CHAPTER 17

RENAL ASSESSMENT

INTRODUCTION

Background

Renal dysfunction and overt renal disease are not generally considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, renal failure due to acute intoxication from another phenoxy herbicide (MCPP) has been shown in two human cases, along with other severe toxic symptoms.[1]

In man and animals, 2,4-D, 2,4,5-T, and TCDD are excreted by the kidney, largely through a first-order kinetic process.[2-6] In most experimental animals, the kidney has been shown to contain only unmetabolized TCDD, while urine contains only metabolized TCDD compounds. Excretion of these compounds appears to be a function of the proximal convoluted tubules.[8-10] 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 role of primary nephrotoxicity.[11-14] In a number of experimental animals, the kidneys have been shown to be a site of TCDD deposition almost on the order of the liver in terms of the percentage of dose taken up per gram of tissue (adipose tissue shows the greatest uptake followed by liver, adrenals, and kidney).[7] It has been hypothesized that this high uptake rate may cause high exposures over prolonged times and lead to neoplastic growth or other damage.[15] Kidney-specific effects include an increase in retinyl esters in rats (which may be a response to TCDD-induced vitamin A deficiency), lipid peroxidation with low doses in some species of mice, enlarged kidneys in mink, and a high specificity for renal cytosol binding in hamsters.[15-18]

A variety of experimental pharmacokinetic studies have been conducted in man using both ingested 2,4-D and 2,4-5-T.[4-6,19,20] Most of these studies suggested an unconjugated excretion of these compounds by first-order kinetics. No acute deleterious renal 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.[21] Horses exposed to this arena and other contaminated arenas also frequently manifested hematuria. A thorough 5-year followup examination of the girl was essentially normal and did not reveal any renal sequelae.[22]

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.[23-25] A contemporary study of a residentially exposed cohort showed negative renal findings.[26]

A Times Beach, Missouri, 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.[27] Published morbidity studies of Monsanto workers reported essentially negative urinalysis findings, although data were not presented.[28,29]

Baseline Summary Results

The 1982 Baseline examination assessed renal disease and function by questionnaire and basic laboratory 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 blood urea nitrogen, creatinine clearance, presence of occult blood, five or more urine white blood cells per high-power field, 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 for the two groups, as were the means of blood urea nitrogen, urine specific gravity, and urine white blood cell count. 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. Known noncompliance to urine collection was much more frequent ($p<0.001$) 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 postprandial glucose levels (<120 mg/dl, ≥ 120 mg/dl). Blood urea nitrogen increased with age and urine 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.

1985 Followup Study Summary Results

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.

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

The unadjusted analysis of proteinuria showed no group differences 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. 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 enlisted personnel. A series of stratified analyses found no statistical differences for the Black enlisted strata of both groups. The approximate tenfold increase in hematuria in both groups over that observed at Baseline, was most likely due to different laboratory techniques (reagent-strip testing vs. microscopic observation).

Similar results were found for leukocyturia, i.e., a nonsignificant unadjusted analysis, 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.

Blood urea nitrogen levels did not vary significantly by group based on the unadjusted analysis. 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 blood urea nitrogen level in Black Comparisons than in Black Ranch Hands. Overall, the blood urea nitrogen results were similar to those observed at the Baseline examination.

Unadjusted urine specific gravity levels manifested marginally significant group differences (p=0.082). 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 vs. 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 blood urea nitrogen levels between the two examinations. The unadjusted mean blood urea nitrogen value increased slightly from the Baseline to the followup examination, but the increases were symmetrical in the two groups and non-significant.

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 a group difference.

Parameters of the 1987 Renal Assessment

Dependent Variables

The 1987 renal assessment was based on questionnaire and laboratory data.

Questionnaire Data

In the self-administered family and personal history questionnaire, each study participant was asked whether they had ever experienced kidney trouble or kidney stones. A composite variable, history of kidney disease/stones, was constructed by assigning yes for any participant who responded with a yes to at least one of the two questions. This composite variable, based on self-reported and unverified information, was analyzed as a measure of the renal system function of each participant.

No 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 analyzed 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 four covariates (age, race, occupation, and diabetic class) were examined in the analysis of renal data, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Diabetic class was defined as diabetic (verified history of diabetes or $\geq$200 mg/dl glucose), impaired (140 mg/dl$\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 trichotomized for presentation purposes (e.g., dependent variable-covariate associations and interaction summaries).

Relation to Baseline and 1985 Followup Studies

The six variables analyzed in the 1987 followup were analyzed in the Baseline and 1985 followup studies.

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

Statistical Methods

The basic statistical analysis methods used in the analysis of the renal data are described in Chapter 7. Table 17-1 summarizes the statistical analyses performed for the 1987 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.

Although no participants were excluded for medical reasons in the renal assessment as stated above, some dependent variable and covariate data were missing. The number of participants with missing data is provided in Table 17-2 by group and variable.

RESULTS

Ranch Hand and Comparison Group Contrast

The results of the unadjusted and adjusted Ranch Hand and Comparison group analyses are summarized in Tables 17-3 and 17-4, respectively. Table N-1 of Appendix N contains the dependent variable-covariate associations for the renal assessment. The summary of group-by-covariate interactions for group contrasts on the renal variables is provided in Table N-2 of Appendix N.

TABLE 17-1.

