Table XIII-3

QUESTIONNAIRE PSYCHOLOGICAL INDICES
(HIGH SCHOOL EDUCATION)

Index	Group	N	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Fatigue	Ranch Hand	573	15.33	6.24	< 0.001
	Comparison	430	13.64	5.52	
Anger	Ranch Hand	573	11.27	4.74	0.002
	Comparison	430	9.99	3.64	
Erosion	Ranch Hand	572	22.34	7.90	< 0.001
	Comparison	429	20.00	6.70	
Anxiety	Ranch Hand	555	24.62	8.67	< 0.001
	Comparison	419	21.91	7.73	
Depression (Severity)	Ranch Hand	141	5.79	3.15	0.89
	Comparison	60	5.30	2.85	

Table XIII-4

QUESTIONNAIRE PSYCHOLOGICAL INDICES
(COLLEGE EDUCATION)

Index	Group	N	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Fatigue	Ranch Hand	447	12.79	4.55	0.88
	Comparison	335	12.83	4.45	
Anger	Ranch Hand	447	9.55	3.09	0.71
	Comparison	335	9.46	3.08	
Erosion	Ranch Hand	448	20.12	5.80	0.94
	Comparison	336	19.90	5.54	
Anxiety	Ranch Hand	437	21.23	6.74	0.63
	Comparison	328	20.51	5.96	
Depression (Severity)	Ranch Hand	60	5.22	2.80	*
	Comparison	39	4.46	2.11	

*Data too sparse for valid analysis

When an unadjusted analysis of reported depression (yes, no) was performed, there was a statistically significant group difference (P=0.002) with the Ranch Handers reporting more depression then the comparisons. This is not necessarily inconsistent with the analysis of severity (P=0.89).

Table XIII-5

ISOLATION INDEX, ADJUSTED FOR EDUCATION

Group	Index Score						
	≤5	6-7	8-9	10-11	12-13	≥14	Total
Ranch Hand	16	81	535	269	91	48	1040
Comparison	3	75	425	200	49	18	770

P = 0.002

The questionnaire responses to the questions concerning fatigue, anger, erosion, anxiety, and depression were analyzed with the exposure index, using a general linear model. When Blacks and non-Blacks were combined, the anger index was observed to be suggestively associated with exposure (P = 0.13) in officers but not in either of the enlisted occupational strata. All other exposure analyses had P values in excess of 0.40.

Educational level is a major influence on responses to the psychological assessment portion of the questionnaire. The responses to these questions did not differ between college educated Ranch Handers and comparisons, but all indices except depression did differ significantly in the high school educated participants. These variables were all subjectively measured, and the specific subsets of questions were not validated. It is unclear from these data whether these differences reflect a herbicide effect unique to the largely high school educated enlisted group or an educationally related response to a highly emotional public issue. This difference may also be a reflection of post-Vietnam stress in the frontline Ranch Hand personnel in contrast to the reduced stress in the comparison group stationed in support areas of SEA.

2. Physical Examination Parameters

During the physical examination, the Cornell Index, the Minnesota Multiphasic Personality Inventory (MMPI), the Halstead-Reitan Battery and the Wechsler Adult Intelligence Scales were used to assess psychologic functioning. Again, results were comparable whether using rank or educational attainment as stratification variables, and only the educational analyses are presented.

a. Cornell Index

The Cornell Index is a subjective 10 to 15 minute self-administered inventory of neuropsychiatric symptoms and complaints. It has been standardized and is a widely used testing instrument. Grading of the responses to the Cornell results in an overall index and separate indices for each of the ten subelements of the instrument. A total index score of 8 or less is considered to be normal. The overall index scores for the Ranch Hand and comparison groups were contrasted using the Kolmogorov-Smirnov technique after stratification for educational level (Table XIII-6). High school educated participants demonstrated a highly significant group differential (P <0.001) but the index scores in the college groups were not different.

Table XIII-6

ANALYSIS OF CORNELL INDEX BY GROUP
(KOLMOGOROV-SMIRNOV TWO-SAMPLE TEST)

Educational Level	Group	Mean Score	Standard Deviation	P Value
High School	Ranch Hand	9.21	10.35	< 0.001
	Comparison	6.44	7.79	
College	Ranch Hand	3.66	5.43	0.59
	Comparison	3.44	4.58	

The subelement scores were analyzed by log-linear techniques using 6 categories of response. These results are displayed in Table XIII-7, and the results of a similar analysis, using data from all available comparisons, are included as well. These results were all adjusted for educational level, since education was found to affect test scores in a highly significant manner (P <0.0001). Categorical analysis of the subelements revealed significant group differences between the Ranch Handers and the original comparisons in all areas except depression and the neurocirculatory system (NCS). This finding in depression on the Cornell Index is inconsistent with the significant observation noted in the responses to the in-home questionnaire, and may reflect the presence of differential reporting. The NCS scores were suggestive of group differences with a P value of 0.12. Analysis of the entire comparison group revealed similar findings.

Table XIII-7

CATEGORICAL ANALYSIS OF GROUP DIFFERENCES IN THE CORNELL INDEX
(ADJUSTED FOR EDUCATION)*

| Parameter | P Value: Ranch Hand Versus | |
	Original Comparisons	All Comparisons
Fear and Inadequacy	0.02	0.06
Depression	0.39	0.16
Nervousness and Anxiety	0.002	0.009
Neurocirculatory System	0.12	0.14
Startle	0.004	0.04
Psychosomatic	0.002	0.002
Hypochondria	0.05	0.12
Gastrointestinal System	0.01	0.01
Sensitivity	0.08	0.29
Troublesomeness	0.06	0.06

* All of these parameters were significantly affected by education level
(P <0.0001)

Analysis of the Ranch Hand group's overall Cornell Index by degree of
exposure was performed, using log-linear techniques. The Cornell Index was
compared with exposure level (low, medium, and high) and education (high school
and college) after stratification for occupation. In each occupational cate-
gory, the index was clearly influenced by educational level but not by degree
of herbicide exposure. Table XIII-8 contains the results of these analyses.

