

Urinary Occult Blood

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

For the unadjusted analysis of the relative frequency of Ranch Hands with hematuria, the association with initial dioxin was not significant for the minimal assumption (Table 14-5 [a]: p=0.242). The unadjusted analysis under the maximal assumption exhibited a marginally significant positive association between urinary occult blood and initial dioxin (Table 14-5 [b]: p=0.059, Est. RR=1.20). Under this assumption, the relative frequencies of Ranch Hands with hematuria for the low, medium, and high initial dioxin categories were 4.9, 7.8, and 10.2 percent.

Under the minimal assumption, the adjusted analysis of urinary occult blood was not significant (Table 14-5 [c]: p=0.138). For the maximal assumption, the adjusted analysis displayed a significant association between urinary occult blood and initial dioxin (Table 14-5 [d]: p=0.047, Est. RR=1.22). Race was a significant covariate (p=0.001) that remained in the final adjusted model.

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

In the unadjusted analysis under the minimal assumption, the interaction between current dioxin and time since tour was not significant for urinary occult blood (Table 14-5 [e]: p=0.547). Under the maximal assumption, the unadjusted analysis of hematuria also contained a nonsignificant interaction between current dioxin and time (Table 14-5 [f]: p=0.482). There was a marginally significant positive association of hematuria with current dioxin when time exceeded 18.6 years (p=0.082, Est. RR=1.23). Within this stratum, the relative frequencies of Ranch Hands with hematuria for low, medium, and high current dioxin were 3.8, 10.6, and 10.6 percent.

Under the minimal assumption, the adjusted analysis of urinary occult blood exhibited a nonsignificant interaction between current dioxin and time (Table 14-5 [g]: p=0.421). This adjusted model contained a significant interaction between race and diabetic class (p=0.028).

Under the maximal assumption, the interaction of current dioxin and time was not significant in the adjusted analysis of urinary occult blood (Table 14-5 [h]: p=0.525). However, there was a positive association between urinary occult blood and current dioxin for time more than 18.6 years that was marginally significant (p=0.076, Est. RR=1.24).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the relative frequencies of Ranch Hands and Comparisons with hematuria, the four current dioxin categories did not differ significantly (Table 14-5 [i]: p=0.484).

The homogeneity of the relative frequencies of urinary occult blood among the four current dioxin categories also was investigated using an adjusted model that contained a significant interaction between diabetic class and categorized current dioxin (Table 14-5 [j]: p=0.046). To investigate the interaction, results for each diabetic class stratum were examined separately. For the impaired stratum, there was a marginally significant difference with respect to urinary occult blood among the four current dioxin categories (Appendix Table

TABLE 14-5.

Analysis of Urinary Occult Blood

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=521)	Low	130	5.4	1.16 (0.91,1.47)	0.242
	Medium	260	10.4		
	High	131	8.4		
b) Maximal (n=742)	Low	185	4.9	1.20 (1.00,1.44)	0.059
	Medium	371	7.8		
	High	186	10.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.22 (0.94,1.57)	0.138	RACE*DIAB (p=0.030)
d) Maximal (n=742)	1.22 (1.01,1.47)	0.047	RACE (p=0.001)

[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 14-5. (Continued)

Analysis of Urinary Occult Blood

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						0.547[b]
(n=521)	≤18.6	4.2 (72)	7.0 (128)	5.6 (54)	1.23 (0.77,1.94)	0.385[c]
	>18.6	8.6 (58)	12.9 (132)	10.4 (77)	1.04 (0.77,1.39)	0.819[c]
f) Maximal						0.482[b]
(n=742)	≤18.6	5.7 (106)	6.8 (191)	6.0 (83)	1.07 (0.77,1.48)	0.700[c]
	>18.6	3.8 (79)	10.6 (179)	10.6 (104)	1.23 (0.97,1.55)	0.082[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			0.421[b]	RACE*DIAB (p=0.028)
(n=519)	≤18.6	1.32 (0.83,2.10)	0.238[c]	
	>18.6	1.05 (0.76,1.44)	0.765[c]	
h) Maximal			0.525[b]	RACE (p=0.002)
(n=742)	≤18.6	1.09 (0.78,1.52)	0.620[c]	
	>18.6	1.24 (0.98,1.58)	0.076[c]	

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

TABLE 14-5. (Continued)

Analysis of Urinary Occult Blood

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	7.8	All Categories		0.484
Unknown	345	7.0	Unknown vs. Background	0.89 (0.54,1.45)	0.637
Low	196	10.7	Low vs. Background	1.43 (0.85,2.41)	0.183
High	187	8.6	High vs. Background	1.11 (0.63,1.98)	0.717
Total	1,514				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.521**	DXCAT*DIAB (p=0.046) RACE (p=0.006)
Unknown	344	Unknown vs. Background	0.92 (0.56,1.50)**	0.738**	
Low	194	Low vs. Background	1.43 (0.84,2.41)**	0.184**	
High	187	High vs. Background	1.14 (0.64,2.03)**	0.659**	
Total	1,509				

**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.
DXCAT: Categorized current dioxin.

M-1: p=0.069); the unknown versus background contrast was marginally significant (p=0.093, Est. RR=3.23). For the other two strata, neither the overall contrast nor the individual contrasts were significant. Without the interaction included in the adjusted model, the overall contrast of the four current dioxin categories was not significant with respect to the frequency of hematuria (Table 14-5 [j]: p=0.521).