Statistical Analysis for the Renal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
History of Kidney Disease/Stones	Q-SR	D	Yes No	AGE RACE OCC DIAB	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Urinary Protein (mg/dl)	LAB	D	Absent Present	AGE RACE OCC DIAB	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Urinary Occult Blood (RBC/HPF)	LAB	D	Normal: Absent Abnormal: ≥ 1	AGE RACE OCC DIAB	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Urinary White Blood Cell Count (WBC/HPF)	LAB	D	Normal: ≤ 2 Abnormal: ≥ 2	AGE RACE OCC DIAB	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Blood Urea Nitrogen (BUN)(mg/dl)	LAB	C	--	AGE RACE OCC DIAB	UC:TT AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM L:RM
Urine Specific Gravity	LAB	C	--	AGE RACE OCC DIAB	UC:TT AC:GLM CA:CC,GLM,TT UE:GLM,TT AE:GLM

TABLE 17-1. (continued)

Statistical Analysis for the Renal Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born 1923-1941 Born ≤1922
Race (RACE)	MIL	D	Nonblack Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Diabetic Class (DIAB)	LAB/Q-V	D	Diabetic: past history or ≥200 mg/dl glucose Impaired: ≥140-<200 mg/dl glucose Normal: <140 mg/dl glucose

Abbreviations:

Data Source:
LAB--1987 SCRF laboratory results
MIL--Air Force military records
Q-SR--1987 Family and Personal History questionnaire (self-reported)
Q-V--1987 NORC questionnaire (verified)

Data Form:
C--Continuous analysis only
D--Discrete analysis only
D/C--Appropriate form for analysis (either discrete or continuous)

Statistical Analyses:
UC--Unadjusted core analyses
AC--Adjusted core analyses
CA--Dependent variable-covariate associations
UE--Unadjusted exposure index analyses
AE--Adjusted exposure index analyses
L--Longitudinal analyses

TABLE 17-1. (continued)

Statistical Analysis for the Renal Assessment

Abbreviations (continued):

Statistical Methods:
CC--Pearson's product moment correlation coefficient
CS--Chi-square contingency table test
FT--Fisher's exact test
GLM--General linear models analysis
LR--Logistic regression analysis
RM--Repeated measures analysis
TT--Two-sample t-test

TABLE 17-2.

Number of Participants With Missing Data for the Renal Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
History of Kidney Disease/Stones	DEP	0	2	2
Urinary Protein	DEP	0	1	1
Urinary Occult Blood	DEP	0	1	1
Urinary White Blood Cell Count	DEP	0	1	1
Blood Urea Nitrogen	DEP	1	2	3
Urine Specific Gravity	DEP	0	1	1
Diabetic Class	COV	5	7	12

Abbreviations: DEP--Dependent variable (missing data)
COV--Covariate (missing data)

TABLE 17-3.

Unadjusted Analysis for Renal Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
History of Kidney Disease/ Stones	n	995	1,297		
	Number/%				
	Yes	108 10.9%	143 11.0%	0.98 (0.75,1.28)	0.952
	No	887 89.1%	1,154 89.0%		
Urinary Protein	n	995	1,298		
	Number/%				
	Present	47 4.7%	60 4.6%	1.02 (0.69,1.51)	0.986
	Absent	948 95.3%	1,238 95.4%		
Urinary Occult Blood	n	995	1,298		
	Number/%				
	Abnormal	83 8.3%	94 7.2%	1.17 (0.86,1.59)	0.368
	Normal	912 91.7%	1,204 92.8%		
Urinary White Blood Cell Count	n	995	1,298		
	Number/%				
	Abnormal	71 7.1%	92 7.1%	1.01 (0.73,1.39)	0.999
	Normal	924 92.9%	1,206 92.9%		
Blood Urea Nitrogen	n	994	1,297		
	Mean[a]	14.6	14.7	--	0.339
	95% C.I.[a]	(14.4,14.8)	(14.5,14.9)		
Urine Specific Gravity	n	995	1,298		
	Mean	1.0198	1.0200	--	0.477
	95% C.I.	(1.0194,1.0202)	(1.0197,1.0203)		

[a]Transformed from square root scale.

--Estimated relative risk not applicable for continuous analysis of a variable.

TABLE 17-4.

Adjusted Analysis for Renal Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
History of Kidney Disease/ Stones	n	995	1,297	0.98 (0.75,1.27)	0.853	AGE (p<0.001)
Urinary Protein	n	990	1,292	1.02 (0.68,1.52)**	0.928**	GRP*OCC (p=0.027) AGE (p=0.001) DIAB (p<0.001)
Urinary Occult Blood	n	995	1,298	1.17 (0.86,1.59)**	0.321**	GRP*RACE (p=0.016) OCC (p=0.039)
Urinary White Blood Cell Count	n	995	1,298	1.01 (0.73,1.39)	0.966	AGE (p=0.010) RACE (p=0.002)
Blood Urea Nitrogen	n Adj. Mean**[a] 95% C.I.**[a]	990 14.1 (13.7,14.5)	1,292 14.3 (13.9,14.7)	--	0.229**	GRP*RACE (p=0.040) AGE*RACE (p=0.014) AGE*OCC (p=0.023) AGE*DIAB (p=0.007)
Urine Specific Gravity	n Adj. Mean 95% C.I.	995 1.0198 (1.0194, 1.0201)	1,298 1.0196 (1.0192, 1.0200)	--	0.497	AGE*OCC (p=0.035)

GRP: Group (Ranch Hand, Comparison).
**Group-by-covariate interaction ($0.01 < p \leq 0.05$)--adjusted relative risk/mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.
[a]Transformed from square root scale.
--Adjusted relative risk not applicable for continuous analysis of a variable.

Questionnaire Variable

History of Kidney Disease/Stones

As shown in Table 17-3, the unadjusted analysis of history of kidney disease/stones did not reveal a significant difference between the Ranch Hand and Comparison groups (p=0.952).

Based on the pooled group data, the covariate test of association with age was statistically significant (p<0.001). There was a history of kidney disease/stones reported for 7.7 percent of the participants born in or after 1942, 13.1 percent of those born between 1923 and 1941, and 15.5 percent of those born in or before 1922.

In the adjusted analysis of history of kidney disease/stones, no significant difference between the Ranch Hands and the Comparisons was detected (p=0.853). Age was a significant covariate in this analysis (p<0.001).

Laboratory Examination Variables

Urinary Protein

In the unadjusted analysis of urinary protein, no significant difference was identified between the Ranch Hand and Comparison groups (p=0.986).

