CHAPTER 17

RENAL ASSESSMENT

INTRODUCTION

Renal dysfunction and overt renal disease are not considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or TCDD.

In man and animals, 2,4-D, 2,4,5-T, and TCDD are excreted by the kidney, largely in the unmetabolized state via a first-order kinetic process.[1-5] Excretion of these compounds appears to be a function of the proximal convoluted tubules.[6-8] In experimental animals, renal damage is generally noted only when very high or lethal doses of TCDD have been administered, an observation that reflects the severe systemic toxicity of TCDD as contrasted to a doubtful rôle of primary nephrotoxicity.[9-12]

A variety of experimental pharmacokinetic studies have been conducted in man using both ingested 2,4-D and 2,4,5-T.[3-5,13,14] Most of these studies suggested an unconjugated excretion of these compounds by first-order kinetics. No acute deleterious effects, as detected by urinalysis or blood chemistries, were either noted or recorded for the volunteer subjects.

In contrast, following significant exposure to a horse arena filled with TCDD-contaminated waste products, a 6-year-old girl developed hemorrhagic cystitis, pyelonephritis, and proteinuria.[15] Horses exposed to this arena and other contaminated arenas also frequently manifested hematuria. A thorough 5-year followup examination of the young girl was essentially normal and did not reveal any renal sequalae.[16]

Most dioxin morbidity studies have only briefly mentioned renal disease and function, and then in the context of routine data collected at physical examination rather than as a specific clinical focus. Some studies of significant occupational exposure have been almost devoid of commentary on renal dysfunction.[17-19] A contemporary study of a residentially exposed cohort showed negative renal findings.[20]

The Times Beach, Missouri, pilot study demonstrated historical "trends" of increased urinary tract disease by questionnaire, along with a compatible pattern of leukocyturia and hematuria manifest at physical examination, but none of the observations was statistically significant.[21] The Monsanto industrial morbidity studies reported essentially negative urinalysis findings, although data were not presented.[22,23]

Baseline Summary Results

The 1982 Baseline examination assessed renal disease and function by questionnaire and basic urinalysis testing.

Based on questionnaire information, the Ranch Hand group reported significantly more kidney disease than the Comparisons (p=0.039), but this finding was not substantiated by laboratory test results, even when all abnormalities were summed over the five tests of BUN, creatinine clearance, presence of occult blood, five or more urine WBC's per high-power field (HPF), and the presence of urine protein. The Comparison group manifested a twofold increase in proteinuria (p=0.055). The distributions of creatinine clearance levels were similar in both groups, as were the means of the BUN, urine specific gravity, and WBC's/HPF. Difficulty in assessing the degree and significance of hidden noncompliance to the full 24-hour urine collection made the interpretation of the creatinine clearance test results somewhat problematic. Of some interest, known noncompliance to urine collection was observed much more frequently (p<0.001) in the elderly participants. Of 18 herbicide exposure analyses, only 1 (enlisted flyer category) was statistically significant vis-a-vis a history of kidney disease, and it did not demonstrate a linear increase from low to high exposure.

The validity of the renal assessment was reinforced by the demonstrated effects of the covariates of age (born in or after 1942, born before 1942) and 2-hour status after postprandial glucose levels (less than 120 mg/dl, greater than or equal to 120 mg/dl). Blood urea nitrogen increased with age and specific gravity decreased (p<0.001 for both), while an abnormally high postprandial glucose level indicative of diabetes was associated only with an increasing urine specific gravity, as expected.

Overall, the Baseline renal assessment suggested an excess of historical kidney disease in the Ranch Hand group that was not corroborated by laboratory urinalysis testing.

Parameters of the 1985 Renal Assessment

Because of the essentially negative Baseline results, the fact that kidney disease is not a prime clinical endpoint, and the manifest compliance problems with a 24-hour urine collection, the 1985 examination process did not emphasize further inquiry into renal disease and function.

The onsite NORC questionnaire did not specifically probe for a 1982-1985 interval history of kidney disease, although severe cases may be captured by the generic question, "any other major condition?" or by a detailed extraction of review-of-systems data obtained at the physical examination. Laboratory testing parameters included all the Baseline dependent variables except the creatinine clearance level (omitted because the plasma creatinine assay was deleted from the test battery). Also, the analysis of composite renal abnormalities was deleted. In addition, the 24-hour urine collection was reduced to a 12-hour collection (5:30 a.m. to 5:30 p.m.) to ease participant burden while still maintaining validity for the porphyrin analyses (see Chapter 13). The accuracy of the 12-hour urine collection was not assessed during the 1985 examination.

Renal data analyses paralleled the Baseline analysis except for deleting one of the dependent variables and a composite analysis, adding the covariate of race, and defining the covariate of diabetic class as diabetic, impaired, or normal. No clinical exclusion categories applied to the renal analysis. Minor numerical differences in the tables are due to rare missing dependent variable or covariate data. Adjusted statistical analyses using the above covariates were based on 1,016 Ranch Hands and 1,293 Comparisons and used logistic regression and analysis of covariance methods. When age was used as a covariate in the logistic regression models, the continuous form was used mathematically, but for summary table purposes, age is displayed as a dichotomy. Parallel analyses using the Original Comparisons can be found in Appendix O (see Tables O-3 through O-5). Tests of association between dependent variables and covariates emphasized Fisher's exact test and Pearson's chi-square test for discrete dependent variables and t-tests and analysis of variance techniques for continuous dependent variables.