Table XIII-8

EXPOSURE ANALYSIS OF THE CORNELL INDEX
(ADJUSTED FOR EDUCATIONAL LEVEL)

| Occupational Category | P Value | |
	Cornell Versus Exposure	Cornell Versus Education
Officer	0.91	0.09
Enlisted, flying	0.53	0.05
Enlisted, ground	0.26	0.04

Analysis of the overall Cornell Index identified significant group dif-
ferences among high school-educated individuals (P <0.001), with the Ranch
Handers having a significantly higher mean (abnormal) score. However, this

finding was not observed among the college educated individuals. Log-linear analyses of the Ranch Handers and original comparisons, adjusted for education, revealed significant differences in 6 of the 10 subscales of the index (P ≤ 0.05) and borderline or suggestive findings in three others (P ≤ 0.12). Despite these group differences, education adjusted exposure analysis of the overall Cornell Index did not identify any association between level of exposure and Cornell Index.

b. <u>Minnesota Multiphasic Personality Inventory (MMPI)</u>

The MMPI, a standardized set of 566 subjective self-administered questions concerning various aspects of behavior and personality, was completed by 1023 Ranch Handers, 767 original comparisons, and 1194 total comparisons. Scoring was performed by machine, using the standard criteria for normality of 30-70. The comparison of the distributional characteristics of the responses to each of the subelements of the MMPI are shown in Tables XIII-9 and XIII-10. The effect of educational level on psychological scores is again seen, with more suggestive and/or significant differences between groups appearing in the high school stratum. The validity scale was not different between Ranch Handers and comparisons in either educational stratum; however, the high school comparisons exhibited a greater degree of denial (K scale) than the high school Ranch Handers. Depression (P = 0.16), paranoia (P = 0.19) and hysteria scales (P = 0.12) were suggestive of group differences in the high school stratum and significant differences were noted in the masculinity/femininity, hypochondria, mania/hypomania, and social introversion scales, with comparisons faring better than the Ranch Handers. The college stratum demonstrated borderline significance in the masculinity/femininity scale (P = 0.09) and a significant difference (P = 0.04) in social introversion. The masculinity/femininity scale is heavily influenced by the range of interests held by the participants. As individuals increase their education and broaden their interests beyond traditional "male" activities, the score tends to rise (Lachar, 1974). This is demonstrated by the means of 57.87 to 59.15 in the college stratum and means of 54.85 to 55.94 in the high school group. The consistent finding of significance in social introversion, with the Ranch Handers being more inwardly directed, is striking, but its clinical relevance is unclear. The percent of the Ranch Handers and comparisons exhibiting abnormal MMPI scores (greater than 70 or less than 30) are shown in Table XIII-11 for those scales with suggestive or significant findings.

The increased score on the denial (K) scale of the MMPI for the enlisted comparison group may be an indication of a relative differential in reporting between the two groups. When considered in the light of an increased enlisted Ranch Hand hypochondria scale on both the Cornell Index and the MMPI, overreporting in the Ranch Hand group is indicated.

Table XIII-9

ANALYSIS OF MMPI TESTING IN HIGH SCHOOL-EDUCATED PARTICIPANTS
(RANCH HAND N = 575; COMPARISON N = 430)

Parameter	Group	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Validity	Ranch Hand	1.85	4.54	0.99
	Comparison	1.73	4.07	
Defensiveness (L Scale)	Ranch Hand	51.99	7.84	0.98
	Comparison	52.03	8.15	
Consistency (F Scale)	Ranch Hand	51.95	9.29	0.44
	Comparison	50.65	7.16	
Denial (K Scale)	Ranch Hand	53.95	8.86	0.03*
	Comparison	55.63	8.12	
Hypochondria	Ranch Hand	59.74	13.36	0.05
	Comparison	57.22	10.95	
Depression	Ranch Hand	60.47	13.98	0.16
	Comparison	58.39	11.96	
Hysteria	Ranch Hand	60.12	9.96	0.12
	Comparison	58.90	8.23	
Psychopathic/Deviate	Ranch Hand	56.38	11.00	0.86
	Comparison	55.89	10.52	
Masculinity/Femininity	Ranch Hand	55.94	8.32	0.01
	Comparison	54.85	8.94	
Paranoia	Ranch Hand	51.72	8.66	0.19
	Comparison	50.68	8.33	
Psychasthenia (Anxiety)	Ranch Hand	57.27	12.23	0.47
	Comparison	55.59	10.07	
Schizophrenia	Ranch Hand	57.53	13.42	0.45
	Comparison	55.97	9.71	
Mania/Hypomania	Ranch Hand	56.03	10.36	0.01
	Comparison	54.49	10.31	
Social Introversion	Ranch Hand	52.31	10.38	0.006
	Comparison	50.80	9.50	

*Comparisons greater than Ranch Hand

Table XIII-10

ANALYSIS OF MMPI TESTING IN COLLEGE-EDUCATED PARTICIPANTS
(RANCH HAND N = 448; COMPARISON N = 337)

Parameter	Group	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Validity	Ranch Hand	1.48	4.14	0.47
	Comparison	1.95	4.49	
Defensiveness (L Scale)	Ranch Hand	50.26	7.68	0.99
	Comparison	50.33	7.29	
Consistency (F Scale)	Ranch Hand	48.74	5.84	0.99
	Comparison	48.44	5.36	
Denial (K Scale)	Ranch Hand	58.46	7.53	0.99
	Comparison	58.41	7.64	
Hypochondria	Ranch Hand	55.42	9.34	0.96
	Comparison	54.65	8.45	
Depression	Ranch Hand	55.34	10.77	0.99
	Comparison	54.57	9.98	
Hysteria	Ranch Hand	59.75	7.38	0.98
	Comparison	59.32	7.01	
Psychopathic/Deviate	Ranch Hand	55.21	9.33	0.68
	Comparison	55.66	8.90	
Masculinity/Femininity	Ranch Hand	59.15	8.72	0.09
	Comparison	57.87	8.98	
Paranoia	Ranch Hand	53.62	6.96	0.63
	Comparison	53.26	6.64	
Psychasthenia (Anxiety)	Ranch Hand	53.62	8.04	0.84
	Comparison	54.18	8.36	
Schizophrenia	Ranch Hand	54.70	7.94	0.79
	Comparison	54.89	7.88	
Mania/Hypomania	Ranch Hand	55.22	9.55	0.51
	Comparison	54.05	10.03	
Social Introversion	Ranch Hand	46.83	8.67	0.04
	Comparison	47.50	7.98	

Table XIII-11

MMPI ABNORMALITY BY GROUP

Level	MMPI Scale	Group	% Below 30	% Above 70
High School	Denial	Ranch Hand	0.0	1.7
		Comparison	0.0	3.7
	Hypochondria	Ranch Hand	0.0	18.1
		Comparison	0.0	10.9
	Depression	Ranch Hand	0.2	18.1
		Comparison	0.0	12.2
	Hysteria	Ranch Hand	0.0	14.1
		Comparison	0.0	7.9
	Masculinity/	Ranch Hand	0.0	4.5
	Femininity	Comparison	0.0	5.6
	Paranoia	Ranch Hand	0.0	2.4
		Comparison	0.0	1.9
	Mania/Hypomania	Ranch Hand	0.3	8.5
		Comparison	0.2	8.6
	Social Intro-version	Ranch Hand	0.0	6.8
		Comparison	0.0	4.9
College	Masculinity/	Ranch Hand	0.0	11.6
	Femininity	Comparison	0.0	11.0
	Social Intro-version	Ranch Hand	0.0	1.6
		Comparison	0.3	1.8

Log-linear analysis of the MMPI data, using dichotomous (normal/abnormal) responses was also conducted (Table XIII-12). Educational level was again found to exert a highly significant influence in all scales, with P values all less than 0.01.

