Table XVI-6-6

PERCENT ABNORMAL LOW TESTOSTERONE VALUES
BY GROUP, AGE AND BODY FAT CATEGORY*

Age	Group	% Testosterone Low Abnormal in 10-25% Body Fat Subgroup		% Testosterone Low Abnormal in > 25% Body Fat Subgroup	
≤40	RH	2.00	(7/350)	7.89	(6/76)
≤40	COM	3.52	(8/227)	10.64	(5/47)
>40	RH	3.46	(16/463)	16.15	(21/130
>40	COM	4.00	(15/375)	19.09	(21/110)

* Abnormally high individuals and lean individuals (less than 10% body fat) were removed from the analysis due to sample size limitations.

Analysis of covariance is less vulnerable to the data limitations of sparse or empty cells than are log-linear models. Thus, the Ranch Hand group was contrasted with the comparison group in terms of the 5 endocrinological variables using analysis of covariance adjusting for age and percent body fat. In these analyses, all variables except group indicators were used as continuous variables. In the analysis of thyroid hormones, data from individuals with thyroidectomies were removed, and in the analysis of testosterone levels, individuals with orchiectomies were removed. In the analysis of glucose levels, all participant data were used irrespective of dietary compliance as compliance was not found to influence glucose levels.

Table XVI-6-7 provides unadjusted and adjusted means. When a group-by-age or group-by-body fat interaction was observed with P < 0.10, adjusted means, and age and body fat main effects are not reported.

One overall group difference is noted in Table XVI-6-7. Specifically, the Ranch Handers show a higher testosterone level than do comparison participants (P = 0.02 unadjusted, 0.06 adjusted). Both increasing age and increasing body fat were found to be associated with decreasing testosterone level with slopes being -3.8 ng/dl per year of life and -12.6 ng/dl per % body fat.

Table XVI-6-7

RANCH HAND - COMPARISON GROUP MEANS OF ENDOCRINE VARIABLES

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Means	Adj'd Mean	P Value for Adj'd Means	Remarks about Adjusting Covariates
T3	Com	770	30.14	0.21	*	*	Group-by-age interaction
Uptake (%)	RH	1037	30.28				(P = 0.026)
T4	Com	770	8.39	0.31	8.39	0.38	None significant at P<.05
(µg/dl)	RH	1038	8.46		8.45		
FTI	Com	770	2.51	0.07	2.51	0.13	Age (P<.001)
	RH	1038	2.54		2.54		% Body fat (P<.001)
GLU 2HR	Com	773	102	0.37	*	*	Group-by-age interaction
(mg/dl)	RH	1045	104				(P=.006)
TEST	Com	772	634	0.02	637	0.06	Age (P<.001)
(ng/dl)	RH	1039	654		652		% Body fat (P<.001)

Two other group differences are noted in Table XVI-6-7; however, these are associated with group-by-age interactions. In both the Ranch Hand and comparison groups, decreasing T3 uptake is observed associated with advancing age, but the slope was found to be -0.0068% per year in the comparison group while it is -0.0495% per year in the Ranch Hand group. Glucose levels, measured 2 hours into the glucose tolerance test, were observed to increase with age in both the comparison and Ranch Hand group; however, the rate of increase is 0.77 mg/dl per year in the comparison group and 1.53 mg/dl per year in the Ranch Hand group.

Dose-response data within the Ranch Hand group are provided in Tables XVI-6-8, XVI-6-9 and XVI-6-10. No overall statistically significant dose-response relationships were detected; however, 5 exposure group by covariate interactions were noted. These interactions are summarized in Table XVI-6-11. No interactions are seen with respect to the variables T3 or T4.

Table XVI-6-8

RANCH HAND OFFICERS
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	110	30.9	0.39	30.8	0.88	Age (P=0.033)
	M	126	30.6		30.7		% Body fat (P=0.039)
	H	125	30.6		30.6		
T4	L	110	8.21	0.12	8.23	0.89	None
	M	126	8.15		8.15		
	H	125	8.22		8.22		
FTI	L	110	2.51	0.59	*	*	Age-exposure interaction (P=0.042)
	M	126	2.47				
	H	125	2.49				
GLU 2 HR	L	111	106.7	0.90	*	*	% Body fat-exposure interaction (P=0.041)
	M	128	104.2				
	H	125	106.8				
TEST	L	111	614.8	0.85	*	*	% Body fat-exposure interaction (P=0.011)
	M	127	614.2				
	H	123	604.5				

Table XVI-6-9

RANCH HAND - FLYING ENLISTED PERSONNEL
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	59	29.6	0.57	29.6	0.59	None
	M	59	30.0		30.0		
	H	64	30.0		30.1		
T4	L	59	8.85	0.32	8.85	0.32	None
	M	59	8.48		8.49		
	H	64	8.48		8.50		
FTI	L	59	2.60	0.45	*	*	% Body fat-exposure interaction (P=0.03)
	M	59	2.51				
	H	64	2.60				
GLU 2 HR	L	59	102.3	0.88	102.3	0.78	Age (P=0.01)
	M	59	105.9		108.0		
	H	66	105.6		103.8		
TEST	L	59	663.5	0.98	659.8	0.90	% Body fat (P<0.001)
	M	58	657.8		653.5		
	H	66	658.5		666.7		

Table XVI-6-10

RANCH HAND - GROUND ENLISTED PERSONNEL
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	151	29.8	0.30	29.9	0.18	Age (P<0.001)
	M	176	30.2		30.1		% Body fat (P<0.003)
	H	148	30.3		30.4		
T4	L	151	8.58	0.89	8.59	0.89	None
	M	177	8.67		8.67		
	H	148	8.59		8.58		
FTI	L	151	2.55	0.69	2.55	0.53	Age (P=0.01)
	M	177	2.58		2.56		% Body fat (P=0.03)
	H	148	2.60		2.61		
GLU 2 HR	L	151	99.9	0.60	*	*	% Body fat-exposure interaction (P=0.09)
	M	179	104.8				
	H	148	103.7				
TEST	L	151	686.4	0.97	685.6	0.93	Age (P=0.02)
	M	179	680.5		678.2		% Body fat (P<0.001)
	H	146	683.0		684.4		

Table XVI-6-11

ENDOCRINE DOSE - COVARIATE INTERACTIONS

	T3	T4	FTI	GLU 2 Hr	TEST
Ranch Hand Officers	No interactions	No interactions	Age-exposure interaction (P=0.042)	% Body fat-exposure interaction (P=0.041)	% Body fat-exposure interaction (P=0.011)
Ranch Hand Flying Enlisted	No interactions	No interactions	% Body fat-exposure interaction (P=0.03)	No interaction	No interactions
Ranch Hand Ground Enlisted	No interactions	No interactions	No interactions	% Body fat-exposure interaction (P=0.09)	No interactions

The FTI shows an age-exposure interaction among the officers and a % body fat-exposure interaction in the flying enlisted Ranch Hand group. Among the officers, FTI increased by 0.0041 per year of life in the low exposure group but decreased by 0.0127 and 0.0079 per year in the medium and high exposure groups respectively. No effect of body fat was suggested by the officer data. Among the flying enlisted, FTI did not appear affected by age, but increased with increasing % body fat in the low and medium exposure groups (0.00295 and 0.00378 per % body fat respectively) while it decreased with body fat (-0.0241 per % body fat) in the high exposure group. These FTI effects are interesting; however, the lack of consistency between occupational and exposure categories leads to doubt that an actual herbicide effect exists.

Both Ranch Hand officers and ground enlisted personnel show comparable body fat-exposure interactions affecting glucose levels. The glucose level-body fat slopes are given in Table XVI-6-12. In both the officer and ground enlisted categories, the low exposed individuals show a decreasing blood glucose with increasing % body fat, but this relationship changes to a positive correlation in the medium and high exposure categories.