RESULTS AND DISCUSSION

Questionnaire Data

History of renal disease was assessed by a self-administered review-of-systems question list at the physical examination. Specific structured questions on renal disease were not incorporated in the NORC questionnaire. The review-of-systems questions, i.e., "kidney trouble?" "kidney stones?" were open-ended with respect to time, and reflected conditions that arose at any time in the past.

These questionnaire data did not show a significant difference between the Ranch Hand and Comparison groups, as reflected by the analysis in Table 17-1.

Tests of association between the historical presence of kidney disease in both groups and the covariates of race, occupation, diabetes, and age are given in Table 17-2.

TABLE 17-1.

Unadjusted Analysis of History of Kidney Disease/Kidney Stones by Group

	History of Kidney Disease/Stones						
	Yes		No				
Group	Number	Percent	Number	Percent	Total	Est. Relative Risk (95% C.I.)	p-Value
Ranch Hand	94	9.3	920	90.7	1,014	0.93 (0.70,1.23)	0.619
Comparison	128	9.9	1,163	90.1	1,291		

TABLE 17-2.

Association Between Kidney Disease/Kidney Stones and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		History of Kidney Disease/Stones					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	66	6.9	894	93.1	960	<0.001[a]
	Born <1942	156	11.6	1,189	88.4	1,345	
Race	Nonblack	214	9.9	1,949	90.1	2,163	0.106[a]
	Black	8	5.6	134	94.4	142	
Occupation	Officer	83	9.6	781	90.4	864	
	Enlisted Flyer	36	9.3	350	90.7	386	0.969[b]
	Enlisted Groundcrew	103	9.8	952	90.2	1,055	
Diabetic* Class	Diabetic	14	8.0	161	92.0	175	
	Impaired	41	14.5	242	85.5	283	0.011[b]
	Normal	166	9.0	1,677	91.0	1,843	

[a]Fisher's exact test.

[b]Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

These results showed that there was no significant effect due to race or occupation. In contrast, there was a significant effect due to diabetic class (p=0.011), with participants in the impaired diabetic class having a significantly higher proportion of past kidney disease than those in the normal or diabetic classes. Older participants also had a significantly higher history of past renal events than younger participants (p<0.001).

A logistic regression analysis of the history of kidney disease and kidney stones using the above four covariates gave a result very similar to the unadjusted analysis (Adj. RR: 0.95, 95% C.I.: [0.71,1.25], p=0.693). Race and occupation were not significant covariates. However, diabetic class and age were significant covariates (p=0.041 and p<0.001, respectively).

These analyses showed that there was no difference in the history of renal disease between the Ranch Hand and Comparison groups, and that the proportions of past kidney disease and kidney stones were significantly influenced by age and diabetic class. While these findings are consistent with traditional expectations in renal disease, they were in direct contrast to the findings of the 1982 Baseline examination, which revealed a significant excess of historical kidney disease in the Ranch Hand group, and group data that were not influenced by age or glucose levels.

It is concluded that there were no significant group differences in past renal disease.

Physical Examination Data

No physical examination procedures were used to evaluate the renal system as most procedures are invasive and beyond the scope of this voluntary examination. Accordingly, the renal system was evaluated primarily by laboratory data.

Laboratory Data

Five renal variables were quantitated 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-power microscopic examination after centrifugation for 5 minutes. Urine specific gravities were measured by Ames' Multisticks; those urines exceeding normal limits were remeasured by standardized refractometers. BUN levels were assayed by a DuPont Automated Chemical Analyzer, model 500. The SCRF laboratory normal values from these variables are given in Table 17-3.

TABLE 17-3.

Laboratory Norms for Five Renal Variables

Renal Variable	Normal	Abnormal
Urine Protein	Absent	Present
Occult Blood	Absent	≥1 RBC/HPF
WBC/HPF	≤2	>2
BUN (mg/dl)	7-22	≥23
Specific Gravity	1.005-1.03	≤1.004

In this section, urinary protein, hematuria, and leukocyturia were analyzed as discrete variables, whereas BUN and urine specific gravity were analyzed as continuous variables. The number and percent of subjects with abnormal values for the discrete variables are displayed in the summary Table 17-4, along with the number of participants, the unadjusted means, and standard errors of the continuous variables.

TABLE 17-4.

Summary of Renal Laboratory Variables by Group

Renal Variable	Ranch Hand Number Abnormal	Ranch Hand Percent Abnormal	Comparison Number Abnormal	Comparison Percent Abnormal	Unadjusted p-Value
Urine Protein	37	3.6	40	3.1	0.485
Occult Blood	182	17.9	208	16.1	0.239
WBC/HPF	102	10.0	107	8.3	0.145

Renal Variable	Ranch Hand Unadjusted Mean (Sample Size)	Ranch Hand Standard Error	Comparison Unadjusted Mean (Sample Size)	Comparison Standard Error	Unadjusted p-Value
BUN (mg/dl)	14.21* (1,016)	--	14.30* (1,293)	--	0.554
Specific Gravity	1.0157 (1,016)	0.0002	1.0152 (1,292)	0.0002	0.082

*Arithmetic mean calculated on square root scale and transformed to original units.

--Standard error not given, since analysis performed on square root scale.

The following statistical power statements apply to several variables displayed in Table 17-4. At a standard α -level of 0.05 and a power of 0.80, the sample sizes were sufficient to detect a 1.28-fold increase in the frequency of percent abnormal values for urinary occult blood, and a 1.43-fold increase in the percentage of leukocyturia, both over that observed in the Comparison group. Further, the sample sizes were adequate to reveal a 2.9 percent mean shift in the BUN value relative to the mean observed in the Comparison group.