Urinary White Blood Cell Count

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analysis of the percent of Ranch Hands with abnormal urinary white blood cell counts displayed a nonsignificant association with initial dioxin (Table 14-6 [a] and [b]: p=0.786 and p=0.343, respectively).

Under the minimal assumption, the adjusted analysis of urinary white blood cell count exhibited a significant interaction between initial dioxin and age (Table 14-6 [c]: p=0.025). The results were investigated separately for Ranch Hands born in or after 1942 and Ranch Hands born before 1942. For the younger Ranch Hands, there was a marginally significant positive association between initial dioxin and urinary white blood cell count (Appendix Table M-1: p=0.075, Est. RR=1.40). The percentages of younger Ranch Hands with abnormal urinary white blood cell counts were 7.0, 7.2, and 8.4 percent for low, medium, and high initial dioxin. For the older Ranch Hands, a nonsignificant negative association was found (p=0.307). In a secondary model, without the initial dioxin-by-age interaction, the association between initial dioxin and urinary white blood cell count was not significant (Table 14-6 [c]: p=0.592).

Under the maximal assumption, the adjusted analysis contained a significant interaction between initial dioxin and diabetic class (Table 14-6 [d]: p=0.034). To investigate this interaction, the association between urinary white blood cell count was examined for Ranch Hands within each diabetic class category: normal, impaired, and diabetic. For Ranch Hands classified as normal, there was a marginally significant positive association (Appendix Table M-1: p=0.070, Adj. RR=1.26). For Ranch Hands categorized as impaired on diabetic class, there was a marginally significant negative association (Appendix Table M-1: p=0.075, Adj. RR=0.53). For Ranch Hands classified as diabetic, there was a positive, but nonsignificant, association between initial dioxin and urinary white blood cell count (p=0.928). The percentages of Ranch Hands in the normal diabetic class who had abnormal urinary white blood cell counts were 4.7, 5.2, and 9.4 percent for low, medium, and high initial dioxin. The corresponding percentages in the impaired diabetic class were 15.4, 7.0, and 3.7 percent, respectively. An adjusted model, without the interaction of initial dioxin and diabetic class, displayed a nonsignificant association between urinary white blood cell count and initial dioxin (Table 14-6 [d]: p=0.500).

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

In the unadjusted analysis of urinary white blood cell count, the interaction of current dioxin and time since tour was not significant for the minimal and maximal cohorts (Table 14-6 [e] and [f]: p=0.323 and p=0.326, respectively). Under the maximal assumption, Ranch Hands with time more than 18.6 years exhibited a marginally significant positive association (p=0.087, Est. RR=1.27). Within this stratum, the relative frequencies of Ranch Hands who

TABLE 14-6.

Analysis of Urinary White Blood Cell Count

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=521)	Low	130	10.8	1.04 (0.80,1.34)	0.786
	Medium	260	6.9		
	High	131	7.6		
b) Maximal (n=742)	Low	185	6.0	1.10 (0.91,1.34)	0.343
	Medium	371	6.7		
	High	186	9.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.08 (0.82,1.41)**	0.592**	INIT*AGE (p=0.025) RACE (p=0.065)
d) Maximal (n=740)	1.07 (0.88,1.31)**	0.500**	INIT*DIAB (p=0.034) RACE (p=0.055)

[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.
INIT: Log_2 (initial dioxin).

TABLE 14-6. (Continued)

Analysis of Urinary White Blood Cell Count

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						0.323[b]
(n=521)	≤18.6	15.3 (72)	4.7 (128)	11.1 (54)	0.92 (0.60,1.39)	0.680[c]
	>18.6	5.2 (58)	7.6 (132)	7.8 (77)	1.20 (0.85,1.69)	0.295[c]
f) Maximal						0.326[b]
(n=742)	≤18.6	7.6 (106)	8.4 (191)	8.4 (83)	1.04 (0.78,1.40)	0.789[c]
	>18.6	2.5 (79)	6.7 (179)	7.7 (104)	1.27 (0.97,1.68)	0.087[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			0.383**[b]	CURR*TIME*RACE (p=0.034)
(n=519)	≤18.6	0.93 (0.61,1.41)**	0.732**[c]	DIAB (p=0.139)
	>18.6	1.18 (0.84,1.67)**	0.348**[c]	
h) Maximal			0.346[b]	RACE (p=0.060)
(n=740)	≤18.6	1.02 (0.76,1.38)	0.877[c]	DIAB (p=0.086)
	>18.6	1.25 (0.94,1.65)	0.123[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).

**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 14-6. (Continued)

Analysis of Urinary White Blood Cell Count

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	6.4	All Categories		0.653
Unknown	345	5.2	Unknown vs. Background	0.81 (0.47,1.41)	0.457
Low	196	6.6	Low vs. Background	1.05 (0.56,1.97)	0.890
High	187	8.0	High vs. Background	1.28 (0.70,2.34)	0.415
Total	1,514				

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

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.668	RACE (p=0.088)
Unknown	345	Unknown vs. Background	0.83 (0.48,1.44)	0.506	
Low	196	Low vs. Background	1.04 (0.56,1.97)	0.893	
High	187	High vs. Background	1.30 (0.71,2.38)	0.387	
Total	1,514				

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

had abnormal urinary white blood cell counts were 2.5, 6.7, and 7.7 percent for low, medium, and high current dioxin.