Table XVI-6-12

CHANGE IN GLUCOSE LEVEL PER % BODY FAT
(mg/dl PER % BODY FAT)
BY HERBICIDE EXPOSURE LEVEL IN TWO RANCH HAND GROUPS

Exposure Category	Ranch Hand Officers	Ranch Hand Ground Enlisted
Low	+1.18	-0.30
Medium	+2.94	+1.75
High	+1.26	+1.36

A % body fat by exposure interaction is also observed to affect testosterone levels in Ranch Hand officers with a very low probability that the effect could be due to chance (P = 0.011). Low exposed officers show a decrease in serum testosterone levels of 4.5 ng/dl per % body fat while medium and high exposed officers show decreases of 16.6 ng/dl and 15.3 ng/dl per % body fat respectively.

3. Summary

The Ranch Hand group was found to differ from the comparison group with respect to proportions of individuals in normal and abnormal thyroid hormone categories. The difference is a tendency toward hyperthyroxinemia which is directionally opposite to what would be expected on the basis of subacute animal studies. On the other hand, decreasing T3 uptakes are associated with advancing age in both groups with the slope being much steeper in the Ranch Hand group. Finally, no meaningful association of thyroid hormone levels with the exposure index were found. Thus, in sum, no definite herbicide effect on thyroid function can be considered demonstrated; however, it also cannot be confidently asserted that a herbicide effect on thyroid function has not occurred. As a group, Ranch Hand personnel have higher testosterone levels than comparison individuals and Ranch Hand officers evidence a decrease in testosterone level with increasing body fat that is related to herbicide exposure category (higher exposures are associated with greater decreases in testosterone with body fat). Since subacute animal studies have shown decreased catabolism of testosterone, higher serum levels could be expected. Thus, this finding in the present study may reflect an herbicide effect, whose long-term impact will require further clinical evaluation.

Overall, Ranch Hand blood glucose levels are not statistically significantly different from those of comparison individuals. However, positive associations of glucose levels with age are greater in the Ranch Hand group than in the comparison group, and in both the Ranch Hand officer and ground enlisted groups significant exposure - body fat interactions exist on glucose levels. Thus, a subtle toxicological effect of herbicide on glucose metabolism may have been detected. It will be important and interesting to follow these groups in time with respect to the incidence of diabetes.

Chapter XVII

INDIVIDUAL HEALTH ASSESSMENT

1. Personal Habits and Characteristics

The personal characteristics of the Ranch Hand and comparison individuals were obtained from the in-home questionnaire. The areas of tobacco, alcohol, and marijuana use, personal and family income, education, religion, active duty, retired/separated status, and risk-taking behavior received particular attention. The number of Ranch Hand and comparison group individuals reporting a listing of past traumatic injuries, poisonings, and/or toxic effects (ICD-9-CM Codes 960-999) were also determined.

The smoking and alcohol use habits of the study subjects are displayed in Table XVII-1.

Table XVII-1
HISTORY OF TOBACCO AND ALCOHOL USE AMONG THE STUDY PARTICIPANTS

	Group							
	Original Comparisons		Ranch Hand		All Comparisons			
Habit	Yes (%)	No	Yes (%)	No	Yes (%)	No	P (Original Comparisons vs. Ranch Hand)	P (Ranch Hand vs. All Comparisons)
Current Use of Cigarettes	313 (40.5%)	459	478 (45.7%)	567	484 (39.6%)	739	P = 0.03	P = 0.003
Past History of Cigarettes	552 (72.3%)	212	758 (73.2%)	278	861 (71.1%)	350	P = 0.67	P = 0.28
Past History of Cigar Use	92 (11.9%)	680	99 (9.5%)	942	141 (11.5%)	1081	P = 0.10	P = 0.12
Past History of Pipe Use	157 (20.4%)	613	200 (19.4%)	829	246 (20.2%)	970	P = 0.62	P = 0.64
Past History of Marijuana Use	22 (2.8%)	750	53 (5.1%)	992	62 (5.1%)	1160	P = 0.02	P = 1.00
Current Use of Alcohol	447 (58.6%)	316	609 (58.9%)	425	694 (57.3%)	518	P = 0.89	P = 0.43
Past History of Alcohol Use	478 (63.0%)	281	635 (62.2%)	386	773 (64.7%)	421	P = 0.74	P = 0.21

The mean number of cigarettes currently smoked and the mean number of alcohol-containing drinks consumed per day by those currently reporting use of these substances were determined. Similarly, the mean pack-years, cigar-years, pipe-years, drink-years and marijuana joint-years were determined for the groups in the study. These data are presented in Table XVII-2.

Table XVII-2

MEAN USE OF TOBACCO PRODUCTS AND ALCOHOL
IN THOSE REPORTING USE OF THESE SUBSTANCES

	Mean Usage Level					
	Original Comparisons		Ranch Hand		All Comparisons	
Substance	Mean	(Median)	Mean	(Median)	Mean	(Median)
Cigarettes per day (current use)	28.28	(30)	27.21	(25)	27.72	(30)
Cigarette pack-years (cumulative)	23.47	(20.12)	23.89	(20.91)	22.92	(19.58)
Cigar-years (cumulative)	21.26	(8.11)	19.12	(9.38)	20.80	(7.33)
Pipe-years (cumulative)	26.96	(6)	26.32	(7.23)	26.26	(5.71)
Marijuana Joint-years (cumulative)	7.60	(2.52)	7.12	(3.54)	8.26	(2.88)
Alcohol drinks per day (current use)	2.33	(2)	2.35	(2)	2.38	(2)
Drink-years (cumulative)	36.48	(26.31)	40.48	(24.23)	34.87	(25.08)

In most of the cumulative measurements (e.g., pack-years) the median level of use was lower than the mean level, indicating that the heavy users of these substances skewed the distributions. However, in the measurements of current use, there was little evidence for this effect.

The median income levels of the Ranch Handers and the original comparison were the same with personal income ranging from $20,000 - $24,999 and total family income ranging from $30,000 - $34,999. The median personal income of the entire comparison group was also in the $20,000 - $24,999 range, but the median family income remained in this same category.

The educational backgrounds of the groups were not significantly different. Religious preferences of the groups were also similar. These data are shown in Tables XVII-3 and XVII-4.

Table XVII-3

EDUCATIONAL BACKGROUND BY GROUP

	Group					
	Original Comparisons		Ranch Hand		All Comparisons	
Educational Level	Number	(%)	Number	(%)	Number	(%)
High School/GED	430	(55.63)	580	(55.50)	661	(54.01)
Associate Degree	53	(6.86)	67	(6.41)	96	(7.84)
BA/BS Degree	152	(19.66)	197	(18.85)	249	(20.34)
Graduate Degree	132	(17.07)	187	(17.89)	206	(16.83)
Unknown	6	(0.78)	14	(1.34)	12	(0.98)

P = 0.78 (Original Comparisons vs. Ranch Hand)

P = 0.48 (Ranch Hand vs. All Comparisons)

Table XVII-4

RELIGIOUS PREFERENCE BY GROUP

Religion	Original Comparisons Number	(%)	Ranch Hand Number	(%)	All Comparisons Number	(%)
Protestant	699	(66.89)	531	(68.69)	816	(66.68)
Catholic	218	(20.86)	162	(20.96)	263	(21.49)
Jewish	9	(0.86)	12	(1.55)	16	(1.31)
Other	34	(3.25)	20	(2.59)	49	(4.00)
None	85	(8.13)	48	(6.21)	80	(6.54)

P = 0.29 (Original Comparisons vs. Ranch Hand)   P = 0.50 (Ranch Hand vs. All Comparisons)

The current military status of each individual was determined as either active duty, retired, separated, reserve status, or deceased, and there were no statistically significant differences between the Ranch Handers and the subset of original comparisons (P = 0.23); however, there was a significant difference (P = 0.01) between the Ranch Handers and the total comparison group. These data are presented in Table XVII-5.