Urinary Protein

As displayed in Table 17-4, the Ranch Hand group had a prevalence rate of urinary protein of 3.6 percent versus 3.1 percent in the Comparison group (Est. RR: 1.18, 95% C.I.: [0.75,1.86], p=0.485). This difference was not significant.

Tests of association were conducted with pooled participant data using the covariates of race, occupation, diabetic class, and age. These tests are presented in Table 17-5.

TABLE 17-5.

Association Between Urinary Protein and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		Presence of Urinary Protein					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	34	3.5	927	96.5	961	0.641[a]
	Born <1942	43	3.2	1,304	96.8	1,347	
Race	Nonblack	65	3.0	2,100	97.0	2,165	0.002[a]
	Black	12	8.4	131	91.6	143	
Occupation	Officer	18	2.1	845	97.9	863	
	Enlisted Flyer	11	2.8	376	97.2	387	0.010[b]
	Enlisted Groundcrew	48	4.5	1,010	95.5	1,058	
Diabetic* Class	Diabetic	20	11.4	155	88.6	175	
	Impaired	18	6.4	264	93.6	282	<0.001[b]
	Normal	39	2.1	1,808	97.9	1,847	

[a]Fisher's exact test.

[b]Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

These results suggested no age effect, but significant associations for the covariates of race (p=0.002), occupation (p=0.010), and diabetic class (p<0.001) were noted. The significant covariate effects were attributable to higher percentages of urinary protein abnormalities in Blacks versus nonblacks, enlisted groundcrew versus officers or enlisted flyers, and diabetes (past history [unverified] or greater than or equal to 200 mg/dl glucose) versus impaired glucose tolerance (at least 140 but less than 200 mg/dl glucose) versus normal glucose tolerance (less than 140 mg/dl glucose).

The prevalence rates of urinary protein abnormalities were adjusted by logistic regression models using the above four covariates. Race and occupation demonstrated significant effects (p=0.023 and p=0.023, respectively), while age did not (p=0.294). Because of a significant interaction between group and diabetic class (p=0.047), stratified analyses were conducted to provide further clarification. The results are shown in Table 17-6.

The adjusted relative risk, 95 percent confidence interval, and group p-value for each diabetic class are shown in Table 17-7.

TABLE 17-6.

Frequency of Urinary Protein by Diabetic Class and Group

		Presence of Urinary Protein				
		Yes		No		
Diabetic Class	Group	Number	Percent	Number	Percent	Total
Diabetic	Ranch Hand	7	9.0	71	91.0	78
	Comparison	13	13.4	84	86.6	97
Impaired	Ranch Hand	5	4.7	101	95.3	106
	Comparison	13	7.4	163	92.6	176
Normal	Ranch Hand	25	3.0	807	97.0	832
	Comparison	14	1.4	1,001	98.6	1,015

TABLE 17-7.

Adjusted Relative Risks for Urinary Protein by Diabetic Class

Diabetic Class	Adjusted Relative Risk	95% C.I.	p-Value
Diabetic	0.66	(0.25, 1.77)	0.414
Impaired	0.66	(0.23, 1.93)	0.453
Normal	2.23	(1.15, 4.32)	0.018

This analysis showed that the estimated prevalence of urinary protein is lower in the Ranch Hand group than in the Comparison group for the diabetic and glucose-impaired strata. Conversely, for the normal diabetic class, the Ranch Hand group manifested a significant increased prevalence of positive urinary protein as contrasted with the Comparison group.

These followup examination results were different from the 1982 Baseline examination, which showed significantly more proteinuria in the Comparison group. The prevalence of proteinuria in the followup examination was about 75 percent higher than the prevalence observed in the Baseline study. The interaction of group and diabetic class suggested Ranch Hand increases in proteinuria for normal glucose tolerance participants.

Urinary Occult Blood

Hematuria was determined by microscopic examination. For both groups combined, the frequency distribution of RBC count data was: 0 RBC/HPF, 82.15 percent; 1-2 RBC/HPF, 15.13 percent; 3-5 RBC/HPF, 2.03 percent; and greater than 5 RBC/HPF, 0.69 percent.

As noted in Table 17-4, the prevalence of urinary occult blood in the Ranch Hand group (17.9%) was slightly higher than the rate observed for the Comparison group (16.1%). The unadjusted analysis showed no significant group differences for occult blood (Est. RR: 1.14, 95% C.I.: [0.91,1.42], p=0.239).

Tests of association with the covariates of race, occupation, diabetic class, and age were conducted using combined group data for urinary occult blood, and these results are given in Table 17-8.

TABLE 17-8.

Association Between Urinary Occult Blood and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		Presence of Urinary Occult Blood					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	148	15.4	812	84.6	960	0.115[a]
	Born <1942	242	18.0	1,105	82.0	1,347	
Race	Nonblack	355	16.4	1,809	83.6	2,164	0.016[a]
	Black	35	24.5	108	75.5	143	
Occupation	Officer	118	13.7	745	86.3	863	
	Enlisted Flyer	76	19.6	311	80.4	387	0.005[b]
	Enlisted Groundcrew	196	18.5	861	81.5	1,057	
Diabetic Class*	Diabetic	33	18.9	142	81.1	175	
	Impaired	52	18.5	229	81.5	281	0.296[b]
	Normal	305	16.5	1,542	83.5	1,847	

[a] Fisher's exact test.