Under the minimal assumption, the adjusted analysis contained a significant interaction among current dioxin, time, and race (Table 14-6 [g]: p=0.034). Investigation of the interaction showed that, among Black Ranch Hands, the adjusted relative risks for the two time strata differed marginally (Appendix Table M-1: p=0.063). For Black Ranch Hands with time of 18.6 years or less, a nonsignificant negative association was found between urinary white blood cell count and current dioxin (p=0.293). For Black Ranch Hands with time more than 18.6 years, a nonsignificant positive association was found (p=0.462). For non-Black Ranch Hands, the adjusted relative risks did not differ significantly between time strata (p=0.711). After excluding the interaction of current dioxin, time, and race from the adjusted model, the interaction of current dioxin and time was not significant (Table 14-6 [g]: p=0.383).

Because dioxin may affect diabetic status, an additional adjusted analysis without diabetic class was performed for the minimal cohort. In that adjusted model, the interaction of current dioxin, time, and race also was significant (Appendix Table M-2 for models without adjustment for diabetic class: p=0.033). The results from this model subsequently were examined separately for Black and non-Black Ranch Hands. For Black Ranch Hands, the interaction of current dioxin and time became significant (Appendix Table M-3 for interactions without adjustment for diabetic class: p=0.024). For Black Ranch Hands with time of 18.6 years or less, a nonsignificant negative association was found between urinary white blood cell count and current dioxin (p=0.216). For Black Ranch Hands with time more than 18.6 years, a nonsignificant positive association was found (p=0.307). For non-Black Ranch Hands, the current dioxin-by-time interaction was not significant (p=0.633). Excluding the interaction of current dioxin, time, and race from the analysis resulted in a nonsignificant interaction between current dioxin and time (see Appendix Table M-2 for data analyses without adjustment for diabetic class: p=0.345).

In the adjusted analysis under the maximal assumption, the interaction of current dioxin and time was not significant (Table 14-6 [h]: p=0.346) for the analysis of urinary white blood cell count. Because dioxin may influence diabetic status, an adjusted model without diabetic class also was used. The adjusted relative risks for that model did not differ significantly between time strata (Appendix Table M-2 for data analyses without adjustment for diabetic class: p=0.342). Under this assumption, the Ranch Hands with time more than 18.6 years exhibited a positive association of borderline significance (p=0.083, Adj. RR=1.28) between urinary white blood cell count and current dioxin.

As was the case for kidney disease, both the unadjusted and the adjusted analyses exhibited larger relative risks for Ranch Hands with earlier tours (time>18.6 years) than Ranch Hands with later tours (time≤18.6 years). In general, these relative risks were nonsignificant.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the unadjusted and adjusted analyses, the simultaneous contrast of the four current dioxin categories indicated that Ranch Hands and Comparisons did not differ significantly on

the presence of abnormal urinary white blood cell count (Table 14-6 [i] and [j]: p=0.653 and p=0.668, respectively).

Blood Urea Nitrogen

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted analysis of blood urea nitrogen exhibited a marginally significant negative association with initial dioxin (Table 14-7 [a]: p=0.067). The blood urea nitrogen means for the low, medium, and high initial dioxin categories were 15.1, 14.3, and 14.3 mg/dl.

The unadjusted analysis under the maximal assumption displayed a significant negative association between blood urea nitrogen and initial dioxin (Table 14-7 [b]: p=0.022). For the initial dioxin categories, the mean levels of blood urea nitrogen were 15.0, 14.4, and 14.6 mg/dl.

Under the minimal and maximal assumptions, the adjusted models contained the covariates of age and race. After adjusting for these covariates, the association between blood urea nitrogen and initial dioxin was not significant (Table 14-7 [c] and [d]: p=0.209 and p=0.154, respectively).

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

Under the minimal assumption, the unadjusted analysis of blood urea nitrogen indicated that the interaction of current dioxin and time since tour was not significant (Table 14-7 [e]: p=0.214); thus, the association between current dioxin and blood urea nitrogen did not differ significantly between time strata. For time of 18.6 years or less, there was a marginally significant negative association between blood urea nitrogen and current dioxin (p=0.070). For low, medium, and high initial dioxin, the means for blood urea nitrogen were 15.5, 14.5, and 14.6 mg/dl within this time stratum.

For the maximal assumption, the current dioxin-by-time interaction also was nonsignificant (Table 14-7 [f]: p=0.538). A significant negative association between current dioxin and blood urea nitrogen existed; however, it occurred in the stratum with time more than 18.6 years (p=0.035). For that time stratum, the blood urea nitrogen means were 15.8, 14.0, and 14.2 mg/dl.

For the adjusted analysis of blood urea nitrogen under the minimal assumption, the interaction of current dioxin and time was not significant (Table 14-7 [g]: p=0.233).

Under the maximal assumption, the adjusted analysis contained a significant interaction between current dioxin, time, and diabetic class (Table 14-7 [h]: p=0.037). To explore the interaction, analyses were performed separately for each diabetic class category. For Ranch Hands classified as normal, the current dioxin-by-time interaction was marginally significant (Appendix Table M-1: p=0.052). For this stratum, there was a significant negative association between blood urea nitrogen and current dioxin for the more than 18.6 years stratum (Appendix Table M-1: p=0.039) and a nonsignificant positive association for the other time stratum (p=0.501). The other diabetic class strata exhibited nonsignificant current

TABLE 14-7.