Table XVII-5

MILITARY STATUS BY GROUP

Military Status	Original Comparisons Number	(%)	Ranch Hand Number	(%)	All Comparisons Number	(%)
Active Duty	113	(14.64)	153	(14.66)	184	(16.74)
Retired	420	(54.40)	515	(49.33)	593	(53.96)
Separated	196	(25.39)	305	(29.21)	247	(22.47)
Reserve Forces	39	(5.05)	64	(6.13)	69	(6.28)
Deceased*	4	(0.52)	7	(0.67)	6	(0.55)

P = 0.23 (Original Comparisons vs. Ranch Hand)   P = 0.01 (Ranch Hand vs. All Comparisons)

*Deceased subsequent to the physical examination.

Risk-taking behavior patterns were assessed by a series of questions (i.e., "Have you participated three or more times in ....activity?") that emphasized participation in potentially dangerous recreational activities. These data are tabulated in Table XVII-6.

Table XVII-6

RISK-TAKING BEHAVIOR BY GROUP

Activity	Original Comparisons Yes (%)	Original Comparisons No	Ranch Hand Yes (%)	Ranch Hand No	All Comparisons Yes (%)	All Comparisons No
Scuba Diving	88 (11.40)	684	103 (9.87)	941	155 (12.68)	1067
	P = 0.29				P = 0.04	
Auto, Boat or Motorcycle Racing	77 (9.97)	695	132 (12.64)	912	140 (11.46)	1082
	P = 0.08				P = 0.39	
Acrobatic Flying	25 (3.24)	747	29 (2.78)	1015	39 (3.19)	1183
	P = 0.57				P = 0.57	
Sky Diving	12 (1.55)	760	14 (1.34)	1030	29 (2.37)	1193
	P = 0.71				P = 0.07	
Hang Gliding	4 (0.52)	768	6 (0.57)	1038	13 (1.06)	1209
	P = 0.87				P = 0.20	
Mountain Climbing	35 (4.53)	737	61 (5.84)	983	63 (5.16)	1159
	P = 0.22				P = 0.47	
One or More Risk-taking activities	172 (22.3)	601	253 (24.2)	792	308 (25.2)	916
	P = 0.33				P = 0.60	

Only in motor vehicle racing (automobile, boats and motorcycles) was there a borderline suggestion of a difference in risk-taking behavior between the Ranch Handers and the original comparison subset. In contrast, there was a statistically significant difference between the Ranch Handers and the entire comparison group in scuba diving (P = 0.04) and a borderline difference (P = 0.07) in sky diving. In both of these instances, the comparisons had higher rates of participation. In combining all activities, there was no significant difference in risk-taking behavior between the Ranch Handers and the original or entire comparison group.

Table XVII-7 contains the distribution of reported past injuries and poisonings by ICD code for each group. Conditional unadjusted chi-square testing reveals no significant group differences in these distributions.

Table XVII-7

DISTRIBUTION OF REPORTED INJURIES AND POISONINGS BY GROUP

	Group		
Injury (ICD Code)	Original Comparisons	Ranch Hand	All Comparisons
Fractures, Dislocations, Sprains (800-848)	11	11	17
Intracranial, chest; abdominal and pelvic injuries; open wounds; nerve and spinal cord injuries (850-897; 925-929; 950-957)	3	4	8
Late effects; superficial injuries and contusions; burns (905-924; 940-949)	5	2	6
Traumatic complications (958-959)	5	9	8
Poisonings, toxic effects; other specified causes (960-989)	3	0	4

Original Comparisons vs. Ranch Hand: P = 0.23

Ranch Hand vs. All Comparisons: P = 0.31

2. Health Abnormalities Detected at Physical Examination

Throughout previous chapters, health of the participants has been assessed in a variety of interrelated ways. Normal-abnormal categorizations, or con- tinuously distributed clinical variables have been defined organ system by isolated organ system, categorized into physical, mental, reproductive, bio- chemical, and machine-results parameters, all of which were qualified by over- all historic and diagnostic impressions. This research approach has not been suitable to assess total individual health. Since such a task would involve complete listings of all past abnormalities and current normalities- abnormalities by individual, these citations would exceed the scope of this report. This chapter section attempts to assess the overall health of indi- viduals in three ways: the summation of abnormalities of major components of each of the 12 organ systems; the summation of a weighted score of the same abnormalities; and a summary count of medical codes for historical disease and disease suspected/detected at the physical examination.

a. Summation of Individual Abnormalities

In 8 of the 12 clinical areas, virtually all individuals were found to have complete examination data, and all of the selected parameters of individ- ual health could be evaluated. Table XVII-8 provides the number of Ranch Hand and original comparison group individuals with incomplete data who were not included in the tabulation for each organ system.

Table XVII-8

DISTRIBUTION OF INDIVIDUALS WITH INCOMPLETE DATA
OMITTED FROM ANALYSIS OF INDIVIDUAL HEALTH

Organ System	Ranch Hand	Comparison
General Health	8	6
Malignancy	0	0
Reproductive	473	352
Neurological	31	19
Psychological	4	0
Hepatic	0	0
Dermatology	0	0
Cardiovascular	4	3
Hematologic	0	0
Pulmonary	5	3
Renal	0	0
Endocrine	9	3

The assessment of the reproductive system is based solely on the sperm count. Those individuals noncompliant for the collection of semen or those having had vasectomies or orchiectomies were excluded from this analysis. In the psychologic, hepatic and neurologic clinical areas, there were sufficient numbers of individuals with missing data to warrant separate analyses of individuals with complete data and individuals with partial data. The data and results of the analysis of abnormalities by organ system are presented in Table XVII-9. As noted for the psychologic, neurologic and hepatic data, subset analyses were accomplished.

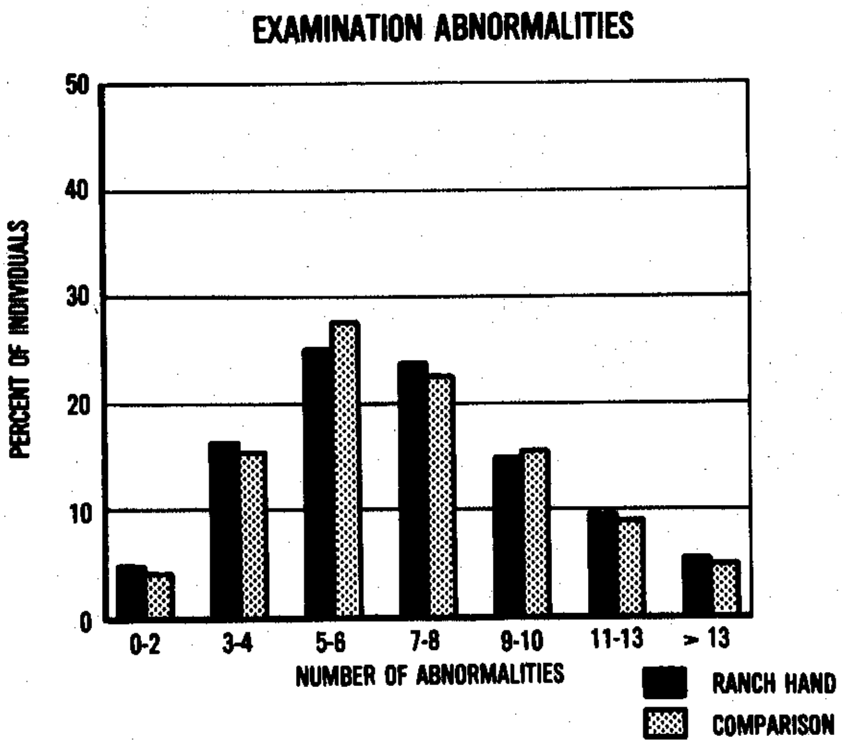
Table XVII-9

COUNT DATA
NUMBER OF HEALTH ABNORMALITIES BY ORGAN SYSTEM AND GROUP
(UNADJUSTED FOR MATCHING VARIABLES OR RISK FACTORS)