[b] Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

As reflected in Table 17-8, there was no significant effect due to diabetic class or age. However, Blacks had a significantly higher prevalence of urinary occult blood than nonblacks (p=0.016), and significant effects were also due to occupation (p=0.005), with officers having a lower proportion of positive occult blood determinations than enlisted personnel.

An adjusted analysis of urinary occult blood proportions was conducted by logistic regression techniques. Multiple significant three-factor interactions were noted, e.g., group-by-occupation-by-race (p=0.008), group-by-age-by-diabetic class (p=0.045), and group-by-occupation-by-diabetic class (p=0.017). Consequently, a series of analyses stratified by race were performed to determine adjusted relative risks for nonblacks and Blacks separately. The adjusted results for nonblack participants are given in Table 17-9.

TABLE 17-9.

Adjusted Analysis for Urinary Occult Blood for Nonblacks by Group

	Presence of Urinary Occult Blood					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	166	17.4	789	82.6	955	Adj. RR: 1.13
Comparison	189	15.6	1,020	84.4	1,209	95% C.I.: (0.91,1.42), p-Value: 0.291

The covariates of occupation and age contributed significant effects (p<0.001 and p=0.002, respectively) to this analysis. Diabetic class was not significant (p=0.863), and was consequently not included in the final model. No significant group differences were found (p=0.291).

Table 17-10 shows the frequencies for Black participants.

The adjusted analysis of the data on Blacks showed a significant interaction of group and occupation (p=0.003). Table 17-11 presents frequencies and percents for the presence of urinary occult blood for each group, stratified by occupation.

This table demonstrates that the group-by-occupation interaction for Blacks was due to the Ranch Hand officers having a lesser prevalence of occult blood abnormalities than Comparison officers, while conversely, Ranch Hand enlisted personnel showed a higher prevalence of abnormalities than enlisted Comparisons. Because of the absence of hematuria in Black Ranch Hand officers, no relative risk was calculated. Consequently, the Black enlisted occupational categories were combined and investigated further through logistic regression techniques. This analysis did not show a difference of urinary occult blood percentages in the Ranch Hand Black

TABLE 17-10.

Frequency of Urinary Occult Blood for Blacks by Group

Group	Presence of Urinary Occult Blood: Yes Number	Yes Percent	No Number	No Percent	Total
Ranch Hand	16	26.7	44	73.3	60
Comparison	19	22.9	64	77.1	83

TABLE 17-11.

Frequency of Urinary Occult Blood for Blacks by Occupation and Group

Occupation	Group	Presence of Urinary Occult Blood: Yes Number	Yes Percent	No Number	No Percent	Total
Officer	Ranch Hand	0	0.0	7	100.0	7
	Comparison	3	42.9	4	57.1	7
Enlisted Flyer	Ranch Hand	3	30.0	7	70.0	10
	Comparison	1	5.9	16	94.1	17
Enlisted Groundcrew	Ranch Hand	13	30.2	30	69.8	43
	Comparison	15	25.4	44	74.6	59

enlisted and the Comparison Black enlisted strata (Est. RR: 1.62, 95% C.I.: [0.73,3.63], (p=0.239). The effects of age (p=0.817), occupation (p=0.171), and diabetic class (p=0.145) were not statistically significant, and were not included in the final adjusted analysis.

In conclusion, both unadjusted and adjusted stratified analyses (by race) did not reveal a consistent and plausible excess of hematuria in the Ranch Hand group. The tenfold or greater increase in the cross-sectional prevalence of hematuria compared to the Baseline examination (1.3% of both groups) to this followup examination may be due to a different sensitivity of the laboratory techniques of reagent-strip testing versus microscopic observation. Nonetheless, an approximate prevalence of 17 percent hematuria merits reevaluation at the next followup examination.

Urinary White Blood Cell Count

Leukocyturia was assessed by microscopic examination. As noted in Table 17-3, more than two white blood cells per high-power field (WBC/HPF) were considered abnormal by the SCRF laboratory. This is in distinct contrast to the cutpoint of five WBC/HPF used at the Baseline examination.

Table 17-4 shows the group frequencies of abnormal urine WBC's. The unadjusted analysis revealed a nonsignificant group effect (Est. RR: 1.24, 95% C.I.: [0.93,1.64], p=0.145).

Tests of association were conducted between the frequency of abnormal WBC counts in both groups and the covariates of race, occupation, diabetic class, and age. The results revealed a significantly higher prevalence of abnormal counts for Blacks than nonblacks (p<0.001), an effect due to occupation (p=0.023), with a lower prevalence of abnormalities for officers than enlisted personnel and an effect due to diabetic class (p=0.046), with a lower prevalence of abnormal WBC counts in the normal diabetic class than in either the impaired or diabetic classifications. Age was noncontributory (p=0.508).

Adjusted analyses of leukocyturia by group were performed by logistic regression techniques. A significant three-way interaction for group, age, and race was detected (p=0.004), requiring further stratified analyses. A summary of the frequencies for nonblacks is presented in Table 17-12.

TABLE 17-12.

Frequency of Urinary WBC/HPF for Nonblacks by Group

	Urinary WBC/HPF				
	Abnormal		Normal		
Group	Number	Percent	Number	Percent	Total
Ranch Hand	92	9.6	864	90.4	956
Comparison	88	7.3	1,121	92.7	1,209

The logistic regression adjustment of the data for nonblacks showed significant covariate effects for occupation (p=0.046) and diabetic class (p=0.031), and a significant interaction between group and age (p=0.018). Consequently, additional analyses were conducted stratifying by age (born in or after 1942, born before 1942), and are shown in Table 17-13.

TABLE 17-13.