As shown in Table N-1 of Appendix N, covariate tests of associations showed that age, race, and diabetic class were statistically significant (p=0.030, p=0.047, and p<0.001, respectively). The percentage of participants with urinary protein present increased with age (3.5% for those born in or after 1942, 5.4% for those born between 1923 and 1941, and 8.3% for those born in or before 1922). The percentage of abnormalities in Blacks was 8.8 compared to 4.4 in nonblacks. The analysis of diabetic class showed that 12.8 percent of the diabetic participants had urinary protein present compared to 4.7 percent and 3.6 percent in the glucose-impaired and normal classes, respectively.

In the adjusted analysis of urinary protein, there was a significant group-by-occupation interaction (p=0.027). Age and diabetic class were significant effects in the model (p=0.001 and p<0.001, respectively). Stratifying by occupation, there was a significant group difference for enlisted flyers with a higher percentage of abnormalities in the Comparisons (Adj. RR: 0.30, 95% C.I.: [0.10,0.93], p=0.036). No significant differences were detected for the officer and enlisted groundcrew categories (p=0.182 and p=0.670, respectively). No significant group difference was revealed when the group-by-occupation interaction was deleted from the model (p=0.928).

Urinary Occult Blood

The unadjusted analysis of urinary occult blood showed no statistically significant difference between the two groups (p=0.368).

The results of the covariate associations suggested no age or diabetic class effects, but significant associations for race (p=0.015) and occupation (p=0.022) were noted. Blacks had a higher percentage of abnormalities than nonblacks (13.9% vs. 7.3%). For occupation, the highest percentage of abnormalities was for enlisted flyers (10.2%). There were 6.0 percent and 8.3 percent abnormalities in the officer and enlisted groundcrew categories, respectively.

There was a significant group-by-race interaction in the adjusted analysis (p=0.016). Occupation was a significant covariate in the model (p=0.039). The Black Ranch Hands had a significantly higher percentage of abnormalities than Black Comparisons (Adj. RR: 3.75, 95% C.I.: [1.33,10.60], p=0.013). No group difference was detected for nonblacks (p=0.858). Without the group-by-race interaction in the model, there was no significant difference between the Ranch Hands and Comparisons (p=0.321).

Urinary White Blood Cell Count

No significant difference was detected between the Ranch Hands and Comparisons in the unadjusted analysis of urinary white blood cell count (p=0.999).

Based on pooled group data, race was statistically significant (p=0.006), and diabetic class was borderline significant (p=0.073). Blacks had 13.9 percent abnormalities as compared to 6.7 percent abnormalities in nonblacks. For diabetic class, there were 9.4 percent abnormalities in the impaired class and 9.1 percent among diabetic participants. The percentage of abnormalities in the normal diabetic class was 6.4.

No significant group difference in urinary white blood cell count was detected in the adjusted analysis (p=0.966). Age and race were significant factors in the analysis (p=0.010 and p=0.002, respectively).

Blood Urea Nitrogen

In the unadjusted analysis of blood urea nitrogen, there was no significant difference between the two groups (p=0.339).

The covariate associations with blood urea nitrogen revealed that age (p<0.001), race (p=0.003), and occupation (p<0.001) were significant. Diabetic class was borderline significant (p=0.057). There was a positive correlation with age (r=0.195). The mean for nonblacks (14.8 mg/dl) was higher than for Blacks (13.5 mg/dl). For occupation, the officers had the highest mean (15.3 mg/dl), followed by the enlisted groundcrew (14.3 mg/dl) and enlisted flyers (14.2 mg/dl). The diabetic participants had a mean of 15.2 mg/dl as compared with means of 14.6 mg/dl and 14.5 mg/dl for the normal and glucose-impaired classes, respectively.

There were four significant interactions in the adjusted analysis of blood urea nitrogen: group-by-race (p=0.040), age-by-race (p=0.014), age-by-occupation (p=0.023), and age-by-diabetic class (p=0.007). Investigating the group-by-race interaction further, no significant group difference was

detected for nonblacks (p=0.506); however, the Black Comparisons had a statistically significant higher adjusted mean than the Black Ranch Hands (14.5 mg/dl vs. 13.1 mg/dl, p=0.022). Without the group-by-race interaction in the model, no significant group difference was found (p=0.229).

Urine Specific Gravity

No significant difference was detected between the Ranch Hands and Comparisons in the unadjusted analysis of urine specific gravity (p=0.477).

Using the Ranch Hand and Comparison data combined, age (p<0.001), race (p=0.045), and occupation (p<0.001) were found to be statistically significant. The analysis showed that urine specific gravity was negatively correlated with age (r=-0.100). The mean urine specific gravity for Blacks and nonblacks was 1.0209 and 1.0198, respectively. The mean of the enlisted groundcrew was 1.0209 as compared to means of 1.0196 and 1.0189 for enlisted flyers and officers, respectively.

In the adjusted analysis of urine specific gravity, no difference between the Ranch Hands and Comparisons was identified (p=0.497). Age-by-occupation was a significant interaction in the model (p=0.035).

Exposure Index Analysis

The unadjusted and adjusted results of the exposure index analyses of the Ranch Hands are presented in Tables 17-5 and 17-6, respectively. An overall summary of exposure index-by-covariate interactions is provided in Table 17-7; detailed results are contained in Table N-3 of Appendix N. The final interpretation of these exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. This report is expected in 1991.

Questionnaire Variable

History of Kidney Disease/Stones

The unadjusted and adjusted analyses identified no statistically significant results. However, in the unadjusted analyses, the high versus low exposure contrast for the officers and the medium versus low contrast for enlisted groundcrew were borderline significant (p=0.098 and p=0.076, respectively). For the officers, 16.0 percent of the high exposure category reported a history of kidney disease/stones as compared to 8.5 percent of the low exposure category (Est. RR: 2.06, 95% C.I.: [0.94,4.50]). Within the enlisted groundcrew cohort, 12.9 percent of the low exposure category and 6.3 percent of the medium exposure category reported a history of kidney disease/stones (Est. RR: 0.46, 95% C.I.: [0.20,1.02]).