Organ System	Group	Number of Abnormalities						Unadjusted P Values
		0	1	2	3	4	5-6	
General Health	RH	791	228	18	-	-	-	0.27
	C	573	186	8	-	-	-	
Malignancy	RH	997	48	0	-	-	-	0.01
	C	755	17	1	-	-	-	
Reproductive	RH	374	198	-	-	-	-	0.34
	C	263	158	-	-	-	-	
Neurological		0	1	2	3	4-9		
(Full Data Subset)	RH	113	268	238	126	84		0.17
	C	112	179	186	92	57		
(Subset with 1 Missing Parameter)	RH	59	64	36	20	6		0.79
	C	40	46	27	9	6		
		0	1	2	3	4	5-6	
Psychological								
(Full Data Subset)	RH	341	301	121	10	-	-	0.29
	C	243	234	75	3	-	-	
(Subset with 1 Missing Parameter)	RH	143	114	11	-	-	-	0.38
	C	129	83	6	-	-	-	
Hepatic								
(Full Data Subset)	RH	184	206	143	68	26	3	0.45
	C	134	134	94	54	18	7	
(Subset with 3 Missing Parameters)	RH	114	134	90	44	29	4	0.27
	C	74	115	77	42	24	0	
Dermatologic	RH	470	575	-	-	-	-	0.97
	C	347	426	-	-	-	-	
Cardiovascular	RH	491	324	151	53	16	6	0.92
	C	365	232	117	42	12	2	
Hematologic	RH	428	432	147	35	3	-	0.59
	C	341	311	98	20	3	-	
Pulmonary	RH	655	289	52	32	12	-	0.05
	C	463	232	56	15	4	-	
Renal	RH	1002	42	1	-	-	-	0.70
	C	740	31	2	-	-	-	
Endocrine	RH	787	207	36	6	-	-	0.20
	C	551	182	33	4	-	-	

These data demonstrate statistically significant group differences only for malignancy (a result of the identified increase in skin cancer in the Ranch Hand Group) and in pulmonary function (due to more abnormalities in the comparison group). All other analyses were not statistically significant. The reader is cautioned that the data in Table XVII-9 are crude counts, unadjusted for the matching variables or risk factors known to affect organ system parameters. The number of abnormalities per organ system may be considered a crude index of severity. All individuals and their abnormality counts were summed, regardless of the degree of completeness of their data. The frequency distribution of these abnormalities is shown in Figure XVII-1.

Figure XVII-1

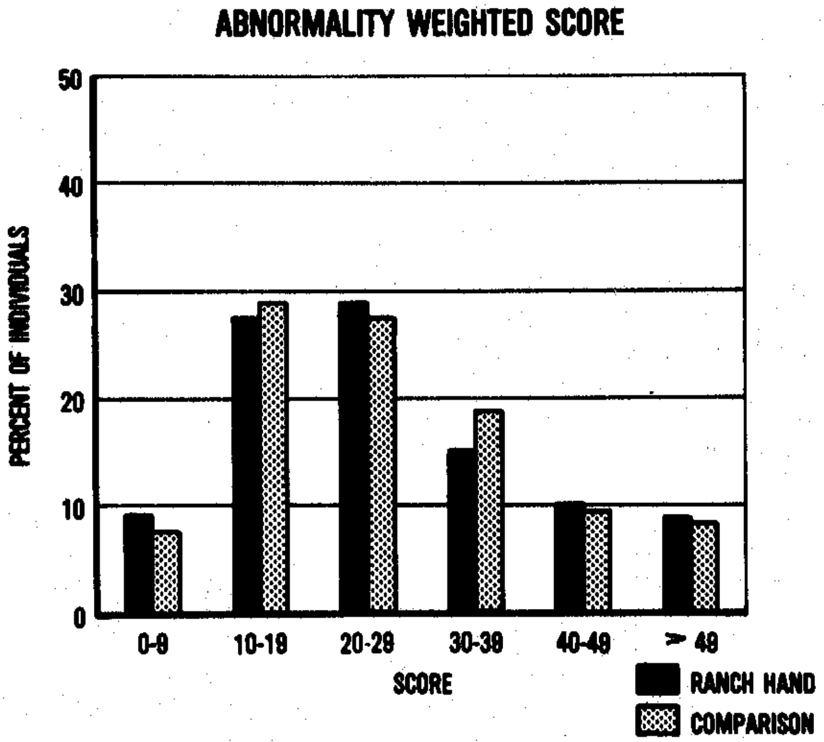


There was a maximum of 61 abnormalities in this analysis. The median number of abnormalities in both the Ranch Hand and comparison groups was seven. There were 0.96% of the Ranch Handers and 1.55% comparison individuals who had no abnormalities, and 2.58% and 2.07%, respectively, with 16 or more abnormalities. Log linear analysis of these distributions revealed no differences between the groups for numbers of abnormalities or degree of completeness of data (P values of 0.26 and 0.59, respectively).

b. Weighted Score of Individual Abnormalities

The count of abnormalities (Table XVII-9) was subjected to a weighting scale of 1 to 10 depending on the clinical seriousness of each abnormality. While such weighting is arbitrary, the resulting data serve as a complementary analytic technique to the basic count of abnormalities in which, for example, acne is considered to be equivalent to systemic cancer or a major ECG abnormality. The assignment of a weight to each abnormality was made before organ system results were known. Appendix VII contains a listing of all parameters and their relative weight scores for each organ system. The weighted score histogram is depicted in Figure XVII-2.

Figure XVII-2



Scores between zero and nine were achieved by 9.09% of the Ranch Handers and 7.24% of the comparisons, with 8.80% of the Ranch Handers and 8.02% of the comparisons scoring above 50 (out of a maximum possible score of 236). The median score was in the 20 to 24 range for both groups. The weighted score analysis showed statistical significance for cancer, again due to the aggregation of skin cancer in the Ranch Hand group. Statistical differences of interest were noted for renal disease (P = 0.09), general health (P = 0.114), and hepatic disease (P = 0.11). The relevance of these P values is minimal in view of the predominantly negative analyses observed in the clinical chapters. All weighted scores were combined across clinical areas and no statistically significant differences were noted (P = 0.20).

From these analyses on crude and weighted abnormalities, it is clear that there were not significantly more ill or more severely ill individuals in the Ranch Hand group than in the comparison group.

c. Physical Examination Diagnostic Codes

The diseases or conditions listed by the diagnostician in the diagnostic summary of the review of systems, the medical history, and the physical examination were coded according to the 9th ICD-CM manual. These diseases were coded as being reported by history, or suspected or actually diagnosed conditions. One individual could account for more than one diagnosed disease or condition. The diagnostician listed 219 suspected diseases among the 1045 Ranch Handers and 160 suspected conditions in the 773 original comparisons (P = 0.91). In both groups, there were 0.21 suspected diagnoses per individual. Similarly, 1949 definitive diagnoses were made in the Ranch Handers and 1437 in the original comparisons yielding an average of 1.87 diagnoses per Ranch Hander and 1.86 per comparison individual (P = 0.96). While the mean numbers of suspected and definitive diagnoses were essentially the same in both groups, the mean number of diseases and conditions reported by the participants were different in the two groups. There were 113 diseases reported by history in the Ranch Handers, but only 57 in the comparisons (mean number of conditions of 0.11 per person and 0.07 per person (P = 0.02), respectively). The similarity in diagnosed and suspected conditions in the two groups parallels the findings in the analysis of examination abnormalities. The difference in reported conditions may reflect differential reporting, or actual difference in past health. However, if past illness was different in the two groups, these experiences have apparently not resulted in long-term sequelae detected at the examination.