Adjusted Analyses for Urinary WBC/HPF for Nonblacks by Age Category and Group

Age	Group	Urinary WBC/HPF				Total	Summary Statistics
		Abnormal		Normal			
		Number	Percent	Number	Percent		
Born ≥1942	Ranch Hand	41	10.8	339	89.2	380	Adj. RR: 2.42
	Comparison	24	4.8	478	95.2	502	95% C.I.: (1.43,4.09)
							p-Value: 0.001
Born <1942	Ranch Hand	51	8.9	525	91.1	576	Adj. RR: 0.99
	Comparison	64	9.1	643	90.9	707	95% C.I.: (0.67,1.46)
							p-Value: 0.956

As depicted by the above table, the adjusted rate of nonblack young Ranch Hands with abnormal urinary white blood cell counts was significantly greater than that for nonblack Comparisons (p=0.001 adjusted for occupation and diabetic class). Demonstrating the interaction involving age and group, the adjusted rate of nonblack older Ranch Hands with abnormal urinary WBC counts was nonsignificant and less than older nonblack Comparisons (p=0.956 adjusted for occupation and diabetic class).

Similar analyses were conducted for Black participants. Rates of abnormal urinary white blood cell count levels were 16.7 percent and 22.9 percent (n=60 and 83) for Black Ranch Hands and Black Comparisons, respectively. Significant interactions involving group and occupation (p=0.002) and group and age (p=0.001) were found. Additional analyses stratified by occupation were performed. Frequencies stratified by occupation are shown in Table 17-14.

This table clearly shows how the proportions of WBC abnormalities vary by group within the various occupational categories. However, because of the lack of abnormalities in the Black Ranch Hand officer stratum, an adjusted relative risk was not calculated for this occupation. Thus, Black enlisted categories were combined and subjected to further logistic regression techniques. The analysis showed yet another interaction, between group and age (p=0.026), requiring an additional stratification by age. Results of these analyses are presented in Table 17-15.

TABLE 17-14.

Frequency of Urinary WBC for Blacks by Occupational Category and Group

		Urinary WBC/HPF Count				
		Abnormal		Normal		
Occupation	Group	Number	Percent	Number	Percent	Total
Officer	Ranch Hand	0	0.0	7	100.0	7
	Comparison	2	28.6	5	71.4	7
Enlisted Flyer	Ranch Hand	3	30.0	7	70.0	10
	Comparison	3	17.6	14	82.4	17
Enlisted Groundcrew	Ranch Hand	7	16.3	36	83.7	43
	Comparison	14	23.7	45	76.3	59

TABLE 17-15.

Adjusted Analyses for Urinary WBC/HPF for Black Enlisted Flyers and Groundcrew by Age and Group

		Urinary WBC/HPF Count					
		Abnormal		Normal			
Age	Group	Number	Percent	Number	Percent	Total	Summary Statistics
Born ≥1942	Ranch Hand	4	13.8	25	86.2	29	Adj. RR: 0.41
	Comparison	13	28.3	33	71.7	46	95% C.I.: (0.12,1.40)
							p-Value: 0.153
Born <1942	Ranch Hand	6	25.0	18	75.0	24	Adj. RR: 2.17
	Comparison	4	13.3	26	86.7	30	95% C.I.: (0.53,8.79)
							p-Value: 0.279

In the presence of relatively small sample sizes, these results demonstrated that the prevalence of abnormal urinary white cell counts in Black enlisted personnel did not vary significantly by group for either age category, although the reversal of group proportions for different ages was prominent and fully reflective of the group-by-age interaction. It is noted that the Black group-by-age interaction is opposite the nonblack group-by-age interaction (see Table 17-13), explaining the significant three-way interaction involving group, age, and race.

In summary, the unadjusted analysis of urinary WBC/HPF abnormalities showed no group differences, but the adjusted analyses showed significant effects for diabetic class and occupation for nonblack enlisted participants, and a group-by-age interaction for both Black and nonblack enlisted participants. Only for younger nonblack participants was a significant group effect seen (Ranch Hands>Comparisons).

The observations from this examination were consistent with the negative Baseline findings.

Blood Urea Nitrogen (BUN)

BUN was analyzed as a continuous variable using two sample t-tests, analysis of variance, and analysis of covariance techniques. The data were transformed to the square root scale for analysis. Adjusted analyses used the covariates of race, occupation, diabetic class, and age, as in analysis of discrete dependent variables.

As noted in Table 17-4, unadjusted group summary statistics revealed no significant differences in mean BUN levels (p=0.554). The groups were combined and contrasted to the covariates, and results are presented below.

These tests of covariate association showed a significant racial effect (p=0.007), with a higher mean BUN level for nonblacks than Blacks; a significant effect for occupation (p<0.001), with officers having a higher mean level than both enlisted categories; a significant age effect (p<0.001), with a higher mean BUN level for older than for younger participants; and a marginally significant (p=0.059) difference due to diabetic class, with participants in the impaired category having the highest mean BUN level.

An analysis of covariance using the above four covariates demonstrated the significant effects of age (p<0.001), occupation (p=0.015), and significant group-by-race (p=0.022) and race-by-diabetic class (p=0.024) interactions.

Table 17-16 presents mean BUN values, adjusted by the covariates and covariate interactions, stratified by race. Test results for the equality of adjusted means between groups are given in the p-value column.

As noted from this table, Black Comparisons had a significantly higher adjusted mean BUN level than Black Ranch Hands (p=0.017), and there was no group difference for nonblacks.