Table XIII-12

LOG-LINEAR ANALYSIS OF THE MMPI SCALES BY GROUP
(ADJUSTED FOR EDUCATION)

Scale	P Value of Group Difference
Hypochondria	< 0.001
Depression	0.02
Hysteria	0.002
Psychopathic/Deviate	0.39
Masculinity/Femininity	0.84
Paranoia	0.26
Psychasthenia	0.21
Schizophrenia	0.007
Mania/Hypomania	0.52
Social Introversion	0.32

Several of these analyses appear to be inconsistent with the results of the Kolmogorov-Smirnov testing, making inference more difficult. Most of the statistically significant group differences found in the distributional analyses were in the high school group, but the log-linear analysis revealed highly significant group differences (P = 0.02) between the Ranch Hand and comparison groups after adjustment for education. Matched pair analyses, using the original comparison subset, were conducted on the hysteria, hypochondria, and masculinity/femininity scales, with respective P values of 0.02, 0.02, and 0.66. These results mirror those of the log-linear analysis in Table XIII-12.

The initial group analyses of the MMPI were performed without consideration for the variable of race. A repeat analysis of MMPI scores was also conducted for the 63 Ranch Handers and 45 originally selected comparisons who were Black. The results of this analysis are presented in Table XIII-13. Wherever the sample size permitted, the analyses were adjusted for education; however, sparseness of data prevented adjustment in the analysis of the psychasthenia, schizophrenia, and masculinity/femininity scales and prevented any analysis for the paranoia and social introversion scales. The borderline significant finding in the schizophrenia scale (P = 0.07) is somewhat parallel to the significant P value for schizophrenia (P = 0.007) in Table XIII-12. These findings do not suggest that the factor of race is at all responsible for the overall differences in MMPI scores between the Ranch Hand and comparison groups.

Table XIII-13

MMPI ANALYSIS AMONG BLACK PARTICIPANTS

Scale	Adjusted for Education	P Value of Group Difference
Hypochondria	Yes	0.15
Depression	Yes	0.91
Hysteria	Yes	0.31
Psychopathic/Deviate	Yes	0.73
Mania/Hypomania	Yes	0.70
Psychasthenia	No	0.20
Schizophrenia	No	0.07
Masculinity/Femininity	No	0.31
Paranoia	N/A	-
Social Introversion	N/A	-

Exposure analysis of the Ranch Hand group, using log-linear techniques revealed a mixed pattern of significant, borderline and suggestive findings. These results are summarized in Table XIII-14. Education remains a significant factor, but consistency across occupational groups is not evident, since stratification by occupational group mirrored stratification by education. Table XIII-15 displays the exposure index data, and the percentage of abnormal MMPI scale results, for the exposure analyses with P values of concern. Only the hysteria scale in the officers attending college and the psychopathic deviate scale in both high school and college officers showed consistent increases in abnormality with increasing exposure. However, the number of abnormal scores in all of these scales was quite low and inferential accuracy is compromised.

Table XIII-14

P VALUES OF THE MMPI/EXPOSURE ANALYSES
(ADJUSTED FOR EDUCATION)

Parameter	P Value Parameter Versus Exposure			P Value Parameter Versus Education		
		Enlisted			Enlisted	
	Officer	Flying	Ground	Officer	Flying	Ground
Hypochondria	0.21	0.97	0.02	0.18	0.10	0.03
Depression	0.70	0.11	0.16	0.46	0.12	0.27
Hysteria	0.21**	0.76	0.0005	0.34	0.62	0.04
Psychopathic Deviate	0.001*	1.00	0.15	0.17	0.20	0.16
Masculinity/Femininity	0.09	0.81	0.09	0.28	0.04	0.005
Paranoia	1.00	0.64	0.53	0.72	0.83	0.20
Psychasthenia	0.89	0.05	0.48	0.29	0.56	0.07
Schizophrenia	0.09	0.12	0.73	0.43	0.50	0.03
Mania/Hypomania	0.32	0.13	0.29	0.86	0.81	0.41
Social Introversion	0.39	0.33	0.78	0.77	0.93	0.02

*Significant confounding by education present
**Significant three-way interaction present

Table XIII-15

DOSE RESPONSE PATTERNS

Parameter	Group	Exposure Level	Number Normal	Number Abnormal (%)
Hypochondria	Enlisted Ground	Low	110	38 (25.7%)
		Medium	153	25 (14.0%)
		High	119	29 (19.6%)
Depression	Enlisted Flying	Low	48	10 (17.2%)
		Medium	41	18 (30.5%)
		High	55	11 (16.7)
	Enlisted Ground	Low	111	37 (25.0%)
		Medium	148	30 (16.9%)
		High	119	29 (19.6%)
Hysteria*	Officers (High School)	Low	10	0 (0%)
		Medium	14	5 (26.3%)
		High	24	0 (0%)
	Officers (College)	Low	97	3 (3.0%)
		Medium	104	5 (4.6%)
		High	91	9 (9.1%)
	Enlisted Ground	Low	115	33 (22.3%)
		Medium	163	15 (8.4%)
		High	132	16 (10.8%)
Psychopathic/Deviate*	Officers (High School)	Low	10	0 (0%)
		Medium	19	0 (0%)
		High	23	1 (4.2%)
	Officers (College)	Low	100	0 (0%)
		Medium	102	7 (6.4%)
		High	90	10 (10%)
	Enlisted Ground	Low	127	21 (14.2%)
		Medium	164	14 (7.9%)
		High	131	17 (11.5%)
Masculinity/Femininity	Officers	Low	105	5 (4.5%)
		Medium	113	15 (11.7%)
		High	111	13 (10.5%)
	Enlisted Ground	Low	135	13 (8.8%)
		Medium	172	6 (3.4%)
		High	136	12 (8.1%)
Psychasthenia	Enlisted Flying	Low	54	4 (6.9%)
		Medium	48	11 (1.9%)
		High	62	4 (6.1%)
Schizophrenia	Officers	Low	108	2 (1.8%)
		Medium	119	9 (7.0%)
		High	121	3 (2.4%)
	Enlisted Flying	Low	55	3 (5.2%)
		Medium	49	10 (16.9%)
		High	59	7 (10.6%)
Mania/Hypomania	Enlisted Flying	Low	53	6 (10.2%)
		Medium	50	9 (15.3%)
		High	63	3 (4.8%)

*Data are presented by educational level when the education/exposure
interactions are statistically significant.

Analysis of the MMPI data from the Ranch Hand and original comparison groups revealed significant group differences in the hypochondria, depression and hysteria scales (P ≤ 0.02), after adjustment for education. Stratified analysis based on level of education revealed statistically significant group differences for the hypochondria and masculinity/femininity scales (P ≤ 0.05). However, there were no statistically significant group differences among college-educated individuals, and only in the masculinity/femininity scale was borderline significance reached (P = 0.09). Exposure analyses did not reveal any consistent patterns of statistical significance between occupational categories, level of exposure and MMPI scores.

c. Halstead-Reitan

The Halstead-Reitan Neuropsychological Test Battery was administered to each participant to assess the functional integrity of the central nervous system. An impairment index for each participant was calculated based upon the scores of the category, tactual performance, speech-sounds, Seashore rhythm, and finger-tapping portions of the battery. The impairment index ranged from zero to seven, based on the number of subtests in which the participant scored abnormally. Impairment was declared if the index equalled or exceeded three. Larger numbers of participants were deleted from these analyses; since seven distinct tests contributed to the impairment index. The absence of any one made calculation of the index impossible. Analysis of dicotomous variables (normal/abnormal), adjusted for education, revealed no overall group differences (P = 0.74).