3. Summary

The anecdotal comments of the examining physicians and psychologists suggested that the study participants were remarkably healthy both physically and mentally for a group of mid-aged men. These comments were made about the entire group of participants based on the medical experience of each examiner, without knowledge of which individuals were Ranch Handers and which were comparisons. The statistical analyses discussed in this chapter support the clinical impressions of the examiners.

Both the Ranch Handers and the original comparisons had somewhat similar health habits, although significantly more Ranch Handers are current cigarette smokers and more had reported smoking marijuana in the past. The two groups were also similar in risk-taking activities, religion, education, income, and military status.

The distribution of identified health abnormalities by individual, and the weighted scores of these abnormalities were not significantly different in the Ranch Hand and comparison groups. Similarly, the mean number of diagnoses per individual at the conclusion of the examination was not different in the two groups.

Overall, the health of individuals in the two groups appears to be quite comparable. As individuals, they seem to be in quite good health for men of their age. These findings and observations are most likely a result of the healthy worker effect, previously noted in the baseline mortality study.

Chapter XVIII

FUTURE COMMITMENTS

The large volume and complexity of the data collected during this baseline phase of the Ranch Hand II study have made it difficult to completely fulfill all aspects of the analytic plan envisioned in the study protocol. While most of the major anticipated analyses have been completed and included in this report, other important tasks remain to be done. The results cited in this report logically lead toward a commitment by the USAF and the study principal investigators to pursue further evaluations of these data, and follow the study participants over time. There are 5 key areas requiring additional effort: (1) database refinement, (2) definition of requirements and examination refinements for the follow-up phase of the study, (3) refinement and expansion of exposure indices (4) additional statistical analyses and (5) collaborative activities with other organizations involved in herbicide/dioxin research.

1. Database Refinement

The database derived from the questionnaire and from the physical examination was very extensive in size and scope, and a quality control program was initiated to identify coding, keypunching, and editing errors in the database provided by the contractors. This data validation has been an on-going task, and is not yet complete in some areas. After the remaining questionnaire and physical examination data have been validated by comparison with the source documents, epidemiologic and statistical analyses of these data will be completed. Additionally, validation of illnesses and conditions reported on the in-home questionnaire will continue to be accomplished as medical records and birth certificates are received. Methods of validating smoking histories, and a reassessment of flying status and its impact on compliance will be pursued. The completion of this process will provide a verified database for subsequent analyses. This process will also allow an assessment of the degree of differential reporting present in the study.

2. Follow-up Examination Requirements

One of the purposes of the baseline phase was to identify clinical areas requiring in-depth evaluation in the follow-up portions of the study. Focused questionnaire and physical examination formats will be developed for use during the reexamination scheduled for 1985. At that time detailed evaluation of skin cancer, and known risk factors affecting its occurrence will be obtained. Additional data on fertility and reproductive history will be gathered and updates of conceptions and live births occurring since the baseline questionnaire will be obtained. The cardiovascular status of the participants will also be closely examined, using doppler measurements of peripheral pulses and electrocardiographic monitoring during stress testing. New, fully validated psychological scales will be used to assess additional psychological parameters such as sleep patterns. Further immunologic evaluations with strict laboratory quality control will also be accomplished. Steps will also be taken to insure that all participants comply with dietary and 24-hour urine collection requirements. At the time of the follow-up physical examination, all participants will be requested to authorize an autopsy at the time of their deaths and have copies of those reports and tissue specimens provided to the Air Force. The participants will also be asked to forward copies of hospitalization summaries and other significant medical events to the Air Force for inclusion in their records at Brooks AFB.

3. Exposure Index Refinement

The index of exposure to phenoxy herbicide and dioxin used in this report is not as complete or refined as planned in the study protocol. As it is currently calculated, each of the major occupational categories (Officers, Enlisted Flying, and Enlisted Ground) must be analyzed separately since the index is not necessarily equivalent in each category. A series of flights in a C-123 aircraft is planned. The aircraft will be configured and flown to simulate the Vietnam spray missions and a herbicide simulant will be released. Industrial hygiene sampling techniques will be used to measure differential exposure for aircrewmembers, ground support personnel, and administrative staff members. These data will then be used to calculate a weighting factor for use in the exposure index. In this way, a common index can be applied to all 3 occupational categories. The individual records of flying time ("Form 5's") will be used wherever possible to more clearly define the opportunity for in-flight exposures. Adjustment of the exposure analyses for confounding factors such as age and time spent in Southeast Asia will also be conducted to refine the index and make it more specifically a measure of herbicide exposure. This exposure index will also be modified to assess the degree of exposure to other chemicals such as arsenical herbicides (Herbicide Blue) and malathion.

4. Additional Statistical Analyses

Expanded statistical analyses and procedures are planned on the baseline data of this study. More detailed statistical power estimates will be developed for the analyses contained in this report, and an overall assessment of the ability of this study to detect adverse health effects in the populations studied will be made. Specifically, the analyses of reported and verified birth defects will be reaccomplished with the nature of the anomalies categorized as severe, moderate, and of minor medical consequence. The defects will also be classified as being congenital or teratogenic in origin. The results of the semen analyses and the father's occupation will also be considered. Efforts will be made to more fully define and correct sources of potential bias in the subsets of the comparison group so that all analyses can be conducted using the entire group of comparison individuals. This will maximize study power, and allow the use of the replacement strategy outlined in the protocol. Additional matched pair analyses will also be conducted in each clinical area, thus taking full advantage of the most powerful statistical techniques. The full spectrum of clinical end points and covariables will be analyzed as well. Case by case reviews of individuals with testicular, bladder, oropharyngeal, and skin cancer and those with pulse abnormalities will be conducted. This review may highlight additional risk factors and may suggest alternative epidemiologic and statistical methodologies for subsequent reanalysis (e.g., case-control studies).

Other techniques will be used to address correlations between clinical areas in the data. An organ system does not operate independently, and interactions between systems will be evaluated in subsequent reports. The effects of differential reporting are potentially significant in this study, and analyses aimed at differences in reporting between groups, and between study participants and their spouses will be evaluated. Questionnaire data was collected from the next-of-kin of deceased individuals and from totally noncompliant individuals, and time constraints have not permitted an analysis of these data. However, these are potentially valuable sources of information and appropriate evaluation will be conducted as time permits. Additional testing using more multi-variate techniques, expanded model-fitting, and goodness-of-fit testing will also be carried out via contract.

5. Collaborative Activities

Over the past 5 years, the principal investigators have worked closely with other organization and scientists involved in the herbicide/dioxin issue, and these collaborative activities will be strengthened and expanded. The common problems encountered by this study and the studies of Vietnam veterans being conducted by the Centers for Disease Control and the Veterans Administration can be more effectively resolved through the sharing of approaches and solutions. Collaboration has benefited all of these studies in the past, and should continue to be of benefit in the future. In addition to U.S. governmental agencies, the principal investigators have interacted with the epidemiologic staffs at DOW Chemical Company, Monsanto Company and with researchers in Australia, New Zealand and Europe. The value of these interactions cannot be overstated, and these contacts will be maintained as the study progresses. More importantly, a closer working relationship will be developed between the principal investigators and the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicide and Contaminants. Continued coordination with this panel will be invaluable as the complex findings of this study emerge over time.

Chapter XIX

INTERPRETATION OF STUDY RESULTS AND CONCLUSIONS

1. Introduction

This section presents a cautionary note to both scientific and lay readers who may wish to assert that this study, in whole or in part, is supportive or nonsupportive of a causal relationship between exposure to Herbicide Orange (and its dioxin contaminant) and adverse health. It is important to recognize that this observational study cannot prove the "negative," nor can it be construed as "definitive" science. The process of determining causality is complex and must entail a methodical consideration of many factors (Lilienfeld and Lilienfeld, 1980).