These results were analogous to the findings at the Baseline examination (although race was not used as a covariate), i.e., no detriment to the Ranch Hand group and a significant covariate effect of age.

TABLE 17-16.

Adjusted Analysis of BUN by Race and Group

Race	Group	Total	Adjusted Mean*	p-Value
Nonblack	Ranch Hand	956	14.15	0.907
	Comparison	1,206	14.17	
Black	Ranch Hand	60	12.40	0.017
	Comparison	83	13.75	

*Converted from square root scale.

Urinary Specific Gravity

The unadjusted means of the urine specific gravity disclosed a marginally significant difference between the Ranch Hand and Comparison groups (p=0.082). The summary statistics of the unadjusted analysis are given in Table 17-4.

By t-tests and analysis of variance, tests of association were performed on the combined groups using the covariates of race, occupation, diabetic class, and age. These tests showed a significant effect of occupation (p<0.001), with officers having the lowest mean urine specific gravity and the enlisted groundcrew category having the highest, and a significant effect (p=0.018) due to diabetic class, with the diabetic category having the highest specific gravity and the normal (nondiabetic) class having the lowest mean value. The effects of age and race were not statistically significant (p=0.382 and p=0.065, respectively).

An analysis of covariance with these four covariates showed significant effects due to diabetic class (p=0.019), and significant group-by-race (p=0.017) and group-by-occupation (p=0.034) interactions. Adjusted group mean specific gravities were stratified by race and by occupation. The results are presented in the summary Table 17-17.

These stratified group data showed a difference for nonblack enlisted groundcrew, but Comparisons had a lower adjusted mean urine specific gravity level than Ranch Hands (low specific gravity representing renal dysfunction).

Noteworthy is the contrast of results between this followup examination and the Baseline examination in 1982. The urine specific gravities of the followup examination appeared to be very substantially lower than those of the Baseline. A probable explanation was the difference in methods of assessing specific gravity. At the Baseline, the Ames' Clinilab automated procedure (falling drop) was used, as contrasted to the Ames' Multistick procedure at the followup. Both examinations used specimens obtained early on the second examination day, and did not use aliquots of 12- or 24-hour urine collections that were used for the porphyrin analyses. Although the

TABLE 17-17.

Adjusted Analysis of Urine Specific Gravity by Race, Occupation, and Group

Race	Occupation	Group	Total	Adjusted Mean	p-Value
Nonblack	Officer	Ranch Hand	373	1.0153	0.734
		Comparison	474	1.0151	
	Enlisted Flyer	Ranch Hand	167	1.0158	0.631
		Comparison	193	1.0161	
	Enlisted Groundcrew	Ranch Hand	416	1.0174	<0.001
		Comparison	538	1.0157	
Black	Officer	Ranch Hand	7	1.0158	0.462
		Comparison	7	1.0186	
	Enlisted Flyer	Ranch Hand	10	1.0144	0.624
		Comparison	17	1.0158	
	Enlisted Groundcrew	Ranch Hand	43	1.0162	0.157
		Comparison	59	1.0183	

covariate effect of age upon specific gravity was not observed at the followup as it had been at the Baseline, both examinations demonstrated the marked effect of diabetes upon specific gravity, i.e., a higher specific gravity was detected in diabetics than in nondiabetics.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). The variables of kidney disease, urinary protein, urinary occult blood, and urinary white blood cell count were investigated (unadjusted for any covariates) using Pearson's chi-square test and Fisher's exact test. Adjusted analyses were performed by logistic regression for these variables, using age, race, diabetic class, and any significant pairwise interactions between the exposure index and these covariates. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts of the proportion of abnormalities between medium and low exposure levels, and between the high and low exposure levels. Age was used as a continuous variable in the adjusted analyses, and dichotomized (born in or after 1942, born before 1942) when age was involved in an interaction with the exposure index.

Analyses of mean blood urea nitrogen and urine specific gravity (continuous variables) were performed, unadjusted for any covariates or interactions, using analysis of variance techniques and t-tests. Analysis of covariance models were used in adjusted analyses. Contrasts of medium versus low exposure and high versus low exposure were also studied. A square root transformation was applied to the blood urea nitrogen data.

Results of the adjusted analyses for these six variables are presented in Tables 17-18 and 17-19, and counterpart results for unadjusted analyses are presented in Table O-1 of Appendix O. Results from further investigation of exposure index-by-covariate interactions are given in Table O-2 of Appendix O.

Unadjusted analyses revealed no significant differences among exposure index levels for any occupation. Further investigation of these variables, for which the medium versus low and the high versus low contrasts were also examined, revealed only two variables having borderline significance: kidney disease in enlisted flyers, high versus low (Est. RR: 0.25, 95% C.I.: [0.05,1.26], p=0.091), and urinary occult blood in enlisted groundcrew, high versus low (Est. RR: 1.77, 95% C.I.: [1.00,3.13], p=0.061). The results for urinary occult blood in enlisted groundcrew supported an increase in the proportion of abnormalities from low to high exposure, whereas the kidney disease data showed the opposite effect.

The frequency of abnormalities (or mean levels closer to the abnormal range for continuous variables) for the different exposure index levels exhibited no graduated pattern across exposure levels. The number of combinations for which the medium exposure level had the smallest proportion of abnormalities (or more abnormal mean level) was greater than the other exposure levels.

Adjusted analyses revealed no significant differences among exposure index levels for any occupational stratum. Interactions were present for four of the six variables, however, and were observed in all occupations. A summary of these interactions is presented in Table 17-20.