A categorical analysis, unadjusted for educational level, was performed. The data and the results of the unadjusted analyses of the Ranch Hand group, the entire comparison group and the subset of original participants are presented in Table XIII-16.

Table XIII-16

UNADJUSTED HALSTEAD-REITAN SCORES BY GROUP

Impairment Index	Original Comparisons N = 559		Ranch Hand N = 771		All Comparisons N = 883	
0	85		124		141	
1	162	66.5%*	226	66.5%*	248	66.0%*
2	125		163		194	
3	77		126		134	
4	60		68		85	
5 or more	50		64		81	

$x^2 = 3.18$
P = 0.67

$x^2 = 1.35$
P = 0.93

* Cumulative % for Impairment Index 0,1,2

Analyses adjusted for education were carried out on the Ranch Handers and the original subset of comparisons (Table XIII-17). Education was again seen to be a significant factor (P < 0.0001).

Table XIII-17

HALSTEAD-REITAN ANALYSIS BY GROUP AND EDUCATION

Educational Level	Group	Degree of Impairment
		0	1	2	3	4	5 or Greater
High School	Ranch Hand	45	108	88	80	54	56
	Comparison	29	69	69	49	38	37
College	Ranch Hand	79	118	75	46	14	8
	Comparison	56	93	56	28	22	13

P Value, adjusted for education = 0.57

An exposure index analysis was also accomplished on the data from the Ranch Hand group. As shown in Table XIII-18, educational level was a significant covariable in the officer and enlisted flying groups, but there were no significant relationships between herbicide exposure and Halstead-Reitan performance.

Table XIII-18

HALSTEAD-REITAN IMPAIRMENT AND EXPOSURE

Occupational Group	Adjusted P Values
	Halstead-Reitan Versus Exposure	Halstead-Reitan Versus Education
Officers	0.88	0.002
Enlisted Flying	0.44	0.05
Enlisted Ground	0.82	0.62

d. Wechsler Adult Intelligence Scale (WAIS)

WAIS testing was completed on 1022 Ranch Handers and 733 original comparison individuals. The test was administered and scored in the standard manner by certified clinical psychologists and psychological technicians. As noted previously, intelligence scores (IQ) by rank were equivalent to IQ scores by education. The distributions of verbal, performance and full-scale IQ scores, by educational level and group, are shown in Figure XIII-2.

Figure XIII-2

FREQUENCY DISTRIBUTION IQ SCORES BY EDUCATIONAL LEVEL AND GROUP
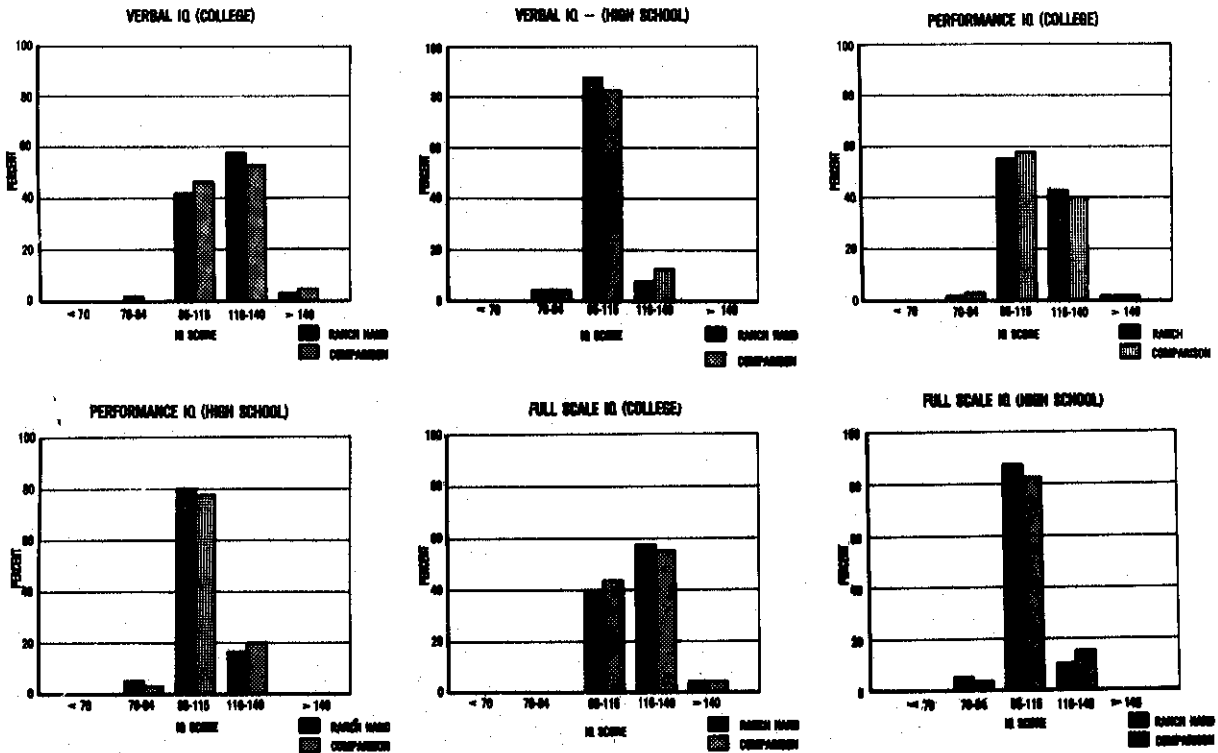
        The IQ scores demonstrated consistent patterns within each educational
stratum. A slight increase in the proportion of both Ranch Hand and comparison
college graduates, with performance IQ's between 85 and 115, was noted. These
distributions were tested for group differences by the Kolmogorov-Smirnov pro-
cedure. Suggestive but nonsignificant differences were noted for performance
and full-scale IQ's in the high school stratum, but no differences were found
among the college-educated group.   These data are shown in Table XIII-19.

Table XIII-19

DISTRIBUTIONAL ANALYSIS OF IQ SCORES

Scale	Education	Group	Mean Score	Standard Deviation	P Value
Verbal	High School	Ranch Hand	110.61	10.65	0.39
		Comparison	101.73	11.34	
	College	Ranch Hand	117.00	12.97	0.73
		Comparison	116.84	13.73	
Performance	High School	Ranch Hand	102.40	11.38	0.14
		Comparison	104.14	11.86	
	College	Ranch Hand	113.70	12.62	0.50
		Comparison	112.37	13.33	
Full Scale	High School	Ranch Hand	101.18	10.71	0.15
		Comparison	102.74	11.32	
	College	Ranch Hand	117.30	12.96	0.37
		Comparison	116.59	13.82	

The distributions were observed to identify outliers, and the percentage of participants with scores in the abnormal range (below 85) was determined. These results are shown in Table XIII-20.