2. Causality Factors

In general, the following factors are very important in making an inference of causality: strength of association; dose-response; biologic plausibility; consistency; time relationships; specificity; and coherence. In an epidemiologic study, not all these factors are required to be present in order to make a correct inference, but clearly, substantial conflict between one or more factors casts doubt on an inference of causality.

In this study, numerous group differences (associations) were detected and expressed in terms of probability (P) values. In any given analysis, statistically significant P values (<0.05) represent the strength of the association, but in and of themselves, do not imply an herbicide causation. As expected under the null hypothesis, most a priori hypothesis tests were negative (P >0.05), but the validity of these findings must be assessed by the power of the given test. As expected, many positive associations were found in the clarifying analyses, or as expressions of the influence of specific risk factors (e.g., age, smoking, etc.). Highly significant associations must also be viewed in the context of relative risk. A very significant association with a relative risk of less than two is generally of minor interest from the traditional epidemiologic perspective. In this study, only four objectively determined group differences of P <0.05 had a relative risk of two or greater. Moreover, statistically significant differences in the group means of a laboratory parameter were often detected, but the overall distributions were similar, the values were within normal range, and the clinical relevance of these shifts was not readily apparent (e.g., LDH, testosterone, T_3, etc.).

A positive linear dose response relationship is a substantial feature in establishing a cause and effect association. A careful counting of the 388 exposure index analyses cited in this report shows that only 11% are statistically significant, and only 2.8% are increasing from low to high exposure. While these proportions are suggestive of chance associations, this possibility should be modified by the fact that positive exposure analyses, although not totally consistent throughout all occupational categories, tend to aggregate in only several of the organ systems. Additionally, it is recognized that the exposure index has not been fitted to the most specific format, as further experimental studies are still in progress. Thus, the exposure index used herein is a very indirect measure of exposure, making these analyses less certain than the observed group differences. Numerous other subcategorical exposure analyses (also predominantly negative) were accomplished, but were not included at the discretion of the author. Descriptive opinions of the positive exposure associations were often the sole choice of the responsible principal investigator within each chapter.

The time interval from herbicide exposure to onset of subclinical or clinical manifestations is an important concept for proper interpretation of these study findings. The observational period for the detection of possible latent health effects ranges from 10-20 years for all Ranch Handers. While 10-20 years may be insufficient time for the induction of many systemic cancers, and possibly skin cancer, clearly it is of sufficient length to have already "caused" transient biochemical aberrations, birth outcome abnormalities, fertility problems, chloracne, porphyria cutanea tarda, neurologic sequelae, psychological deficits, etc. Thus, if the above acute/subacute conditions are found attributable in these data, it must be acknowledged that the end result of many of the disease processes is being observed. That notion must be reconciled with essentially identical mortality rates in both groups to date, as many of the proposed diseases would most likely have exerted a subtle mortality influence. Alternatively, the suggestion that the release of dioxin from fat may result in slow systemic poisoning, if true, may account for a delay of clinical manifestations beyond classically accepted latent periods. Another influential time-onset relationship is that of "crossover," i.e., a sequential time-disease association based upon a linkage to a pulsed exposure. While many pre/post-SEA analyses have been performed in this study, reapplication of exposure to herbicides (to complete the crossover) via non-SEA vocations or avocations has not, as yet, been exploited.

Other causal factors merit oomment. The finding of no cases of soft tissue sarcoma, porphyria cutanea tarda or chloracne in the Ranch Hand group may reflect a lack of specificity and/or a weak toxicity of the received dose of the putative agent (dioxin), or may reflect the low statistical power to detect group differences for these diseases in this study. The absence of these three diseases may also suggest that a synergism with a yet-to-be-discovered factor is required to induce disease. Findings of this study are, as yet, not fully consistent with other human dioxin studies performed in industrial populations. However, this inconsistency may be attributable to different exposure levels. In terms of biological plausibility, there is no discernible syndrome or symptom oluster that has emerged from this study that makes sense, has an identifiable pathogenesis, or has an analogous animal model. A systemic poisoning theory carries with it the expectation of finding more biochemical abnormalities than were detected in this study.

3. Other Factors

Chloracne has been proposed as a prerequisite to systemic disease. This premise is not wholly consistent with spectrum of illness concepts or other studies which have suggested attributable soft tissue sarcoma in predominantly nonchloracne populations. However, if the premise is true to the extent that the induction of chloracne represents moderate to high exposures to dioxin, then overall, it may be inferred that the Ranch Hand group (with no chloracne) has received relatively low exposure vis-a-vis industrial populations. Assuming a dose-response hierarchy, this inference may be extended to the contemplated studies of U.S. military ground personnel, for if the Ranch Hand study is deemed "negative," so probably will be the other studies of comparable size.

The question of the validity of this study is paramount. Overall, the processes of data collection have been quite good. To the extent possible, biases have been minimized in both the data collection and data analytic phases. Notwithstanding, a general predominance of adverse findings can be noted in the Ranch Hand group. A closer inspection of this aggregation suggests that most statistically significant findings are found in the subjective data sets, as contrasted to the objective measures. Many of these subjective findings in the Ranch Hand group are in various stages of medical record verification at this time. Unfortunately, some areas, e.g., psychological testing by questionnaire, can never be totally verified. Throughout this study, there is a suggestion of differential reporting (MMPI K and Hypochondriasis scales), albeit unanalyzed, that must temper the interpretation of the subjective results. For the objective data, there is good evidence that the laboratory measurements and the clinical assessments were reasonably accurate. This study has duplicated the classical effects of numerous risk factors (age, smoking, alcohol, etc.) on the clinical measurements throughout all organ systems. The detected effects of age and smoking in the functional and count immunologic tests are new observations, to the best of our knowledge. Thus, the effects of these risk factors have been taken into account throughout the study and lend strong credence to the accuracy of the overall group associations, whether statistically significant or not. It is our belief that this physical examination has reflected the true health status of all participants and groups to the maximum extent possible.

4. Conclusions

a. Preface

This section places into context the thousands of statistical tests which have been accomplished on the enormous data bases generated by the population ascertainment efforts, and the administration of the in-home questionnaire and the physical examination. The total baseline study, including all preparatory tasks and the Baseline Mortality Report, has spanned more than 5 years, has required approximately 100 man-years of in-house work, and has cost about $11M in direct and indirect costs. The Ranch Hand study has been characterized by solid resource support and stringent timetables throughout all levels of government, intense media interest, and outstanding participation of the study subjects. As part of the mosaic of all dioxin research, the Ranch Hand study has been directed to the herbicide-health effect issue in veterans, and specifically, to heavily exposed Air Force personnel.

b. Study Performance Aspects

Of all live Ranch Hand and comparison individuals who were selected for this study, almost all (99.5%) were contacted, eliminating a major element of bias concern. Participation in the in-home questionnaire was 97% and 93% for the Ranch Handers and comparisons, respectively; and similarly 87% and 76% for physical examination. Differential compliance to the examination may have introduced a participation bias, a bias that is potentially related to the true health status of the participant. Age, race, participation in flying, and military status were also significant factors in determining attendance at the examination, but the relative contribution of each factor has not as yet been determined. Traditionally, individuals in either military or civilian commercial flying occupations do not readily volunteer for physical examinations that might disclose even minor ailments that jeopardize their flying careers.