Analysis of Blood Urea Nitrogen (mg/dl)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	15.1	-0.030 (0.016)	0.067
(n=521)	Medium	260	14.3		
(R^2=0.006)	High	131	14.3		
b) Maximal	Low	185	15.0	-0.028 (0.012)	0.022
(n=742)	Medium	371	14.4		
(R^2=0.007)	High	186	14.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	14.4	-0.021 (0.017)	0.209	AGE (p=0.002)
(n=521)	Medium	260	13.6			RACE (p=0.016)
(R^2=0.039)	High	131	13.8			
d) Maximal	Low	185	14.2	-0.017 (0.012)	0.154	AGE (p<0.001)
(n=742)	Medium	371	13.9			RACE (p=0.007)
(R^2=0.046)	High	186	13.9			

[a]Transformed from square root scale.

[b]Slope and standard error based on square root blood urea nitrogen 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 14-7. (Continued)

Analysis of Blood Urea Nitrogen (mg/dl)

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						0.214[c]
(n=521)	≤18.6	15.5	14.5	14.6	-0.048 (0.027)	0.070[d]
(R^2=0.014)		(72)	(128)	(54)		
	>18.6	14.3	14.2	14.2	-0.006 (0.022)	0.800[d]
		(58)	(132)	(77)		
f) Maximal						0.538[c]
(n=742)	≤18.6	14.5	15.0	14.6	-0.020 (0.019)	0.296[d]
(R^2=0.009)		(106)	(191)	(83)		
	>18.6	15.8	14.0	14.2	-0.035 (0.017)	0.035[d]
		(79)	(179)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.233[c]	AGE (p=0.024)
(n=521)	≤18.6	14.8	14.0	14.3	-0.030 (0.027)	0.272[d]	RACE (p<0.001)
(R^2=0.051)		(72)	(128)	(54)			
	>18.6	13.4	13.5	13.6	0.011 (0.022)	0.630[d]	
		(58)	(132)	(77)			
h) Maximal						0.560**[c]	CURR*TIME*DIAB
(n=740)	≤18.6	13.9**	14.5**	14.2**	-0.004 (0.019)**	0.830**[d]	(p=0.037)
(R^2=0.062)		(106)	(190)	(83)			AGE (p<0.001)
	>18.6	14.8**	13.2**	13.9**	-0.018 (0.017)**	0.271**[d]	RACE (p=0.009)
		(79)	(178)	(104)			

[a]Transformed from square root scale.

[b]Slope and standard error based on square root blood urea nitrogen versus log_2 dioxin.

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

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

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slopes, standard error, and p-value derived from a model 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 14-7. (Continued)

Analysis of Blood Urea Nitrogen (mg/dl)

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	786	14.7	All Categories		0.443
Unknown	345	14.6	Unknown vs. Background	-0.1 --	0.668
Low	196	14.3	Low vs. Background	-0.4 --	0.162
High	187	14.4	High vs. Background	-0.3 --	0.269
Total	1,514		(R^2=0.002)		

j) Ranch Hands and Comparisons - 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	784	13.9	All Categories		0.495	AGE (p<0.001) RACE*DIAB
Unknown	344	13.7	Unknown vs. Background	-0.2 --	0.444	(p=0.025)
Low	194	13.5	Low vs. Background	-0.4 --	0.138	
High	187	13.8	High vs. Background	-0.1 --	0.821	
Total	1,509		(R^2=0.040)			

[a]Transformed from square root scale.

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

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

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

dioxin-by-time interactions (impaired, p=0.115; diabetic, p=0.344). An analysis also was performed that excluded the current dioxin-by-time-by-diabetic class interaction from the model. This secondary analysis indicated that the interaction of current dioxin and time was not significant (Table 14-7 [h]: p=0.560).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted and adjusted analyses, the simultaneous contrast of the four current dioxin categories indicated that Ranch Hands and Comparisons did not differ significantly on their mean levels of blood urea nitrogen (Table 14-7 [i] and [j]: p=0.443 and p=0.495, respectively). For the adjusted analysis, age and a race-by-diabetic class interaction were retained in the model. Pairwise contrasts also were nonsignificant.

Urine Specific Gravity

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analyses exhibited nonsignificant associations between urine specific gravity and initial dioxin (Table 14-8 [a] and [b]: p=0.419 and p=0.217, respectively).

Under the minimal assumption, the adjusted model indicated that the association between urine specific gravity and initial dioxin was not significant (Table 14-8 [c]: p=0.835). In the adjusted analysis under the maximal assumption, there was a significant interaction between initial dioxin and race (Table 14-8 [d]: p=0.046). To explore the interaction, the association between urine specific gravity and initial dioxin was investigated for each race category. For Blacks, there was a negative association between urine specific gravity and initial dioxin that was marginally significant (Appendix Table M-1: p=0.063). The urine specific gravity means for low, medium, and high initial dioxin within this stratum were 1.0234, 1.0205, and 1.0163. The positive association for the non-Black stratum was not significant (p=0.326). An adjusted model without the interaction of initial dioxin and race indicated that the association between initial dioxin and urine specific gravity was not significant (Table 14-8 [d]: p=0.524).

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

Under the minimal and maximal assumptions, the unadjusted analysis of urine specific gravity displayed nonsignificant interactions between current dioxin and time since tour (Table 14-8 [e] and [f]: p=0.444 and p=0.437, respectively).