Table XIII-20

ABNORMAL IQ SCORE BY GROUP AND EDUCATIONAL LEVEL

Educational Level	Scale	Group	% Below 85	% Above 115
High School	Verbal	Ranch Hand	3.7	9.8
		Comparison	3.3	13.7
	Performance	Ranch Hand	5.4	14.3
		Comparison	3.7	18.8
	Full	Ranch Hand	4.0	10.6
		Comparison	3.5	15.1
College	Verbal	Ranch Hand	0.9	58.8
		Comparison	0.3	54.1
	Performance	Ranch Hand	1.1	43.9
		Comparison	1.8	41.1
	Full	Ranch Hand	0.7	61.1
		Comparison	0.3	56.2

Analysis of the WAIS testing scores of the Ranch Hand group, by level of herbicide exposure, revealed no consistent differences in IQ scores. The P values derived from these analyses are presented in Table XIII-21 and show only one statistically significant association (P = 0.04).

Table XIII-21

RESULTS OF IQ SCORES BY EXPOSURE ANALYSIS

Scale	Occupational Group	P Value
Verbal	Officers	0.99
	Enlisted Flying	0.34
	Enlisted Ground	0.82
Performance	Officers	0.99
	Enlisted Flying	0.04
	Enlisted Ground	0.18
Full Scale	Officers	0.99
	Enlisted Flying	0.23
	Enlisted Ground	0.25

2. Summary

In this chapter, a large number of variables were analyzed using several techniques and multiple assessments. Consistent differences between high school-educated Ranch Handers and high school-educated original comparisons are seen throughout these analyses. With the exception of a single statistically significant result for social introversion (P = 0.04), these group differences are not apparent in the college educated stratum. Unstratified but education-ally adjusted analyses of the MMPI scores did, however, reveal group differences which were more like those of the high school stratum. Exposure analyses did not reveal any patterns suggesting any association between psychological testing results and level of herbicide exposure. The relative risks, confidence intervals, and shifts in means for the dependent variables analyzed in this chapter are included in Appendix XVIII.

Table XIII-22

PSYCHOLOGICAL ANALYSIS SUMMARY
(RANCH HAND VERSUS ORIGINAL COMPARISON GROUP)

| | | Analytic Strategy (P Values) | | | | |
| | Adjusted for Education | Stratified Analysis | | Exposure Analysis | | |
Parameter		High School	College	Off	Enl Fly	Enl Gnd
Questionnaire Indices						
Fatigue		<0.001	NS*			
Anger		0.002	NS			
Erosion		<0.001	NS			
Anxiety		<0.001	NS			
Isolation	0.002					
Depression (Severity)		0.89				
Cornell Index		<0.001	NS	NS	NS	NS
Fear and Inadequacy	0.02					
Depression	NS					
Nervousness and Anxiety	0.002					
Neurocirculatory	0.12					
Startle	0.004					
Psychosomatic	0.002					
Hypochondria	0.05					
Gastrointestinal	0.01					
Sensitivity	0.08					
Troublesomeness	0.06					
MMPI						
Hypochondria	<0.001	0.05	NS	NS	NS	0.02
Depression	0.02	0.16	NS	NS	0.11	0.16
Hysteria	0.002	0.12	NS	NS	NS	0.001
Psychopathic Deviate	NS	NS	NS	0.001	NS	0.15
Masculinity/Femininity	NS	0.01	0.09	0.09	NS	0.09
Paranoia	NS	0.19	NS	NS	NS	NS
Psychasthenia	NS	NS	NS	NS	0.05	NS
Schizophrenia	0.007	NS	NS	0.09	0.12	NS
Mania/Hypomania	NS	0.01	NS	NS	0.13	NS
Social Introversion	NS	0.006	0.04	NS	NS	NS
Halstead-Reitan	NS			NS	NS	NS
IQ Scores						
Verbal		NS	NS	NS	NS	NS
Performance		0.14	NS	NS	0.04	0.18
Full Scale		0.15	NS	NS	NS	NS

*Nonsignificant; P > 0.20

The results of the analyses of the psychological data are summarized in Table XIII-22, and demonstrate a greater degree of statistically significant group differences in the more subjective measurements (questionnaire and Cornell Index) than are observed in the more objective assessments (Halstead-Reitan and WAIS). The effect of differential reporting in this evaluation is as yet difficult to assess. However, the high school-educated Ranch Handers did have higher scores on the hypochondria scale of the MMPI and the psychosomatic portion of the Cornell Index than did the appropriate comparisons. Additionally, the high school-educated comparisons scored higher on the MMPI K Scale (denial). These findings suggest that differential reporting may be influencing the analytic results of the in-home questionnaire and the Cornell Index. There may also be a differential response to the intense media interest in the herbicide/dioxin issue between the high school and college strata in this study. The role of "Post Vietnam Stress" in these findings is also unclear at this time. Further clarification of these factors and their impact must await analysis of the data from the follow-up phase of the study. Based on the psychological data collected during the initial in-home questionnaire and physical examination, there is no convincing evidence suggesting the presence of an adverse effect on emotional health caused by herbicide exposure.

Chapter XIV.

EVALUATION OF HEPATIC STATUS

1. Introduction

A very broad spectrum of hepatic phenomena has been reported in association with acute, subacute and chronic administration of TCDD to animals. Significant response differences between species occur, however. Serum enzyme changes (SGOT, SGPT, GGPT, LDH) have not been prominent, although SGPT levels were elevated in at least 1 study (Schantz et al, 1979). Elevated alkaline phosphatase levels have been observed with increased direct bilirubin levels (Kociba et al, 1976). Decreased serum cholesterol levels have also been noted after sublethal exposures (Schantz et al, 1979). TCDD interferes with hemoglobin metabolism affecting delta-aminolevulinic acid synthetase activity (Goldstein et al, 1973) and possibly other enzyme activities, providing, at sufficient doses, signs and symptoms of porphyria.

Motivated by the literature reports of hepatotoxicity, signs and symptoms of hepatic dysfunction were sought in the participants in this study. In this chapter, enzyme levels, bilirubin levels and lipid values are presented, along with determinations reflecting porphyrin metabolism. Clinical history data are also analyzed, along with hepatomegaly determined at physical examination.

2. Biochemical Determinations

a. Analyses Overview

In this section 9 biochemical determinations are studied: SGOT, SGPT, GGPT, alkaline phosphatase (Alk. Phos.), total bilirubin (T. Bili), direct bilirubin (D. Bili), lactic dehydrogenase (LDH), cholesterol (Chol) and triglycerides (Trig). These 9 variables are listed in Table XIV-1, along with the normal-abnormal ranges used in the reported statistical analyses. These ranges were adapted from Kelsey-Seybold laboratory normal ranges.