Early in the study, it was discovered that 18% of the comparison group was ineligible for the study because of inappropriate selection due to a computer programming error. Some selected USAF organizational units containing cargo-hauling aircraft were found not to be engaged in RVN duties (a study requirement). Thus, the direction of the error was for overselection and not for underselection of the comparison group. Ineligible individuals were removed from the randomly ordered comparison set. The replacements for the ineligibles were the next-in-line proper comparisons. For both these "shifted" comparisons and the next-in-line comparisons who were also used as substitutes for noncompliant individuals, later statistical analyses suggested that they differed from the original eligible comparisons in a variety of subtle and often opposite ways. Because of the possible bias suggested in their use, and because of the time constraints of this report, a conservative management decision was made to base the bulk of statistical tests upon a contrast of the original comparisons to the Ranch Hand group. Several analyses, using the entire comparison group, were also performed and found not to differ consistently from the analyses based upon the original comparison group. For those analyses which showed differences between the original versus the total comparison group contrast, it is unclear whether these differences are primarily due to true subset variances or to a sample size effect. A full clarification of the complex biases (selection, compliance, overreporting, etc.) must be conducted before the first follow-up phase of the study.

Most of the stringent quality control aspects of the study were monitored and maintained throughout the data collection phases. As a USAF contract requirement, all contractors were required to maintain "blindness" with respect to the exposure status of each individual, thereby reducing examiner bias to an absolute minimum. In addition, by contract all data are the property of the USAF. Study codes were not provided to the contractors.

c. Clinical Aspects

In terms of overall health, the Ranch Handers perceive their state of health to be poorer than that of the comparisons. This finding parallels the examiner's independent assessment. Percent body fat is similar in both groups as are the hematocrit determinations. A higher proportion of abnormal red cell sedimentation rates is found in comparisons under 40 years of age. The proportions are the same in both groups older than 40. The sedimentation rate, hematocrit, percent body fat, self-perception of health, and age are associated pairwise irrespective of group; these relationships are expected as all variables are traditional indicators of nonspecific illness.

There are no significant group differences for malignant or benign systemic tumors. One case of soft tissue sarcoma is noted in a member of the comparison group. A slight nonsignificant aggregation of genitourinary cancers is identified in the Ranch Hand group, and an aggregation of digestive system cancers is observed in the comparison group. Two Ranch Hand bladder cancers are noted at earlier-than-expected ages. A borderline association between systemic cancer and smoking is observed in both groups. Significantly more nonmelanotic skin cancer is observed and verified by medical record review in the Ranch Handers. The predominant cancer, basal cell carcinoma, is the most common skin cancer in the U.S. White male population, and a proper excision is curative. While this finding is of interest, it is emphasized that these data are not adjusted for sunlight exposure, the recognized primary cause of these cancers. This analysis must await more complete data to be collected at the first follow-up examination. Overall there is no consistent data to show that the Ranch Handers are developing uncommon systemic cancers, or cancer in unusual sites, or at a younger age. Both systemic and skin cancers in the Ranch Hand group do not correlate consistently with the herbicide exposure index.

The fertility and reproductive analyses show mixed findings. As these results are largely based upon subjective self-reports, and must be verified by complete medical record and birth certificate reviews, the findings are judged preliminary at this time. A semen analysis on those participants willing and able to provide a specimen shows essentially identical sperm counts and percent abnormal forms between groups. The finding of an increase in sperm count by age is discounted as physiologically significant because of concomitant noncompliance by increasing age. Four measures of fertility show no difference between the Ranch Hand and comparison groups: number of childless marriages; couples with the desired number of children; the fertility index; and the infertility index. There are no significant findings in conception outcomes for miscarriages; stillbirths, induced abortions, or live births. With respect to live birth outcomes, no group differences are observed for prematurity, learning disability, or infant deaths. Birth defects, as cited by parental history, show no group differences for severe or moderate classifications; however, for minor birth defects (simple birth marks, birth rashes, port wine stains, etc.) Ranch Hand offspring show a significant excess. Reported neonatal deaths and physical handicaps significantly predominate in the Ranch Hand group when contrasted to the full comparison group. All analyses are adjusted for as many of the relevant risk factors as possible, e.g., maternal age, maternal smoking, maternal use of alcohol, paternal age, pre/post-RVN service, etc. Herbicide exposure analyses show several findings of statistical significance but the patterns of association are not fully consistent across all occupational categories.

A thorough neurological assessment of the cranial nerves, peripheral nerves, and central nervous system functioning does not disclose any substantive Ranch Hand-comparison group differences. Past history of neurological disorders is similar for both groups. An increased proportion of abnormal Babinski reflexes are noted in the Ranch Handers but this finding is not statistically significant. Detailed nerve conduction velocities are not associated with group membership but are profoundly influenced by alcohol and diabetes. Similarly, abnormalities in sensation to light touch, vibration, and two reflexes are related to abnormal postprandial glucose levels. Exposure index analyses are predominantly negative.

Detailed psychologic evaluations from the in-home questionnaire and physical examination show consistent findings. Educational level of the participant profoundly influences most all of the subjective test results. Due to the inherently high correlation between military rank and educational level, these variables are considered interchangeable. It is emphasized that the majority of psychologic data are based upon highly subjective self-reporting, most of which can never be fully verified by medical record reviews. There are no group differences for reported past emotional or psychological illnesses. However, the high school educated (mostly enlisted) Ranch Handers demonstrate significant findings or deficits in the following categories: fatigue, anger, anxiety, erosion, fear, startle, psychosomatic behavior, hypochondria, masculinity, and mania/hypomania. It is noted that the high school educated comparisons exhibit a higher degree of denial in most of these categories. These findings are not observed in the college educated Ranch Handers (mostly officers). The Ranch Hand group demonstrates significant hypochondria, depression, hysteria and schizophrenia vis-a-vis the comparison group, after adjustment for education. In sharp contrast, there are no substantial group differences for the more objective functional and performance psychologic tests (e.g., Halstead-Reitan battery, IQ testing). Almost all exposure index analyses are negative. In full context, differential reporting is strongly suggested, albeit unproven. The roles of an overreporting bias and the Post-Vietnam Stress Syndrome will be clarified in subsequent follow-up psychological evaluations.

The hepatic status is assessed by 9 biochemical tests and a variety of questionnaire and medical record data. The results are mixed. Ranch Hand GGPT and LDH levels are slightly higher while cholesterol levels are lower than the comparisons. Alcohol history is associated with most enzymatic elevations in both groups. Ranch Handers report significantly more skin changes compatible with a historical diagnosis of porphyria cutanea tarda (PCT). However, laboratory determinations for delta-aminolevulinic acid, uroporphyrin and coproporphyrin are similar between groups and no cases of PCT were diagnosed at the physcial examination. Reported miscellaneous liver disorders, verified by medical record reviews, are found significantly more in the Ranch Handers. The exposure index analyses are generally inconsistent.

A comprehensive dermatologic evaluation reveals no substantial findings in the Ranch Hand group. No cases of chloracne are diagnosed clinically or by biopsy of suspicious lesions. Questionnaire data show that the incidence, severity, duration, and anatomic locations of past acne do not portray a pattern consistent with significant historical chloracne in the Ranch Handers. The classical "eyeglass" distribution of acne (suggesting chloracne) is the same in both groups. Historical acne correlates with the total cumulative acne found at physical examination. All exposure index analyses are negative.

Examination of the central cardiovascular system reveals no remarkable differences between the groups for systolic blood pressure, diastolic blood pressure, abnormal electrocardiograms, past versus present electrocardiograms, or abnormal heart sounds. As expected, abnormalities in most of these parameters are significantly associated with age, smoking, and a past history of heart disease. The three risk factors: age, smoking, and cholesterol level are strongly associated with each other, and HDL cholesterol is significantly influenced by percent body fat and smoking. An analysis of questionnaire data shows that the Ranch Handers are not having premature heart attacks or generalized heart disease, although subset analyses show differing age and smoking effects. As an unexpected finding, two peripheral pulses are significantly diminished or absent in the Ranch Handers, and several other pulses show weak group differences. Clarifying statistical analyses show that the the aggregate of Ranch Hand peripheral pulses, predominantly leg pulses, are significantly associated with age, past smoking, current smoking, and verified past heart disease. The weak but similar directional findings in the Ranch Hand carotid and femoral pulses are assigned more significance in view of the peripheral pulse observations. State-of-the-art measurement techniques and a specific medical questionnaire will be used to determine the relevance of these pulse deficits at the first follow-up examination. Detailed herbicide exposure analyses show no associations to any of the central or peripheral cardiovascular findings.