Under the minimal assumption, the adjusted analysis of urine specific gravity contained a significant interaction among current dioxin, time, and age (Table 14-8 [g]: p=0.013). The interaction was investigated separately for Ranch Hands born in or after 1942 and those born prior to 1942. For the older Ranch Hands, there was a marginally significant interaction between current dioxin and time (Appendix Table M-1: p=0.053). A nonsignificant positive association between urine specific gravity and current dioxin was found in the older Ranch Hands with time of 18.6 years or less (p=0.125), and a nonsignificant negative association was found for older Ranch Hands with time more than 18.6 years (p=0.237). For the younger Ranch Hands, the current dioxin-by-time interaction was not significant (p=0.645). Without

TABLE 14-8.

Analysis of Urine Specific Gravity

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	130	1.0198	0.0002 (0.0002)	0.419
(n=521)	Medium	260	1.0201		
(R^2=0.001)	High	131	1.0207		
b) Maximal	Low	185	1.0199	0.0002 (0.0002)	0.217
(n=742)	Medium	371	1.0200		
(R^2=0.002)	High	186	1.0202		

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	130	1.0199	<0.0001 (0.0002)	0.835	AGE (p=0.016)
(n=521)	Medium	260	1.0201			
(R^2=0.012)	High	131	1.0205			
d) Maximal	Low	185	1.0199**	0.0001 (0.0002)**	0.524**	INIT*RACE (p=0.046)
(n=742)	Medium	371	1.0201**			AGE (p=0.008)
(R^2=0.019)	High	186	1.0200**			

[a]Slope and standard error based on urine specific gravity 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 14-8. (Continued)

Analysis of Urine Specific Gravity

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						0.444[b]
(n=521)	≤18.6	1.0195	1.0203	1.0212	0.0004 (0.0003)	0.250[c]
(R^2=0.003)		(72)	(128)	(54)		
	>18.6	1.0198	1.0200	1.0205	<0.0001 (0.0003)	0.843[c]
		(58)	(132)	(77)		
f) Maximal						0.437[b]
(n=742)	≤18.6	1.0200	1.0200	1.0206	0.0003 (0.0002)	0.170[c]
(R^2=0.003)		(106)	(191)	(83)		
	>18.6	1.0201	1.0200	1.0203	<0.0001 (0.0002)	0.703[c]
		(79)	(179)	(104)		

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						0.497**[b]	CURR*TIME*AGE
(n=521)	≤18.6	1.0196**	1.0202**	1.0208**	0.0002 (0.0003)**	0.574**[c]	(p=0.013)
(R^2=0.025)		(72)	(128)	(54)			
	>18.6	1.0201**	1.0201**	1.0204**	-0.0001 (0.0003)**	0.723**[c]	
		(58)	(132)	(77)			
h) Maximal						0.441**[b]	CURR*TIME*AGE
(n=742)	≤18.6	1.0196**	1.0200**	1.0202**	0.0002 (0.0002)**	0.425**[c]	(p=0.025)
(R^2=0.014)		(106)	(191)	(83)			
	>18.6	1.0204**	1.0199**	1.0202**	-0.0005 (0.0002)**	0.813**[c]	
		(79)	(179)	(104)			

[a]Slope and standard error based on urine specific gravity 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).

**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 14-8. (Continued)

Analysis of Urine Specific Gravity

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	786	1.0200	All Categories		0.518
Unknown	345	1.0197	Unknown vs. Background	-0.0004 (-0.0011,0.0004)	0.363
Low	196	1.0201	Low vs. Background	0.0001 (-0.0009,0.0010)	0.911
High	187	1.0205	High vs. Background	0.0005 (-0.0005,0.0014)	0.351
Total	1,514		(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	786	1.0206	All Categories		0.797	AGE (p=0.003) RACE (p=0.062)
Unknown	345	1.0204	Unknown vs. Background	-0.0003 (-0.0010,0.0005)	0.479	
Low	196	1.0207	Low vs. Background	0.00004 (-0.0009,0.0009)	0.934	
High	187	1.0209	High vs. Background	0.0003 (-0.0007,0.0012)	0.608	
Total	1,514		(R^2=0.010)			

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 interaction of current dioxin, time, and age in the model, the adjusted model contained a nonsignificant interaction between current dioxin and time (Table 14-8 [g]: p=0.497).

Under the maximal assumption, the adjusted analysis of urine specific gravity also contained a significant interaction among current dioxin, time, and age (Table 14-8 [h]: p=0.025). Because of the interaction with age, the association between urine specific gravity and current dioxin was investigated separately for Ranch Hands born in or after 1942 and those born before 1942. The adjusted analysis of urine specific gravity for the older group of Ranch Hands displayed a significant interaction between current dioxin and time (Appendix Table M-1: p=0.046). For the younger group of Ranch Hands, the current dioxin-by-time interaction was not significant (p=0.540). For older Ranch Hands with time of 18.6 years or less, there was a nonsignificant positive association (p=0.111) between urine specific gravity and current dioxin; for older Ranch Hands with time more than 18.6 years there was a nonsignificant negative association (p=0.226). Without the interaction of current dioxin, time, and age, the adjusted model contained a nonsignificant interaction between current dioxin and time (p=0.441).

In the unadjusted and adjusted analyses, the slopes for the association between urine specific gravity and current dioxin of Ranch Hands with later tours (time≤18.6 years) exceeded the slopes for Ranch Hands with earlier tours (time>18.6 years). However, the slopes of the time strata were nonsignificant.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted analyses indicated that the means for urine specific gravity did not differ significantly for Ranch Hands and Comparisons (Table 14-8 [i] and [j]: p=0.518 and p=0.797, respectively).