In the analyses of these 9 variables, adjustments were made for 4 covariates: current alcohol ingestion (ALC), days of exposure to industrial chemicals (IC), days of exposure to degreasing chemicals (DC), and presence or absence of antibody to hepatitis B surface antigen (anti-HB$_S$Ag). The current alcohol use covariate was taken from the personal medical history administered at the time of the physical examination and is in units of average drinks per day (see Appendix VI, page 2). Current alcohol ingestion was selected as an adjusting variable over the drink years measure developed from the questionnaire, since preliminary testing indicated it correlated better with hepatic endpoints. The industrial chemical and degreasing chemical exposures were derived from the in-home questionnaire (total unprotected exposure).

The data analyzed were from the entire Ranch Hand cohort compliant to the physical examination (N = 1045) and the original comparisons compliant to the physical examination (N = 773). Ten Ranch Handers and 2 comparisons were removed from the analysis because of body temperature of 100°F or more, and the effect of fever on hepatic variables. Individuals whose blood contained hepatitis B surface antigen (HB$_S$Ag) were also removed from the analysis (8 Ranch Handers and 7 comparisons).

b. Group Analyses

Three sets of analyses were run:

(1) Continuous-continuous analyses (CC): In these evaluations both the dependent variables and adjusting covariates, except anti-HB$_S$Ag which is dichotomous, were used as continuous variables in an analysis of covariance.

(2) Continuous-discrete analyses (CD): In these analyses all 4 covariates were used as dichotomous variables while the dependent variables were maintained as continuous.

(3) Discrete-discrete analyses (DD): All variables were analyzed in dichotomous form using the log-linear model for discrete data.

In all 3 analysis settings, group-by-covariate interactions were examined. In addition, the continuous-continuous and continuous-discrete analyses models were fit without interaction terms to provide discussion of appropriate tests when dependent variable relationships with the covariates are the same in both groups. In the continuous-continuous and continuous-discrete analyses the dependent variable was normalized by using a logarithmic (base 10) transformation.

Table XIV-1

NORMAL - ABNORMAL LEVELS OF NINE BIOCHEMICAL DETERMINATIONS
REFLECTING HEPATIC FUNCTION

Determination	Normal	Abnormal
1. SGOT	≤ 41	> 41
2. SGPT	≤ 45	> 45
3. GGPT	≤ 85	> 85
4. Alkaline Phosphatase	≤ 9.7	> 9.7
5. Total Bilirubin	≤ 1.2	> 1.2
6. Direct Bilirubin	≤ 0.36	> 0.36
7. Lactic Dehydrogenase	≤200	>200
8. Cholesterol	≤240	>240
9. Triglycerides	≤150	>150

Table XIV-2 provides unadjusted means, adjusted means, and percent abnormality by groups for the 9 hepatic-related variables. A summary of the 3 classes of analyses is provided in Table XIV-3. The results in this table provide P values for Ranch Hand-comparison group differences.

Table XIV-2

UNADJUSTED MEANS, ADJUSTED MEANS AND PERCENT ABNORMALITY FOR
NINE LIVER-RELATED VARIABLES

Variable	Group	Unadjusted Means	Adjusted Means	Percent Abnormality
SGOT	RH	33.0	33.0	13.9
	COM*	33.1	33.1	14.8
SGPT	RH	20.3	20.3	7.8
	COM	20.5	20.5	8.6
GGPT	RH	40.2	40.1	10.8
	COM	39.3	39.3	10.3
Alk. Phos.	RH	7.68	7.69	17.3
	COM	7.53	7.52	16.9
T. Bili	RH	0.57	0.57	1.8
	COM	0.58	0.58	2.0
D. Bili	RH	0.23	0.23	29.0
	COM	0.24	0.24	29.7
LDH	RH	142.1	142.1	1.7
	COM	141.7	141.7	2.1
CHOL	RH	212.2	212.2	26.0
	COM	216.6	216.6	27.7
TRIG	RH	121.8	121.9	34.7
	COM	124.3	124.1	36.1

*COM denotes original fully compliant comparisons.

Table XIV-3

SUMMARY OF RESULTS
UNMATCHED ANALYSES OF NINE BIOCHEMICAL VARIABLES REFLECTING LIVER FUNCTION

		P Values for Models with Interaction									P Values for models without Interaction				
VAR	ANAL	Gp	ALC	IC	DC	anti HB_aAg	Gp X ALC	Gp X IC	Gp X DC	Gp X anti HB_aAg	Gp	ALC	IC	DC	anti HB_sAg
SGOT	CC	.127	<.001	-*	-	-	.032	-	-	-	.805	<.001	-	-	-
	CD	.278	<.001	-	-	-	-	-	-	-	.867	<.001	-	-	-
	DD	.578	<.001	-	-	-	-	-	-	-					
SGPT	CC	.736	<.001	-	-	-	-	-	-	-	.663	<.001	-	-	-
	CD	.309	.005	-	-	-	-	-	-	-	.662	.003	-	-	-
	DD	.592	-	-	-	-	-	.052	-	-					
GGPT	CC	.731	<.001	-	-	-	-	-	-	-	.483	<.001	-	-	-
	CD	.050	<.001	-	-	.066	-	-	-	-	.421	<.001	-	-	.078
	DD	.782	<.001	-	-	-	-	-	-	-					
ALK PHOS	CC	.405	-	-	-	.009	-	-	-	-	.140	-	.071	-	.009
	CD	.142	.001	-	-	.010	-	-	-	-	.115	.001	.066	-	.011
	DD	.734	-	-	-	-	-	-	-						
TOT BILI	CC	.113	.014	.036	.001	.100	-	-	-	-	.423	.009	.011	<.001	.095
	CD	.606	-	-	-	-	-	-	-	-	.400	-	-	-	.099
	DD	.800	-	-	-	.027	-	-	-						
DIR BILI	CC	.494	.004	-	.032	-	-	-	-	-	.770	.003	-	.016	-
	CD	.371	.091	-	-	-	.069	-	-	-	.755	-	-	-	-
	DD	.869	-	-	-	-	-	-	-						
LDH	CC	.063	.090	-	-	-	.011	-	.037	-	.836	.025	-	.023	-
	CD	.024	-	-	-	-	-	-	-	-	.711	-	-	-	-
	DD	.526	-	-	-	-	.086	-	-	-					
CHOL	CC	.062	<.001	.079	-	-	-	-	-	-	.022	<.001	.061	-	-
	CD	.216	.014	-	-	-	-	-	-	-	.031	.020	-	-	-
	DD	.466	.053	-	-	-	-	-	-						
TRIG	CC	.911	-	-	-	-	-	-	-	-	.601	-	-	-	-
	CD	.284	-	-	-	-	-	-	-	-	.616	-	-	-	-
	DD	.589	-	-	-	-	-	-	-						

* - denotes P > 0.050 for main effects, P > 0.100 for interation effects

In Tables XIV-2 and XIV-3, there is a very slight indication of overall group differences in the GGPT with the Ranch Hand mean greater than the comparison mean and a P value of 0.050 in the CD analysis with interaction terms. However, when interaction terms are not considered, P = 0.421. This may indicate some interaction effects even though they were not detected as statistically significant. Additionally, no difference is detected in the CC or DD

analyses. A stronger indication of overall group difference is seen with LDH; however, it is interesting to note that while the Ranch Hand mean LDH is greater than the comparison mean, the Ranch Hand percent abnormal LDH is less than that of the comparison group. The Ranch Hand cholesterol mean is lower than that of the comparison group and the result appears unlikely to have occurred by chance (P value of 0.062 in the full model CC analysis; P values of 0.022 and 0.031 in the CC and CD analyses respectively not using interaction terms). These group differences in GGPT, LDH and CHOL are all small.