No interaction patterns in either the covariates or occupations were observed. The only contrast observed approaching significance for an adverse effect at higher exposure levels was observed for urinary protein (officers in normal diabetic class, high versus low, p=0.097), but this contrast was highly affected by sparse cell sizes (see Table O-2 of Appendix O).

In summary, six renal variables showed no evidence of an increasing dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates among the exposure index levels were seen within occupational strata. The exposure index level patterns observed at the Baseline examination for kidney disease in the enlisted flyer stratum were not seen at the first followup examination. Overall, both the Baseline and followup examinations showed very little evidence of a dose-response relationship.

TABLE 17-18.

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Kidney Disease	Officer	127	130	123	Overall		0.314
					M vs. L	0.93 (0.37,2.34)	0.878
					H vs. L	1.67 (0.72,3.88)	0.236
	Enlisted Flyer	55	65	57	Overall		0.124
					M vs. L	1.05 (0.34,3.22)	0.935
					H vs. L	0.26 (0.05,1.31)	0.102
	Enlisted Groundcrew	153	163	141	Overall		0.269
					M vs. L	0.57 (0.26,1.26)	0.163
					H vs. L	0.58 (0.25,1.31)	0.189
Urinary Protein	Officer	127	130	123	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
	Enlisted Flyer	55	65	57	Overall		0.657
					M vs. L	0.34 (0.03,4.61)	0.420
					H vs. L	0.41 (0.03,4.99)	0.486
	Enlisted Groundcrew	154	163	142	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

TABLE 17-18. (continued)

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Urinary Occult Blood	Officer	127	130	123	Overall		0.299
					M vs. L	0.80 (0.38,1.71)	0.566
					H vs. L	1.40 (0.70,2.80)	0.345
	Enlisted Flyer	55	65	57	Overall		0.187
					M vs. L	0.97 (0.39,2.43)	0.950
					H vs. L	0.43 (0.15,1.24)	0.118
	Enlisted Groundcrew	154	163	141	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)
Urinary White Blood Cell Count	Officer	127	130	123	Overall		0.488
					M vs. L	0.55 (0.20,1.51)	0.247
					H vs. L	0.85 (0.34,2.10)	0.718
	Enlisted Flyer	55	65	57	Overall		****(1,3)
					M vs. L	****(1,3)	****(1,3)
					H vs. L	****(1,3)	****(1,3)
	Enlisted Groundcrew	154	163	142	Overall		0.424
					M vs. L	0.68 (0.33,1.38)	0.284
					H vs. L	1.05 (0.53,2.08)	0.886

****(1): exposure index-by-diabetic class interaction -- relative risk, confidence interval, and p-value not presented.

****(2): exposure index-by-race interaction -- relative risk, confidence interval, and p-value not presented.

****(3): exposure index-by-age interaction -- relative risk, confidence interval, and p-value not presented.

****(1,3): exposure index-by-diabetic class and exposure index-by-age interaction -- relative risk, confidence interval, and p-value not presented.

TABLE 17-19.

Adjusted Continuous Exposure Index Analyses for Renal Variables

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
Blood Urea Nitrogen	Officer	n Adj. Mean 95% C.I.	127 ****(2) ****(2)	130 ****(2) ****(2)	123 ****(2) ****(2)	Overall M vs. L H vs. L	****(2) ****(2) ****(2)
	Enlisted Flyer	n Adj. Mean 95% C.I.	55 13.59 (12.02, 15.26)	65 13.76 (12.32, 15.27)	57 13.77 (12.30, 15.32)	Overall M vs. L H vs. L	0.961 0.808 0.804
	Enlisted Groundcrew	n Adj. Mean 95% C.I.	154 13.31 (12.50, 14.15)	163 13.18 (12.41, 13.98)	142 13.08 (12.30, 13.88)	Overall M vs. L H vs. L	0.829 0.722 0.544

TABLE 17-19. (continued)

Adjusted Continuous Exposure Index Analyses for Renal Variables

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
Urine Specific Gravity	Officer	n Adj. Mean 95% C.I.	127 1.0161 (1.0131, 1.0191)	130 1.0167 (1.0138, 1.0197)	123 1.0165 (1.0136, 1.0194)	Overall M vs. L H vs. L	0.755 0.457 0.647
	Enlisted Flyer	n Adj. Mean 95% C.I.	55 1.0159 (1.0128, 1.0191)	65 1.0157 (1.0129, 1.0185)	57 1.0142 (1.0113, 1.0171)	Overall M vs. L H vs. L	0.378 0.861 0.205
	Enlisted Groundcrew	n Adj. Mean 95% C.I.	154 1.0166 (1.0148, 1.0184)	163 1.0166 (1.0149, 1.0183)	142 1.0164 (1.0147, 1.0182)	Overall M vs. L H vs. L	0.974 0.976 0.854

****(2): exposure index-by-race interaction -- adjusted mean, confidence interval, and p-value not presented.

TABLE 17-20.

Summary of Exposure Index-by-Covariate Interactions for Renal Variables

Variable	Occupation	Covariate	p-Value
Urinary Protein	Officer	Diabetic Class	0.004
Urinary Protein	Enlisted Groundcrew	Race	0.023
Urinary Occult Blood	Enlisted Groundcrew	Age	0.032
Urinary White Blood Cell Count	Enlisted Flyer	Age	0.015
Urinary White Blood Cell Count	Enlisted Flyer	Diabetic Class	0.029
Blood Urea Nitrogen	Officer	Race	0.009

LONGITUDINAL ANALYSES

One variable, the BUN level, was used to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. This variable was selected from the five renal assays because it was judged that serial BUN levels would be more indicative of long-term renal health than the others; further, both examination measurements were made by the same high-precision automated analyzer, permitting a more valid comparison. Other commentary, contrasting general results of the other four renal variables to the Baseline, has been made for each variable above.