Longitudinal Analysis

Laboratory Examination Variable

Blood Urea Nitrogen

In the renal assessment, longitudinal differences in blood urea nitrogen between the 1982 and 1987 examinations were evaluated (without adjustment for covariates) using initial dioxin, current dioxin and time since tour, and categorized current dioxin. Table 14-9 summarizes the results of analyses relating the longitudinal differences to each of the three measures of dioxin.

The left side of each subpanel of a table provides the means and sample sizes for participants with blood urea nitrogen values at each examination. Based on the difference between 1987 blood urea nitrogen and 1982 blood urea nitrogen, the right size of each subpanel presents slopes, standard errors, and associated p-values (for models using initial dioxin or models using current dioxin and time since tour), or differences of examination mean changes, 95 percent confidence intervals, and associated p-values (for models using categorized current dioxin). The reported statistics are presented subject to the constraint that participants were compliant at both the 1982 and 1987 examinations.

TABLE 14-9.

Longitudinal Analysis of Blood Urea Nitrogen (mg/dl)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Mean[a]/(n) Examination 1982	1985	1987	Slope (Std. Error)[b]	p-Value
a) Minimal (R^2=0.004)	Low	13.9 (124)	15.0 (122)	15.1 (124)	-0.028 (0.021)	0.185
	Medium	13.5 (255)	14.1 (250)	14.3 (255)		
	High	14.0 (125)	13.9 (124)	14.3 (125)		
b) Maximal (R^2=0.003)	Low	13.8 (171)	14.6 (168)	14.8 (171)	-0.023 (0.014)	0.118
	Medium	13.7 (359)	14.3 (352)	14.6 (359)		
	High	13.8 (179)	14.1 (177)	14.3 (179)		

[a]Transformed from square root scale.

[b]Slope and standard error based on difference between square root of 1987 blood urea nitrogen and square root of 1982 blood urea nitrogen versus log_2 dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 14-9. (Continued)

Longitudinal Analysis of Blood Urea Nitrogen (mg/dl)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
c) Minimal (R^2=0.004)	≤18.6	1982	14.3 (69)	13.5 (125)	13.9 (52)	-0.023 (0.034)	0.931[c] 0.491[d]
		1985	15.3 (68)	14.1 (122)	14.2 (51)		
		1987	15.5 (69)	14.5 (125)	14.6 (52)		
	>18.6	1982	13.2 (55)	13.4 (130)	14.2 (73)	-0.019 (0.028)	0.483[d]
		1985	14.1 (54)	14.1 (128)	13.8 (73)		
		1987	14.3 (55)	14.2 (130)	14.1 (73)		
d) Maximal (R^2=0.005)	≤18.6	1982	13.5 (95)	14.1 (185)	13.5 (80)	-0.007 (0.022)	0.344[c] 0.760[d]
		1985	14.6 (92)	14.8 (181)	14.0 (79)		
		1987	14.3 (95)	15.0 (185)	14.4 (80)		
	>18.6	1982	14.1 (76)	13.2 (173)	14.1 (100)	-0.035 (0.020)	0.075[d]
		1985	14.5 (75)	14.0 (171)	14.0 (99)		
		1987	15.8 (76)	14.0 (173)	14.3 (100)		

[a]Transformed from square root scale.

[b]Slope and standard error based on difference between square root of 1987 blood urea nitrogen and square root of 1982 blood urea nitrogen versus log_2 dioxin.

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

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

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 14-9. (Continued)

Longitudinal Analysis of Blood Urea Nitrogen (mg/dl)

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Mean[a]/(n) Examination 1982	1985	1987	Contrast	Difference of Examination Mean Change (95% C.I.)[d]	p-Value[e]
Background	13.8 (685)	14.4 (681)	14.7 (685)	All Categories		0.856
Unknown	13.7 (317)	14.4 (311)	14.5 (317)	Unknown vs. Background	-0.02 --	0.948
Low	13.5 (192)	14.1 (189)	14.3 (192)	Low vs. Background	-0.05 --	0.891
High	13.8 (180)	14.0 (178)	14.4 (180)	High vs. Background	-0.27 --	0.387
	(R^2=0.001)					

[a]Transformed from square root scale.

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

[e]P-value is based on difference of 1987 and 1982 examination mean changes on square root scale.

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

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the association between the change in blood urea nitrogen (as measured by the difference from the 1987 examination value relative to the 1982 Baseline examination value) decreased with initial dioxin. However, both associations were nonsignificant (Table 14-9 [a] and [b]: p=0.185 and p=0.118, respectively).

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

Under the minimal and maximal assumptions, the analysis of the change in blood urea nitrogen between 1982 and 1987 exhibited nonsignificant interactions between current dioxin and time since tour (Table 14-9 [c] and [d]: p=0.931 and p=0.344, respectively). For Ranch Hands having early tours (time greater than 18.6 years), there was a marginally significant negative association between the change in blood urea nitrogen values (1987 relative to 1982) with current dioxin (Table 14-9 [d]: p=0.075) under the maximal assumption.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The change in blood urea nitrogen between the 1982 and 1987 examinations was not significantly different among the four curent dioxin categories (Table 14-9 [e]: p=0.856).

DISCUSSION

In clinical practice, the presence of renal or urinary tract disease can be determined with confidence based on the medical history, physical examination, and the five laboratory indices included in the current analysis.