Further group specific differences are noted in interaction effects with covariables. Ranch Hand SGOT levels are correlated more highly with alcohol ingestion than are comparison SGOT levels. The Ranch Hand SGOT - alcohol regression slope is 0.0178 logarithmic units per drink per day, while the comparison SGOT - alcohol slope is 0.0113 logarithmic units per drink per day. This difference in slopes is statistically significant with $P = 0.032$, and could represent differing hepatic sensitivities to alcohol.

A borderline group by industrial chemical exposure is noted in the DD analysis of SGPT levels. This interaction is shown in Table XIV-4.

Table XIV-4

INDUSTRIAL CHEMICAL EXPOSURE AND % ABNORMAL SGPT IN
RANCH HAND AND COMPARISON GROUPS

	Ranch Hand	Comparison
Exposure	8.84% (38 of 430)	6.71% (23 of 343)
No Exposure	7.19% (42 of 584)	10.1% (42 of 416)

Ranch Hand personnel exposed to industrial chemicals have a higher proportion of abnormal SGPT values than do Ranch Hand personnel who are not exposed to industrial chemicals. The situation is reversed in the comparison group. The relative risk for abnormal SGOT in the Ranch Hand group associated with industrial chemical exposure is 1.23, while the comparison relative risk is 0.66, and this difference carries a P value of 0.052.

Two group-by-covariate interactions are noted in the LDH data. In the comparison group neither alcohol ingestion nor exposure to degreasing chemicals was associated with change in LDH levels, while in the Ranch Hand group, increased levels were noted to occur in association with both exposures. Specifically, in the comparison group the LDH-alcohol slope is -0.0008 logarithmic units per drink per day which is not statistically significantly different from

zero (P = 0.577). Also, the comparison LDH-degreasing chemical slope is -0.08 x 10^{-5} units per exposure day (P = 0.735 against the null hypothesis of zero slope). On the other hand, the Ranch Hand LDH-alcohol slope is 0.0041 units per drink per day (P < 0.001 against hypothesis of zero slope) and the LDH-degreasing slope is 0.51 X 10^{-5} units per exposure day (P = 0.003 against zero slope hypothesis).

c. Exposure Analyses

Analyses within the Ranch Hand cohort are presented contrasting the hepatic clinical variables against the herbicide exposure index. For this exposure index work, separate analyses were run for each of 3 occupational groups: officers, enlisted flying and enlisted ground. The 9 hepatic variables were analyzed as continuous dependent variables after logarithmic transformation. As with the Ranch Hand-comparison group analyses, alcohol use, industrial chemical exposure, degreasing chemical exposure and antibody to Hepatitis B surface antigen were used as adjusting covariates, and individuals with body temperature greater than or equal to 100°F were omitted from the analysis as were individuals with hepatitis B surface antigen. For this exposure index effort, alcohol use, industrial chemical exposure and degreasing chemical exposure were used as continuous variables.

Table XIV-5 is a display of exposure means adjusting for covariates without invoking interaction. Table XIV-6 provides a summary of P values for the testing. Analyses of covariance or generalized linear models with and without interaction were employed.

An overall or main exposure effect on GGPT levels is indicated among officers and enlisted ground personnel. However, clear-cut dose-response patterns are not noted, rather, in the officer cohort the medium exposure subgroup has the highest mean GGPT while in the enlisted ground cohort the subgroup with low exposure has the highest GGPT.

Six exposure group-by-covariate interactions were found at P ≤ 0.050. These interactions are written out in Table XIV-7. In this table, the slope of the dependent variable with respect to the covariate of interest is provided for each of the 3 exposure levels.

An exposure-by-degreasing chemical interaction was noted in SGOT in officers. Low herbicide exposure is associated with a possible depression of SGOT levels with increasing degreasing chemical exposure, while individuals in the high herbicide exposure group show increasing SGOT levels with increasing degreasing chemical exposure.

Table XIV-5

ADJUSTED BIOCHEMICAL MEANS BY EXPOSURE AND OCCUPATIONAL
CATEGORY, WITH TYPICAL SAMPLE SIZES

Variable	Occupational Category	Low Exposure	Medium Exposure	High Exposure
SGOT	Officer	33.3	32.2	33.0
	Enl. F.	31.8	33.5	31.7
	Enl. G.	33.6	32.7	34.1
SGPT	Officer	20.2	19.9	19.4
	Enl. F.	18.5	20.8	18.4
	Enl. G.	21.3	21.1	20.6
GGPT	Officer	37.1	39.5	37.5
	Enl. F.	41.4	45.9	37.8
	Enl. G.	43.0	40.2	40.5
Alk. Phos.	Officer	6.91	7.24	7.47
	Enl. F.	8.13	7.88	7.98
	Enl. G.	7.93	7.85	8.04
T. Bili.	Officer	0.56	0.55	0.57
	Enl. F.	0.53	0.56	0.54
	Enl. G.	0.58	0.58	0.60
D. Bili.	Officer	0.22	0.23	0.23
	Enl. F.	0.18	0.23	0.21
	Enl. G.	0.25	0.24	0.26
LDH	Officer	141.3	139.4	139.3
	Enl. F.	143.1	141.0	149.3
	Enl. G.	142.9	140.8	144.9
Chol.	Officer	214.6	213.0	209.4
	Enl. F.	214.0	212.6	222.5
	Enl. G.	208.7	210.4	211.4
Trig.	Officer	111.9	127.4	129.0
	Enl. F.	129.8	126.4	128.4
	Enl. G.	118.6	114.5	121.1
Typical Sample Sizes	Officer	107	122	120
	Enl. F.	58	58	63
	Enl. G.	143	170	146