Detailed immunological tests, via B and T lymphocyte enumeration and lymphocyte function studies on a randomized subset of all participants, do not demonstrate significant group differences. Because of the high variability of the quality control data, an independent peer review panel evaluated testing methodology and established criteria for analysis. The numbers of T_{11}, T_3, T_4, T_8, B_1, positive cells and total lymphocyte counts are similar in both groups. Smoking history is observed to significantly affect the T_{11}, T_3, T_4, T_8, marker counts and the total lymphocyte count. Age is seen to affect the T_8 count and the total lymphocyte count. No group differences are observed for the functional studies using phytohemagglutinin, concanavallin A, pokeweed mitogen, and tetanus toxoid. Although the baseline proliferation rate (Control #1) was significantly lower in the Ranch Handers, the biologic relevance of this finding is unclear, particularly in the absence of group differences for concanavallin A and phytohemagglutinin stimulation studies. Age is observed to profoundly affect concanavallin A and phytohemagglutinin results while smoking history is seen to significantly influence pokeweed mitogen results. Because of the overall variability of quality control data, interpretation of a specific individual's immunocompetence is not attempted.

Of 8 measured blood elements and parameters, the mean corpuscular volume and the mean corpuscular hemoglobin level are statistically significantly elevated in the Ranch Hand group, but the relative differences are exceptionally minor and are not of clinical relevance or understanding at this time. Seven of the 8 blood measurements are significantly affected by smoking history. Several exposure index analyses demonstrate positive correlations but a consistent pattern by occupational strata is not observed.

There is no group difference in the distribution of reported past pulmonary disease. Forced expiratory volume for one second and forced vital capacity measurements obtained at the physical examination do not reveal group differences that are consistent in character. There are age/smoking/exposure interactions but it is not possible to further delineate these findings at this time. Several statistically significant herbicide exposure index analyses do not conform to classic dose-response relationships.

Ranch Handers report significantly more kidney disease than the comparisons but this history is not corroborated by 6 laboratory measurements obtained at the physical exam. Proteinuria is of borderline significance in the comparison group. Creatinine clearance may be considered of borderline significance in the Ranch Handers, depending on the laboratory value chosen to determine the abnormal category. Because of the substantial problem of compliance to the 24 hour urine collection, little credence is assigned to the creatinine clearance results. Age is observed to influence the blood urea nitrogen and urine specific gravity results while diabetes affected only the specific gravity results. Herbicide exposure analyses are essentially unrevealing.

A comprehensive assessment of thyroid function and insulin and testosterone production show mixed results. Distributional shifts are noted in thyroid function between the Ranch Hand and comparison groups but the test results are generally within the limits of normal values. There are no group differences for diabetes as determined by abnormal 2 hour postprandial glucose levels. Age and percent body fat determinations are associated with abnormalities in T_3 uptake, 2 hour postprandial glucose levels, and testosterone levels. Herbicide exposure analyses show a variety of positive correlations but many are inconsistent across occupational strata.

Evaluations of personal habits and individual health show that Ranch Handers currently smoke cigarettes more than the comparisons, equally participate in high risk sports activities, and have a similar background of traumatic injuries. An unrefined assessment of the total number of abnormalities found at the physical examination show no Ranch Hand aggregations in the high range nor do arbitrary clinically weighted scores. Overall, both groups are comparable in most health respects, and are probably faring better than similarly aged men in the general population.

d. Final Conclusion

This study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and to their families at this time, because this study has not identified statistical group differences for illnesses commonly attributed to dioxin exposure. The data herein suggest that group differences exist which tend to favor the comparisons, but the cause and clinical relevance of these differences is unclear. This baseline report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time.

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Appendix I

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Appendix II

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Appendix III

CONTRACT MANAGEMENT

The Aerospace Medical Division, Air Force Systems Command, Brooks AFB TX, was designated as the primary management agency responsible for the Air Force Health Study. The program is managed by the Commander, USAF School of Aerospace Medicine, with scientific, technical, and business management support from the Epidemiology Division and the Data Sciences Division of the USAF School of Aerospace Medicine and business support from the Director for Systems Acquisition, Aerospace Medical Division, respectively. The Commander, USAF School of Aerospace Medicine, coordinates business and technical inputs from the interfacing organizations and consolidates program status and direction. He is responsible for informing higher headquarters of management or technical situations which could impact the success of the program.

The 3303rd Contracting Squadron, Air Training Command, Randolph AFB TX, provides all procurement support to the Ranch Hand II Program. Contracted efforts, to date, have included software development, statement of work preparation, questionnaire development, questionnaire administration and the conduct of physical examination. To the maximum extent practical, fixed price contracts with cost reimbursement for travel, lodging and stipend expenses were used. The contractor(s) provided data as required to the contracting agency and the Program Manager. Reports were provided on technical progress, expenditure of funds, and overall program progress against the contractual schedules. Data were used to assess program progress and to initiate corrective actions where required.

A contract to assist in the development of a statement of work for the questionnaires was let to Research Statistics, Inc., Houston TX, at a cost of $11,900.

The study questionnaire was developed by the National Opinion Research Center, New York NY, a nationally recognized survey research firm. A sole source contract was awarded on 26 September 1980 and was concluded on 31 July 1981 at a total cost of $348,000.

Louis Harris and Associates, Inc., New York NY, was competitively selected to administer the questionnaire and awarded a contract on 18 September 1981. The original effort was scheduled for completion in April 1982, but due to data collection as well as questionnaire/physical examination contractor interface requirements, the contract was extended to November 1982. The final cost for the questionnaire administration effort was $1.076 million.

A formal source selection process was also used to select the Kelsey-Seybold Clinic, P.A., Houston TX, as the single site for conducting the physical examinations. The initial contract period was scheduled for 10 months (23 November 1981 - 30 September 1982) but was extended to 15 December 1982. The total contract cost was $6.161 million, which included the physical examinations, travel expenses, lodging, meals and stipend allowances.

An Air Force on-site physician monitor in-briefed all study participants and conducted quality control checks on all medical aspects of the physical examination. Additional medical and contracting specialists periodically visited the examination site to ensure adherence to all aspects of the contract. All three contracting efforts were characterized by this type of close interaction and control.

Appendix IV

KELSEY-SEYBOLD NORMAL VALUE REPORT
BLOOD CHEMISTRY

AGE-ADJUSTED NORMALS

AGES	PARAMETERS
10 - 29 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 106-210
	Trig (mg/dl): 30-140
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2
	D Bil (mg/dl): 0-0.36
	Alk Phos (U/dl): 2.5-9.7
	SGOT (U/L): 0-41
	SGPT (U/L): 0-45
	GGTP (U/L): 15-85
	LDH (U/L): 0-200
	CPK (U/L): 35-232
	Alcohol (mg/dl): None
30 - 39 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 119-240
	Trig (mg/dl): 30-150
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2
	D Bil (mg/dl): 0-0.36
	Alk Phos (U/dl): 2.5-9.7
	SGOT (U/L): 0-41
	SGPT (U/L): 0-45
	GGTP (U/L): 15-85
	LDH (U/L): 0-200
	CPK (U/L): 35-232
	Alcohol (mg/dl): None
40 - 49 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 131-265
	Trig (mg/dl): 30-160
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2