TABLE 17-5.

Unadjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Medium		High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
History of Kidney Disease/ Stones	Officer	n	130		124		125		Overall		0.128
		Number/%									
		Yes	11	8.5%	12	9.7%	20	16.0%	M vs. L	1.16 (0.49,2.73)	0.904
		No	119	91.5%	112	90.3%	105	84.0%	H vs. L	2.06 (0.94,4.50)	0.098
	Enlisted Flyer	n	55		63		53		Overall		0.140
		Number/%									
		Yes	6	10.9%	11	17.5%	3	5.7%	M vs. L	1.73 (0.59,5.03)	0.456
		No	49	89.1%	52	82.5%	50	94.3%	H vs. L	0.49 (0.12,2.07)	0.526
	Enlisted Groundcrew	n	147		158		140		Overall		0.133
		Number/%									
		Yes	19	12.9%	10	6.3%	16	11.4%	M vs. L	0.46 (0.20,1.02)	0.076
		No	128	87.1%	148	93.7%	124	88.6%	H vs. L	0.87 (0.43,1.77)	0.838
Urinary Protein	Officer	n	130		124		125		Overall		0.498
		Number/%									
		Present	6	4.6%	4	3.2%	8	6.4%	M vs. L	0.69 (0.19,2.50)	0.808
		Absent	124	95.4%	120	96.8%	117	93.6%	H vs. L	1.41 (0.48,4.20)	0.726
	Enlisted Flyer	n	55		63		53		Overall		0.738
		Number/%									
		Present	2	3.6%	1	1.6%	1	1.9%	M vs. L	0.43 (0.04,4.85)	0.898
		Absent	53	96.4%	62	98.4%	52	98.1%	H vs. L	0.51 (0.05,5.79)	0.999
	Enlisted Groundcrew	n	147		158		140		Overall		0.355
		Number/%									
		Present	6	4.1%	8	5.1%	11	7.9%	M vs. L	1.25 (0.42,3.70)	0.896
		Absent	141	95.9%	150	94.9%	129	92.1%	H vs. L	2.00 (0.72,5.57)	0.270

TABLE 17-5. (continued)

Unadjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Medium		High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Urinary Occult Blood	Officer	n	130		124		125		Overall		0.589
		Number/%									
		Abnormal	8	6.2%	6	4.8%	10	8.0%	M vs. L	0.78 (0.26,2.30)	0.856
		Normal	122	93.8%	118	95.2%	115	92.0%	H vs. L	1.33 (0.51,3.48)	0.740
	Enlisted Flyer	n	55		63		53		Overall		0.828
		Number/%									
		Abnormal	6	10.9%	9	14.3%	6	11.3%	M vs. L	1.36 (0.45,4.10)	0.790
		Normal	49	89.1%	54	85.7%	47	88.7%	H vs. L	1.04 (0.31,3.46)	0.999
	Enlisted Groundcrew	n	147		158		140		Overall		0.243
		Number/%									
		Abnormal	9	6.1%	18	11.4%	11	7.9%	M vs. L	1.97 (0.86,4.54)	0.155
		Normal	138	93.9%	140	88.6%	129	92.1%	H vs. L	1.31 (0.53,3.26)	0.730
Urinary White Blood Cell Count	Officer	n	130		124		125		Overall		0.294
		Number/%									
		Abnormal	6	4.6%	6	4.8%	11	8.8%	M vs. L	1.05 (0.33,3.35)	0.999
		Normal	124	95.4%	118	95.2%	114	91.2%	H vs. L	1.99 (0.71,5.57)	0.276
	Enlisted Flyer	n	55		63		53		Overall		0.161
		Number/%									
		Abnormal	6	10.9%	4	6.3%	1	1.9%	M vs. L	0.55 (0.15,2.07)	0.578
		Normal	49	89.1%	59	93.7%	52	98.1%	H vs. L	0.16 (0.02,1.35)	0.125
	Enlisted Groundcrew	n	147		158		140		Overall		0.272
		Number/%									
		Abnormal	10	6.8%	11	7.0%	16	11.4%	M vs. L	1.03 (0.42,2.49)	0.999
		Normal	137	93.2%	147	93.0%	124	88.6%	H vs. L	1.77 (0.77,4.04)	0.246

TABLE 17-5. (continued)

Unadjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Blood Urea Nitrogen	Officer	n	130	124	124	Overall		0.654
		Mean[a]	15.0	15.5	15.3	M vs. L	--	0.356
		95% C.I.[a]	(14.4,15.7)	(14.8,16.1)	(14.6,16.0)	H vs. L	--	0.587
	Enlisted Flyer	n	55	63	53	Overall		0.491
		Mean[a]	13.5	14.0	14.2	M vs. L	--	0.418
		95% C.I.[a]	(12.5,14.5)	(13.2,14.8)	(13.3,15.1)	H vs. L	--	0.260
	Enlisted Groundcrew	n	147	158	140	Overall		0.114
		Mean[a]	14.7	14.4	13.8	M vs. L	--	0.470
		95% C.I.[a]	(14.1,15.3)	(13.8,15.0)	(13.3,14.3)	H vs. L	--	0.033
Urine Specific Gravity	Officer	n	130	124	125	Overall		0.064
		Mean	1.0187	1.0183	1.0200	M vs. L	--	0.609
		95% C.I.	(1.0177, 1.0198)	(1.0172, 1.0195)	(1.0191, 1.0210)	H vs. L	--	0.072
	Enlisted Flyer	n	55	63	53	Overall		0.197
		Mean	1.0182	1.0200	1.0184	M vs. L	--	0.093
		95% C.I.	(1.0168, 1.0197)	(1.0186, 1.0213)	(1.0167, 1.0201)	H vs. L	--	0.889
	Enlisted Groundcrew	n	147	158	140	Overall		0.051
		Mean	1.0217	1.0205	1.0202	M vs. L	--	0.052
		95% C.I.	(1.0209, 1.0226)	(1.0196, 1.0214)	(1.0193, 1.0212)	H vs. L	--	0.023

[a]Transformed from square root scale.