Though subject to some day-to-day variation related to diet and state of hydration, blood urea nitrogen is considered a reliable index of glomerular filtration, while the integrity and concentrating ability of the renal tubular system are reflected in the urinary specific gravity. In documenting the presence of red or white blood cells in significant numbers, the examination of the urinary sediment can provide valuable clues to the presence of a broad range of infectious, inflammatory, and neoplastic conditions intrinsic to the upper and lower urinary tracts.

Pertinent to the interpretation of the renal assessment data and to the dioxin-by-covariate interactions noted below is the frequent finding in ambulatory medicine of isolated abnormalities in the routine urinalysis of healthy individuals who in fact have no disease of the genitourinary system. With normal fluid balance, the healthy kidneys can excrete up to 100 mg to 150 mg of total protein in 24 hours. The qualitative dipstick test used in the current study is sensitive to protein concentrations as low as 10 mg to 15 mg per deciliter and, particularly in specimens collected after overnight fasting, will often give a trace to 1+ positive reaction in the absence of parenchymal renal disease.

Similarly, on microscopic examination of the urinary sediment, it is not unusual to find a few red or white blood cells in the absence of definable neoplastic or inflammatory cause, trauma, or renal calculi. When documented as an isolated finding in the absence of symptoms or other signs, such intermittent microcyturia usually can be considered benign and safely followed over time.

With reference to the current assessment, in only one of the six renal variables analyzed was there any evidence suggesting of an abnormality that might be explained on the basis of prior dioxin exposure. Under the maximal (but not the minimal) assumption, 10.2 percent of those participants with high (>218 ppt) extrapolated initial serum dioxin levels were found to have hematuria versus 4.9 percent of those with low (25 ppt to 57 ppt) levels. Further, the possibility of a temporal effect is raised inasmuch as the marginally significantly increased incidence of hematuria was limited to those participants most removed (>18.6 years) from service in SEA. Though in clinical practice, most cases of hematuria are of benign origin, the possibility of clinically relevant disease will bear close scrutiny in future examination cycles.

Findings in several subgroup analyses, as presented in the summary of the dioxin-by-covariate interactions, were consistent with a dose-response effect, although a causal relationship would be difficult to explain clinically. For example, in younger (born in or after 1942) Ranch Hand participants a marginally significantly increased incidence of pyuria was related to initial serum dioxin levels, whereas the opposite effect occurred in Ranch Hands born before 1942.

In diabetics, too, results were inconsistent with any health detriment related to dioxin exposure. Ranch Hand participants with mild glucose intolerance and high current serum dioxin levels had a greater incidence of hematuria than Comparisons, but the opposite trend was noted in those with more severe diabetes. Similarly, in nondiabetics, there was an increasing incidence of pyuria related to initial dioxin but directionally opposite effects associated with mild and more severe glucose intolerance.

In summary, with the possible exception of hematuria noted above, the data analyzed in the renal assessment revealed no consistent evidence of any health detriment related to the current body burden of dioxin or to the estimated severity of prior exposure.

SUMMARY

In the renal assessment, six variables were evaluated for an association with serum dioxin levels. Tables 14-10, 14-11, and 14-12 provide the results of analyses based on initial dioxin in Ranch Hands, current dioxin and time since tour in Ranch Hands, and Ranch Hands and Comparisons by current dioxin category.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses based on the minimal assumption, Table 14-10 shows that none of the relationships between initial dioxin and the individual variables was significant, although there was a marginally significant negative association between blood urea nitrogen and initial dioxin. Under the maximal assumption, the unadjusted analyses exhibited a significant negative association between blood urea nitrogen and initial dioxin ($p=0.022$), and a marginally significant positive association for urinary occult blood. The other four dependent variables of the renal assessment exhibited nonsignificant associations with initial dioxin.

The adjusted analyses under the minimal assumption exhibited no significant associations between a dependent variable and initial dioxin. However, the adjusted analysis for urinary white blood cell count contained a significant interaction between initial

TABLE 14-10.

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

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Kidney Disease (D)	ns	NS	ns	NS
Laboratory				
Urinary Protein (D)	ns	NS	ns	ns
Urinary Occult Blood (D)	NS	NS*	NS	+0.047
Urinary White Blood Cell Count (D)	NS	NS	** (NS)	** (NS)
Blood Urea Nitrogen (C)	ns*	-0.022	ns	ns
Urine Specific Gravity[a] (C)	NS	NS	NS	** (NS)

[a]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater.
-: Negative slope.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table M-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

TABLE 14-11.

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

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Kidney Disease (D)	NS	ns	NS	NS	NS	NS
Laboratory						
Urinary Protein (D)	NS	ns	NS	ns	NS	ns
Urinary Occult Blood (D)	ns	NS	NS	NS	NS	NS*
Urinary White Blood Cell Count (D)	NS	ns	NS	NS	NS	NS*
Blood Urea Nitrogen (C)	NS	ns*	ns	ns	ns	-0.035
Urine Specific Gravity[a] (C)	ns	NS	NS	ns	NS	NS

[a]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
-: Negative slope.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

TABLE 14-11. (Continued)

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

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Kidney Disease (D)	****	****	****	NS	NS	NS
Laboratory						
Urinary Protein (D)	NS	ns	NS	ns	NS	ns
Urinary Occult Blood (D)	ns	NS	NS	NS	NS	NS*
Urinary White Blood Cell Count (D)	** (NS)	** (ns)	** (NS)	NS	NS	NS
Blood Urea Nitrogen (C)	NS	ns	NS	** (ns)	** (ns)	** (ns)
Urine Specific Gravity[a] (C)	** (ns)	** (NS)	** (ns)	** (ns)	** (NS)	** (ns)

[a]Negative slope considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
NS/ns: Not significant ($p>0.10$).
NS*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table M-1 for a detailed description of this interaction.
****Log_2 (current dioxin)-by-time-by-covariate interaction ($p\leq0.01$); refer to Appendix Table M-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour more than 18.6 years.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

TABLE 14-12.