BUN was analyzed as a continuous variable by repeated measurements analysis of variance (see Chapter 7, Statistical Methods). A square root transformation was used. The data were not adjusted by covariates. The sample base for this analysis was the number of participants who attended both examinations; the results are given in Table 17-21.

These data indicated a slight and relatively symmetrical increase in the BUN level in both groups. Based upon longitudinal analyses of BUN, there was no evidence to assert a detriment in the renal health of the Ranch Hand group.

SUMMARY AND CONCLUSIONS

A summary of all renal variables, including unadjusted and adjusted analyses, is displayed in Table 17-22.

TABLE 17-21.

Longitudinal Analysis of BUN: A Contrast of Baseline and First Followup Examination Laboratory Means

Group	BUN Means			p-Value (Equality of Difference)
	1982 Baseline	1985 Followup	Total	
Ranch Hand	13.72	14.21	971	0.48
Comparison	13.93	14.30	1,139	

TABLE 17-22.

Overall Summary Results of Unadjusted and Adjusted Analyses for Renal Variables

Variable	Unadjusted	Adjusted
Reported Kidney Disease	NS	NS
Urinary Protein	NS	****
Urinary Occult Blood	NS	****
Urinary Leukocytosis	NS	****
BUN	NS	****
Urine Specific Gravity	NS*	****

NS: Not significant ($p>0.10$).

NS*: Borderline significant ($0.05<p\leq0.10$).

****Group-by-covariate interaction.

A historical assessment of kidney disease/kidney stones by a review-of-systems questionnaire showed no significant differences between the Ranch Hand and Comparison groups. An adjusted analysis did not alter this conclusion as an adjusted relative risk of 0.95 (95% C.I.: [0.71,1.25], p=0.693) was demonstrated. These statistics appeared to be in marked contrast to the Baseline historical findings. Differences vis-a-vis the Baseline were most likely due to a difference in questionnaire techniques.

Current renal function was evaluated by five laboratory variables: urine protein, occult blood, urine, white blood cell counts (WBC's), blood urea nitrogen (BUN), and urine specific gravity. Invasive procedures were not used.

The unadjusted analysis of proteinuria showed no group differences (Est. RR: 1.18, 95% C.I.: [0.75,1.86], p=0.485), but the adjusted analysis showed an interaction of group and diabetic class; appropriate stratified analyses revealed that the prevalence of proteinuria was lower in the Ranch Hands than in the Comparisons in the diabetic and impaired strata, but higher in the normal strata for the Ranch Hands. These results were in contrast to the Baseline findings, which showed a marginally significant proteinuria in the Comparison group (p=0.055), and overall, lower prevalence rates of proteinuria.

The unadjusted prevalence rates for hematuria were similar for both groups (Est. RR: 1.14, 95% C.I.: [0.91,1.42], p=0.239). Three significant interactions involving group membership and covariates precluded a direct adjusted comparison of the estimated prevalence rates. Covariate analyses indicated increased hematuria in Blacks and among enlisted personnel. Ultimately via a series of stratified analyses, statistical equivalence was determined for the Black enlisted strata of both groups. Of particular note was the approximate tenfold increase in hematuria in both groups over that observed at Baseline, a finding most likely due to different laboratory techniques (reagent-strip testing versus microscopic observation).

Similar results were found for leukocyturia, i.e., a nonsignificant unadjusted analysis (Est. RR: 1.24, 95% C.I.: [0.93,1.64], p=0.145), and a significant three-way interaction (group, age, race) in the adjusted analysis. Significant covariate effects were noted for diabetic class and occupation for nonblack participants, whereas age was a significant adjusting variable for Blacks. A significant group difference was found only for the younger, nonblack Ranch Hands. The overall results were consistent with the Baseline findings.

BUN levels did not vary significantly by group (p=0.554, unadjusted). Adjusted analyses showed significant covariate effects for age and occupation and interactions for group and race and for race and diabetic class. An analysis stratified by race revealed no significant group differences for nonblacks, but a significantly higher adjusted mean BUN level in Black Comparisons than in Black Ranch Hands. Overall, the BUN results were similar to those observed at the Baseline examination.

Urine specific gravity levels manifested marginally significant group differences (p=0.082, unadjusted). The adjusted analysis disclosed significant covariate effects of diabetic class and the interactions of group and race and group and occupation. Analyses by race showed no strata with significantly lower mean levels for Ranch Hands. In contrast to the Baseline values, the followup urine specific gravities were lower, a finding most likely attributable to differences in laboratory methodology (falling drop method versus multistick procedure).

Exposure index analyses showed very little evidence of a dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates or mean levels among the exposure index levels were seen within occupational strata.

The longitudinal analysis was based solely upon a contrast of BUN levels between the two examinations. The unadjusted mean BUN value increased slightly from the Baseline to the followup examination, but the increases were symmetrical in the two groups and nonsignificant (p=0.48).

In conclusion, none of the six renal assessment variables showed a significant difference between the Ranch Hand and Comparison groups by unadjusted tests. However, in the adjusted analyses, all renal measurements except reported kidney disease revealed group-by-covariate interactions. These interactions were often complex, making it impossible to reach a firm conclusion as to the presence of an herbicide effect.

CHAPTER 17

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