--Estimated relative risk not applicable for continuous analysis of a variable.

TABLE 17-6.

Adjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
History of Kidney Disease/ Stones	Officer	n	130	124	123	Overall		0.156
						M vs. L	0.98 (0.40,2.36)	0.960
						H vs. L	1.89 (0.86,4.18)	0.115
	Enlisted Flyer	n	55	63	53	Overall		0.128
						M vs. L	1.74 (0.57,5.29)	0.331
						H vs. L	0.47 (0.11,2.02)	0.313
	Enlisted Groundcrew	n	146	156	140	Overall		0.283
						M vs. L	0.53 (0.23,1.20)	0.129
						H vs. L	0.87 (0.42,1.79)	0.699
Urinary Protein	Officer	n	130	124	123	Overall		0.626
						M vs. L	0.76 (0.20,2.92)	0.689
						H vs. L	1.39 (0.44,4.35)	0.574
	Enlisted Flyer	n	55	63	53	Overall		0.212
						M vs. L	0.06 (0.002,1.99)	0.117
						H vs. L	0.45 (0.03,6.84)	0.562
	Enlisted Groundcrew	n	146	156	140	Overall		0.537
						M vs. L	1.36 (0.45,4.06)	0.588
						H vs. L	1.79 (0.63,5.05)	0.274

TABLE 17-6. (continued)

Adjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Urinary Occult Blood	Officer	n	130	124	123	Overall		0.501
						M vs. L	0.67 (0.22,2.05)	0.485
						H vs. L	1.25 (0.47,3.32)	0.650
	Enlisted Flyer	n	55	63	53	Overall		0.830
						M vs. L	1.38 (0.44,4.34)	0.578
						H vs. L	1.05 (0.31,3.53)	0.939
	Enlisted Groundcrew	n	146	156	140	Overall		0.144
						M vs. L	2.26 (0.96,5.35)	0.063
						H vs. L	1.32 (0.52,3.36)	0.560
Urinary White Blood Cell Count	Officer	n	130	124	123	Overall		0.395
						M vs. L	1.06 (0.32,3.51)	0.923
						H vs. L	1.89 (0.66,5.41)	0.238
	Enlisted Flyer	n	55	63	53	Overall		****
						M vs. L	****	****
						H vs. L	****	****
	Enlisted Groundcrew	n	146	156	140	Overall		****
						M vs. L	****	****
						H vs. L	****	****

TABLE 17-6. (continued)

Adjusted Exposure Index for Renal Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Blood Urea Nitrogen	Officer	n	130	124	123	Overall		0.977**
		Adj. Mean**[a]	14.2	14.3	14.2	M vs. L	--	0.860**
		95% C.I.**[a]	(12.8,15.8)	(12.9,15.8)	(12.8,15.7)	H vs. L	--	0.983**
	Enlisted Flyer	n	55	63	53	Overall		0.462
		Adj. Mean[a]	13.0	13.6	13.8	M vs. L	--	0.367
		95% C.I.[a]	(11.4,14.6)	(12.2,15.0)	(12.2,15.4)	H vs. L	--	0.234
	Enlisted Groundcrew	n	146	156	140	Overall		****
		Adj. Mean	****	****	****	M vs. L	--	****
		95% C.I.	****	****	****	H vs. L	--	****
Urine Specific Gravity	Officer	n	130	124	123	Overall		0.064
		Adj. Mean	1.0183	1.0180	1.0197	M vs. L	--	0.691
		95% C.I.	(1.0157, 1.0209)	(1.0154, 1.0206)	(1.0171, 1.0223)	H vs. L	--	0.071
	Enlisted Flyer	n	55	63	53	Overall		0.272
		Adj. Mean	1.0188	1.0204	1.0189	M vs. L	--	0.150
		95% C.I.	(1.0160, 1.0216)	(1.0180, 1.0228)	(1.0163, 1.0215)	H vs. L	--	0.924
	Enlisted Groundcrew	n	146	156	140	Overall		0.059
		Adj. Mean	1.0214	1.0201	1.0201	M vs. L	--	0.042
		95% C.I.	(1.0202, 1.0227)	(1.0189, 1.0214)	(1.0188, 1.0213)	H vs. L	--	0.038

****Exposure index-by-covariate interaction ($p \leq 0.01$)--adjusted mean, confidence interval, and p-value not presented.

**Exposure index-by-covariate interaction ($0.01 < p \leq 0.05$)--adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

[a]Transformed from square root scale.

--Adjusted relative risk not applicable for continuous analysis of a variable.

TABLE 17-7.

Summary of Exposure Index-by-Covariate Interactions
From Adjusted Analyses for Renal Variables*

Variable	Occupation	Covariate	p-Value
Urinary White Blood Cell Count	Enlisted Flyer	Age	0.004
Urinary White Blood Cell Count	Enlisted Flyer	Diabetic Class	0.033
Urinary White Blood Cell Count	Enlisted Groundcrew	Race	0.005
Urinary White Blood Cell Count	Enlisted Groundcrew	Diabetic Class	0.014
Blood Urea Nitrogen	Officer	Age	0.024
Blood Urea Nitrogen	Enlisted Groundcrew	Age	0.006

*Refer to Table N-3 for a further investigation of these interactions.

Laboratory Examination Variables

Urinary Protein

There were no significant differences detected in the unadjusted and adjusted analyses of urinary protein.

Urinary Occult Blood

In the unadjusted analyses, no significant differences were identified. Based on the adjusted analyses, the medium versus low exposure contrast within the enlisted groundcrew cohort was borderline significant (p=0.063). For this contrast, the adjusted relative risk was 2.26 (95% C.I.: [0.96,5.35]).