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

Variable	All	Unadjusted: Unknown versus Background	Unadjusted: Low versus Background	Unadjusted: High versus Background
Questionnaire				
Kidney Disease (D)	NS	NS	ns	NS
Laboratory				
Urinary Protein (D)	NS	ns	ns	ns
Urinary Occult Blood (D)	NS	ns	NS	NS
Urinary White Blood Cell Count (D)	NS	ns	NS	NS
Blood Urea Nitrogen (C)	NS	ns	ns	ns
Urine Specific Gravity[a] (C)	NS	ns	NS	NS

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

TABLE 14-12. (Continued)

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

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Questionnaire				
Kidney Disease (D)	NS	NS	ns	NS
Laboratory				
Urinary Protein (D)	NS	ns	ns	ns
Urinary Occult Blood (D)	** (NS)	** (ns)	** (NS)	** (NS)
Urinary White Blood Cell Count (D)	NS	ns	NS	NS
Blood Urea Nitrogen (C)	NS	ns	ns	ns
Urine Specific Gravity[a] (C)	NS	ns	NS	NS

[a]Negative difference considered adverse for this variable.
C: Continuous analysis.
D: Discrete analysis.
NS/ns: Not significant ($p>0.10$).
** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table M-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

dioxin and age, which after investigation, revealed a marginally significant positive association with initial dioxin for younger Ranch Hands and a nonsignificant negative association for older Ranch Hands. Under the maximal assumption, a significant positive association was found between urinary occult blood and initial dioxin (p=0.047). The adjusted analysis of urinary white blood cell count contained a significant interaction between initial dioxin and diabetic class. Investigation of the interaction revealed a marginally significant positive association with initial dioxin for Ranch Hands classified as normal and a marginally significant negative association for Ranch Hands classified as impaired. A positive, but nonsignificant, association between urinary white blood cells and initial dioxin was found for Ranch Hands classified as diabetic. The adjusted analysis of urine specific gravity displayed a significant interaction between initial dioxin and race. Examination of the interaction revealed a marginally significant negative association for Blacks and a nonsignificant positive association for non-Blacks. The other three renal assessment variables exhibited nonsignificant associations with initial dioxin.

The longitudinal analysis of blood urea nitrogen exhibited no significant associations with initial dioxin under either the minimal or maximal assumptions.

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

In the unadjusted analyses of the six renal assessment variables presented in Table 14-11, the interaction of current dioxin and time since tour was not significant under the minimal assumption. Under the maximal assumption, the unadjusted analyses also contained no significant interactions between current dioxin and time. Urinary occult blood and urinary white blood cell count displayed marginally significant positive associations with current dioxin for time greater than 18.6 years. Blood urea nitrogen displayed a significant negative association (p=0.035) with current dioxin for time more than 18.6 years.

In the adjusted analyses based on the minimal assumption, the current dioxin-by-time interaction generally was nonsignificant for the laboratory variables. The adjusted analyses of urinary white blood cell count and urine specific gravity contained interactions with the covariates of race and age, respectively. Followup models without the respective current dioxin-by-time-by-covariate interactions had nonsignificant interactions between current dioxin and time. For the questionnaire variable "presence of kidney disease," there was a significant interaction with diabetic class.

In the adjusted analyses under the maximal assumption, the interaction of current dioxin and time generally was nonsignificant. The adjusted analyses of blood urea nitrogen and urine specific gravity exhibited significant interactions with the covariates of diabetic class and age, respectively. Similar to the adjusted analyses under the minimal assumption, followup models without the respective current dioxin-by-time-by-covariate interactions also were nonsignificant.

The current dioxin-by-time since tour interaction was nonsignificant in the longitudinal analysis of blood urea nitrogen. However, a marginally significant negative association (p=0.075) between current dioxin and the change in blood urea nitrogen from 1982 to 1987 was detected for Ranch Hands in the maximal cohort with more than 18.6 years since tour.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the six individual renal assessment variables, summarized in Table 14-12, exhibited no significant differences among Ranch Hands and Comparisons based on categorized current dioxin. The adjusted analysis for urinary occult blood contained a significant interaction between categorized current dioxin and diabetic class. Examination of the interaction revealed a marginally significant difference among the four current dioxin categories for the impaired strata and a marginally significant contrast for unknown versus background for the impaired strata. No significant differences were found for the normal or diabetic strata. The adjusted analyses of the other renal assessment variables were nonsignificant. Longitudinal analyses of blood urea nitrogen were nonsignificant with respect to the four current dioxin categories.

CONCLUSION

For some adjusted analyses, diabetic class was a significant covariate in the model. Because dioxin may influence diabetic status, ancillary models without diabetic class also were examined. For the most part, deletion of diabetic class from an adjusted model had no appreciable effect on the outcome of the analysis. The different sets of statistical analyses performed for the renal assessment did not indicate that an association existed between the serum dioxin levels of study participants and their 1987 examination health status. No significant associations with dioxin were observed in the longitudinal analyses of blood urea nitrogen.

CHAPTER 14

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