Urinary White Blood Cell Count

The unadjusted analyses revealed no significant differences among the exposure categories for urinary white blood cell count. A similar non-significant finding was seen in the adjusted analysis for the officer cohort. There were two significant exposure index-by-covariate interactions in both

the enlisted flyer and enlisted groundcrew cohorts. Sparse numbers of abnormalities resulted when the interactions were investigated by stratifying by the covariates.

For the enlisted flyer cohort, the exposure index-by-age and exposure index-by-diabetic class interactions were significant (p=0.004 and p=0.033, respectively). Stratifying by age and diabetic class with this cohort, the overall analysis for the Ranch Hands in the normal diabetic class who were born in or after 1942 and for those in the normal diabetic class born between 1923 and 1941 were borderline significant (p=0.099 for both). Both of the abnormalities in the normal diabetic class for the Ranch Hands born in or after 1942 were in the low exposure category. For the Ranch Hands in the normal diabetic class who were born between 1923 and 1941, there were 12.9 percent abnormalities in the low exposure category as compared to 14.8 percent in the medium exposure category and 0.0 percent in the high exposure category.

There were significant exposure index-by-covariate interactions for race and diabetic class in the enlisted groundcrew cohort (p=0.005 and p=0.014, respectively). The overall exposure level relationship for nonblack Ranch Hands in the normal diabetic class detected a borderline significant dose-response relationship with 3.0 percent, 6.2 percent, and 11.7 percent abnormalities in the low, medium, and high exposure categories, respectively (p=0.053). The high versus low exposure contrast was significant (p=0.036). The overall exposure level analysis for nonblacks classified as diabetic was significant (27.3% low, 30.8% medium, and 0.0% high; p=0.049). Within this stratum, the high versus low exposure contrast was borderline significant (p=0.100). Among the Black Ranch Hands classified as diabetic, there was only one abnormality, which was in the high exposure level (p=0.050).

Blood Urea Nitrogen

There was no evidence of a significant dose-response relationship for blood urea nitrogen for the enlisted flyer cohort in both unadjusted and adjusted analyses. In the officer cohort, there was a significant exposure index-by-age interaction (p=0.024); stratifying by age revealed no significant differences. The unadjusted analysis and the adjusted analysis without the interaction for the officer cohort also did not support a dose-response relationship.

For the enlisted groundcrew cohort, the means for the low, medium, and high exposure categories were 14.7 mg/dl, 14.4 mg/dl, and 13.8 mg/dl, respectively. In the unadjusted analysis, the high versus low exposure contrast was significant (p=0.033). There was a significant exposure index-by-age interaction in the adjusted analysis (p=0.006). Stratifying by age, two contrasts were found to be borderline significant (p=0.074 high vs. low for those born in or after 1942 and p=0.084 medium vs. low for those born in or before 1922). However, neither result supported a relationship of abnormal mean levels increasing as the level of exposure increases.

Urine Specific Gravity

Within the officer cohort, the highest mean was in the high exposure category, and the lowest mean was in the medium exposure category (unadjusted

means: 1.0187 low, 1.0183 medium, and 1.0200 high). The unadjusted and adjusted analyses for the officer cohort were borderline significant (p=0.064 for both). The high versus low exposure contrasts were also borderline significant (p=0.072 unadjusted and p=0.071 adjusted).

In the enlisted flyer cohort, the highest mean level was in the medium exposure category. Although the overall exposure relationships were not found to be significant, the unadjusted analysis of the medium versus low exposure contrast was borderline significant (means: 1.0182 low, 1.0200 medium, and 1.0184 high; p=0.093).

The overall exposure level relationships for the enlisted groundcrew cohort were borderline significant (p=0.051 unadjusted and p=0.059 adjusted). In the unadjusted analysis, the means were 1.0217, 1.0205, and 1.0202 for the low, medium, and high exposure categories, respectively. The high versus low exposure contrast was found to be significant (p=0.023), and the medium versus low contrast was marginally significant (p=0.052). In the adjusted analysis, both contrasts were significant (p=0.042 medium vs. low and p=0.038 high vs. low).

Longitudinal Analysis

Of the renal variables, blood urea nitrogen was investigated to assess longitudinal differences between the 1982 Baseline examination and the 1987 followup examination. As shown in Table 17-8, no significant difference in the change over time was detected (p=0.553). A slight increase in the blood urea nitrogen mean levels from 1982 to 1987 was observed for both groups.

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 present study.

Though subject to some day-to-day variation related to diet and state of hydration, the 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.

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 is pertinent to interpretation of the renal assessment data. With normal fluid balance, the healthy kidneys can excrete up to 100-150 mg of total protein in 24 hours. The qualitative dipstick test used in the current study is sensitive to protein concentrations as low as 10-15 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.

TABLE 17-8.

Longitudinal Analysis of Blood Urea Nitrogen:
A Contrast of 1982 Baseline and 1987 Followup Examination Means

Examination	Group Means[a]		p-Value[a] (Equality of Differences)
	Ranch Hand	Comparison	
1982 Baseline	13.7	14.0	0.553
1985 Followup	14.2	14.4	
1987 Followup	14.5	14.7	

Note: Summary statistics for the 1982 Baseline and 1987 followup are based on 943 Ranch Hands and 1,110 Comparisons who participated in 1982 Baseline and 1987 followup examinations. The p-value given is in reference to ahypothesis test involving 1982 Baseline and 1987 followup results. Summary statistics on 923 of these Ranch Hands and 1,093 of these Comparisons who also participated in the 1985 followup are also included for reference purposes only.

[a]Means transformed from the square root scale; hypothesis test performed on the square root scale.

Similarly, on microscopic examination of the urinary sediment, it is not uncommon to intermittently find a few red or white blood cells in the absence of definable neoplastic or inflammatory cause, trauma, or kidney stones. When documented as an isolated finding in the absence of symptoms or other signs, such intermittent microcyturia can usually be considered benign.

With reference to the current study, no significant group differences in the renal indices were found between the Ranch Hands and Comparisons in the unadjusted analyses. In the dependent variable-covariate analysis, several associations were defined that are consistent with established clinical observations.

In the adjusted analyses, significant covariate associations with age were documented. The twofold increased historical incidence of genitourinary disease would be expected with aging in this all male population with the development of benign prostatic hypertrophy and bladder outlet obstruction.

In association with benign nephrosclerosis of the normally aging kidney, there is a gradual reduction in renal mass (from an average of 260 grams in the young adult to 190 grams in the eighth decade) and a 50 percent reduction in renal plasma flow (from 600 cc/min to 300 cc/min). An age-related increase in blood urea nitrogen and proteinuria would be expected findings and were documented in the current study.

Several of the race-dependent variable associations can be explained on the basis of established clinical correlations. The increased incidence of hypertension with hypertensive nephropathy in Blacks is well recognized and might account for the increased incidence of proteinuria, hematuria, and elevated blood urea nitrogen in this population. Though the numbers are small, microinfarction of the renal medulla in sickle cell trait (8-10% incidence in Blacks) might have been a minor contributing factor in the incidence of hematuria. The cause of the twofold increased incidence of leukocyturia in Blacks is uncertain and the very slight difference in mean specific gravity (1.0209 vs. 1.0198) is not clinically significant.

In the diabetic class, the increased incidence of hypertensive and arteriosclerotic vascular disease and of urinary tract infections related to glycosuria provide reasonable explanation for the significant covariate association of proteinuria, leukocyturia, and elevated blood urea nitrogen in this population.

In summary, the renal assessment data revealed abnormalities in five laboratory indices at a prevalence that is common in ambulatory practice. There were no significant overall differences between the Ranch Hand and Comparison cohorts. Most of the covariate associations can be explained on the basis of established clinical correlations. Finally, when documented as isolated findings, the benign nature of these abnormalities should be emphasized.

SUMMARY

The 1987 renal assessment was based on six variables. The results of the Ranch Hand and Comparison contrasts are summarized in Table 17-9.

The historical assessment of kidney disease/stones based on self-reported data showed no significant differences between the Ranch Hand and Comparison groups. These results are consistent with the results of the 1985 followup but appear to be in marked contrast to the Baseline findings. The Comparison cohort is different between the Baseline report and the 1987 followup study (Original Comparisons vs. all Comparisons), and the definition of kidney disease has been expanded from the Baseline study to include kidney stones. However, when the analysis of the 1987 followup data was restricted to the Original Comparisons and kidney stones were not included in the definition of kidney disease, the prevalence rate of kidney disease was comparable between the two examinations, but the difference between groups was still nonsignificant (p=0.952).

The current renal function was evaluated by five laboratory variables: urine protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, and urine specific gravity.

There was no significant difference detected between the two groups based on the unadjusted analysis of urinary protein. In the adjusted analysis, there was a significant interaction between group and occupation. Stratifying by occupation revealed that the Comparison enlisted flyers had a higher percentage of abnormalities than the Ranch Hand enlisted flyers (p=0.036). After deleting the group-by-occupation interaction, no difference between the two groups was observed. This result differed from the twofold increase of proteinuria observed in Comparisons at Baseline.

TABLE 17-9.

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Renal Variables

Variable	Type of Analysis	Unadjusted	Adjusted
Questionnaire			
History of Kidney Disease/Stones	D	NS	NS
Laboratory			
Urinary Protein	D	NS	** (NS)
Urinary Occult Blood	D	NS	** (NS)
Urinary White Blood Cell Count	D	NS	NS
Blood Urea Nitrogen	C	NS	** (NS)
Urine Specific Gravity	C	NS	NS

D: Discrete analysis performed.
C: Continuous analysis performed.
NS: Not significant ($p>0.10$).
** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table N-2 for a detailed description of this interaction.

No difference was identified between the Ranch Hands and the Comparisons based on the analysis of urinary occult blood without adjustments for covariates. However, after stratifying by race due to a significant group-by-race interaction, the estimated prevalence rate for the Black Ranch Hands was noted as being statistically higher than the corresponding rate for the Black Comparisons ($p=0.013$). The estimated prevalence rates were not detected as being different based on an adjusted model without the group-by-race interaction.

Based on the analyses of urinary white blood cell count, no differences were detected between the two groups in either the unadjusted or adjusted analyses.

The mean blood urea nitrogen levels of the Ranch Hands and Comparisons did not vary significantly when compared without adjustments. The adjusted

analysis detected a significant group-by-race interaction. Stratifying by race revealed that the mean of the Black Comparisons was statistically higher than the mean of the Black Ranch Hands ($p=0.022$). The adjusted means were also not significantly different when estimated without the group-by-race interaction in the model.

There was no evidence that the mean urine specific gravity was different between the Ranch Hands and Comparisons in either the unadjusted or adjusted analysis.

The exposure index analyses showed very little evidence of a dose-response relationship at the 1987 followup examination. No pattern in the relationship of abnormality rates or mean levels was seen within occupational cohort.

The longitudinal analysis was based solely upon the contrast of blood urea nitrogen levels between the 1982 and 1987 examinations. The unadjusted mean levels increased slightly from 1982 to 1987, but the change between the Ranch Hands and Comparisons over time was not significantly different.

In conclusion, none of the six variables of the renal assessment showed a significant difference based on the unadjusted analyses. For three of the variables, the adjusted results supported the findings of the unadjusted analyses; there were significant group-by-covariate interactions for the other variables. Further examination by strata revealed that in one case the Ranch Hand prevalence rate was higher than the Comparison rate and that the opposite relationship existed for another case. In the third instance, the Comparison mean was higher than the mean of the Ranch Hands; however, both means were within the normal range. The adjusted analyses without the group-by-covariate interactions supported the findings of the unadjusted analyses; the renal status of the Ranch Hands and Comparisons was generally similar.

CHAPTER 17

REFERENCES

1. Meulenbelt, J., J.H. Zwaveling, P. van Zoonen, and N.C. Notermans. 1988. Acute MCPP intoxication: Report of two cases. Hum. Toxicol. 7(3):289-292.

2. St. John, L.E., D.G. Wagner, and D.J. Lisk. 1964. Fate of atrazine, kuron, silvex, and 2,4,5-T in the dairy cow. J. Dairy Sci. 47:1267-1270.

3. Erne, K. 1966. Studies on the animal metabolism of phenoxyacetic herbicides. Acta Vet. Scand. 7:264-271.

4. Matsumura, A. 1970. The fate of 2,4,5-trichlorophenoxyacetic acid in man. Jap. J. Environ. Health 12:20-25.

5. Gehring, P.J., C.G. Kramer, B.A. Schwetz, J.Q. Rose, and V.K. Rowe. 1973. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to man. Toxicol. Appl. Pharmacol. 26:352-361.

6. Kohli, J.D., R.N. Khanna, B.N. Gupta, M.M. Dhar, J.S. Tandon, and K.P. Sircar. 1974. Absorption and excretion of 2,4,5-trichlorophenoxyacetic acid in man. Arch. Int. Pharmacodyn. 210:250-255.

7. Olson, J.R. 1986. Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin in guinea pigs. Toxicol. Appl. Pharmacol. 85:263-273.

8. Bjorklund, N.E., and K. Erne. 1971. Phenoxy-acid-induced renal changes in the chicken: I. Ultrastructure. Acta Vet. Scand. 12:243-256.

9. Fowler, B.A., G.E.R. Hook, and G.W. Lucier. 1977. Tetrachlorodibenzo-p-dioxin induction of renal microsomal enzyme systems: Ultrastructural effects on pars recta (S_3) proximal tubule cells of the rat kidney. J. Pharmacol. Exp. Ther. 203(3):712-721.

10. Koschier, F.J., and M. Acara. 1979. Transport of 2,4,5-trichlorophenoxyacetate in the isolated, perfused rat kidney. J. Pharmacol. Exp. Ther. 208:287-293.

11. Gupta, B.N., J.G. Vos, J.A. Moore, J.G. Zinkl, and B.C. Bullock. 1973. Pathological effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ. Health Persp. 5:125-140.

12. Pegg, D.G., W.R. Hewitt, K.M. McCormack, and J.B. Hook. 1976. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on renal function in the rat. J. Toxicol. Environ. Health 2:55-65.

13. Courtney, K.D., J.P. Putnam, and J.E. Andres. 1978. Metabolic studies with TCDD (dioxin) treated rats. Arch. Environ. Contam. Toxicol. 7(4):385-396.

14. Hook, J.B., K.M. McCormack, and W.M. Kluwe. 1978. Renal effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Pentachlorophenol: Chemistry, pharmacology and environmental toxicology, ed. K.R. Rao, pp. 381-388. New York: Plenum Press.

15. Kurl, R.N., J.M. Loring, and C.A. Villee. 1985. Control of 2,3,7,8-tetrachlorodibenzo-p-dioxin binding protein(s) in the hamster kidney. Pharmacology 30:245-254.

16. Jurek, M.A., R.H. Powers, L.C. Gilbert, and S.D. Aust. 1987. The effect of TCDD on acarat activity and vitamin A accumulation in the kidney of male Sprague-Dawley rats. Federation Proceedings 46(6):2291.

17. Mohammadpour, H., W.J. Murray, and S.J. Stohs. 1988. 2,3,7,8-tetrachlorodibenzo-p-dioxin TCDD-induced lipid peroxidation in genetically responsive and nonresponsive mice. Arch. Environ. Contam. Toxicol. 17(5):645-650.

18. Hochstein, J.R., R.J. Aulerich, and S.J. Bursian. 1988. Acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin to mink. Arch. Environ. Contam. Toxicol. 17(1):33-38.

19. Kohli, J.D., R.N. Khanna, B.N. Gupta, M.M. Dhar, J.S. Tandon, and K.P. Sircar. 1974. Absorption and excretion of 2,4-dichlorophenoxyacetic acid in man. Xenobiotica 4(2):97-100.

20. Sauerhoff, M.W., W.H. Braun, G.E. Blau, and P.J. Gehring. 1977. The fate of 2,4-dichlorophenoxyacetic acid (2,4-D) following oral administration to man. Toxicology 8:3-11.

21. Carter, C.D., R.D. Kimbrough, J.A. Liddle, R.E. Cline, M.M. Zack, W.F. Barthel, R.E. Koehler, and P.E. Phillips. 1975. Tetrachlorodibenzodioxin: An accidental poisoning episode in horse arenas. Science 188(4189):738-740.

22. Beale, M.G., W.T. Shearer, M.M. Karl, and A.M. Robson. 1977. Long-term effects of dioxin exposure. Lancet 1(8014):748.

23. Poland, A.P., D. Smith, G. Metter, and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant, with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. Arch. Environ. Health 22(3):316-327.

24. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin in laboratory workers. Br. J. Ind. Med. 32:46-53.

25. Pazderova-Vejlupkova, J., M. Nemcova, J. Pickova, L. Jirasek, and E. Lukas. 1981. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch. Environ. Health 36:5-11.

26. Hoffman, R.E., P.A. Stehr-Green, K.B. Webb, G. Evans, A.P. Knutsen, W.F. Schramm, J.L. Staake, B.B. Gibson, and K.K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255:2031-2038.

27. Stehr, P.A., G. Stein, H. Falk, E. Sampson, S.J. Smith, K. Steinberg, K. Webb, S. Ayres, W. Schramm, H.D. Donnell, and W.B. Gidney. 1986. A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contamination in Missouri. Arch. Environ. Health 41:16-22.

28. Moses, M., R. Lilis, K.D. Crow, J. Thornton, A. Fischbein, H.A. Anderson, and I.J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. Am. J. Ind. Med. 5:161-182.

29. Suskind, R.R., and V.S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372-2380.