Table XIV-6

SUMMARY OF P VALUES FOR EXPOSURE INDEX ANALYSIS OF NINE HEPATIC VARIABLES

		P Values for Models with Interaction									P Values for Models With No Interaction				
VAR	OCC CAT	EXP CAT	ALC	IC	DC	aHb	EXP X ALC	EXP X IC	EXP X DC	EXP X anti HBsAg	Exp Cat	ALC	IC	DC	anti HBsAg
SGOT	OFF	.563	<.001	-*	-	-	-	-	.009	-	.512	<.001	-	.047	-
	ENL.F.	.885	<.001	-	-	.037	-	-	-	-	.538	<.001	-	-	.035
	ENL.G.	.698	<.001	-	-	-	-	-	-	-	.409	<.001	-	-	-
SGPT	OFF	.463	<.001	-	-	-	-	.081	-	-	.812	<.001	-	-	-
	ENL.F.	.909	-	-	-	-	-	-	-	-	.411	-	-	-	-
	ENL.G.	.467	-	-	-	-	-	-	-	-	.862	-	-	-	-
GGPT	OFF	.052	<.001	-	-	-	.089	-	-	-	.696	<.001	-	.040	-
	ENL.F.	.427	<.001	-	-	-	.049	-	-	-	.224	<.001	-	-	-
	ENL.G.	.093	<.001	-	.010	-	-	-	-	-	.574	<.001	-	.020	-
ALK PHOS	OFF	.192	-	-	-	-	<.001	-	-	-	.280	-	-	-	-
	ENL.F.	.685	-	-	-	-	-	-	-	-	.855	-	-	-	-
	ENL.G.	.629	-	-	-	-	-	-	-	-	.710	-	-	-	-
TOT BILI	OFF	.643	-	-	-	-	-	-	-	-	.885	-	-	-	-
	ENL.F.	.449	.029	-	-	-	-	-	-	.086	.560	.011	-	-	-
	ENL.G.	.606	-	-	.010	-	-	-	-	-	.642	-	.023	.008	-
DIR BILI	OFF	.992	-	-	-	-	-	-	-	-	.856	-	-	-	-
	ENL.F.	.399	-	-	-	-	-	.060	-	.006	.310	-	-	-	-
	ENL.G.	.823	-	-	-	-	-	-	-	-	.697	-	-	-	-
LDH	OFF	.516	-	-	-	-	-	-	-	-	.758	-	-	-	-
	ENL.F.	.656	.018	-	-	-	-	-	-	-	.174	.019	-	-	-
	ENL.G.	.300	-	.050	-	-	-	-	-	.049	.360	.034	.036	-	-
CHOL	OFF	.290	-	-	-	-	-	-	-	-	.602	-	-	-	-
	ENL.F.	.310	.031	-	-	-	-	-	-	-	.343	.037	-	-	-
	ENL.G.	.096	-	-	-	-	.026	-	.058	-	.841	-	-	-	-
TRIG	OFF	.394	-	-	-	-	-	-	-	-	.244	-	-	-	-
	ENL.F.	.468	.045	.044	-	-	-	-	-	-	.980	-	-	-	-
	ENL.G.	.890	-	-	-	-	-	-	-	-	.768	-	-	-	-

* - Indicates $P > 0.050$ for main effects $P > 0.100$ for interactions.

Table XIV-7
EXPOSURE – COVARIATE INTERACTION EFFECTS FOR NINE
HEPATIC VARIABLES

Var	Occ Cat	Interact	Level of Interact	Exposure Level	Slope	P Value on Test of Slope Against Null Hypothesis of Zero Slope
SGOT	Officers	Exp × DC	.009	Low	$-.201 \times 10^{-4}$ units/day	.286
				Med	$.021 \times 10^{-4}$ units/day	.924
				High	$.674 \times 10^{-4}$ units/day	.002
GGPT	Enlisted Flying	Exp × ALC	.049	Low	.0828 units/drk/day	<.001
				Med	.0561 units/drk/day	.002
				High	.0288 units/drk/day	.037
ALK PHOS	Officers	Exp × ALC	<.001	Low	-.0442 units/drk/day	<.001
				Med	.0131 units/drk/day	.254
				High	-.0015 units/drk/day	.864
DIR BILI	Enlisted Flying	Exp × Anti HB$_S$Ag	.006	Low	.3713 mgm/dl	.013
				Med	-.2246 mgm/dl	.071
				High	.1752 mgm/ml	.134
LDH	Enlisted Ground	Exp × Anti Hb$_S$Ag	.049	Low	.0329 units	.159
				Med	-.0407 units	.085
				High	-.0330 units	.128
CHOL	Enlisted Ground	Exp × ALC	.026	Low	.0039 mgm/dl/drk/day	.284
				Med	-.0065 mgm/dl/drk/day	.043
				High	.0054 mgm/dl/drk/day	.147

Alcohol use is associated with increasing GGPT levels among enlisted flying personnel, but the increase in GGPT falls smoothly with increasing exposure levels. On the other hand, alcohol use is associated with decreasing alkaline phosphatase levels among Ranch Hand officers in the low exposure group.

There are 2 interactions between exposure group and antibody to Hepatitis B antigen. Direct bilirubin levels are higher in enlisted flying personnel who are antibody positive and are in the low or high exposure groups. Direct bilirubin levels are lower in individuals who are antibody positive but in the medium exposure group. LDH is higher among enlisted ground Ranch Handers who are antibody positive and are in the low herbicide exposure group while LDH levels are lower among antibody positive individuals in the medium and high exposure groups.

An exposure-by-alcohol use interaction effect on cholesterol levels shows positive slopes in the low and high exposure categories but a negative slope in the medium exposure category.

Thus, of the 6 statistically significant interactions noted in this exposure index analysis only 1, the SGOT-degreasing chemical interaction, supports an interpretation of herbicide effect. But this interpretation is markedly weakened by the presence of the 5 uninterpretable patterns.

3. Urinalysis Determinations Related to Porphyrin Metabolism

Three components associated with porphyrin metabolism were determined and are analyzed here: uroporphyrin, coproporphyrin and d-aminolevulinic acid. Data addressing these 3 variables were analyzed looking for differences between the Ranch Hand and comparison groups and looking for associations with indexed herbicide exposure within the Ranoh Hand group.

In examining the uroporphyrin, coproporphyrin and d-aminolevulinic acid data for Ranch Hand - comparison group differences, adjustments were accomplished for the following 6 variables: current alcohol use in drinks per day (ALC), blood urinary nitrogen (BUN), creatinine clearance (CCL), days of exposure to industrial chemicals (IC), days of exposure to degreasing chemicals (DC) and presence or absence of antibody to hepatitis B antigen. Adjustments were accomplished treating the dependent variable and all independent variables except antibody to hepatitis B antigen as continuous variables in a generalized linear model analysis. Since the compounds uroporphyrin, coproporphyrin and d-aminolevulinic acid are all measured in 24-hour urine collections, only data from subjects who complied with the full collection of urine are used in the analysis (620 Ranch Handers and 439 comparisons). Also, febrile participants and individuals with HB_sAg have been removed. In the adjusted analyses the dependent variable was normalized by using a logarithmic (base 10) transformation.

Table XIV-8 provides uroporphyrin, coproporphyrin and d-aminolevulinic acid unadjusted means, adjusted means and percent abnormality. For uroporphyrin, values greater than 60 were considered abnormal, for coproporphyrin, values greater than 235 and for d-aminolevulinic acid, values greater than 7000 were counted as abnormal.

Table XIV-8

UNADJUSTED MEANS, ADJUSTED MEANS AND PERCENT ABNORMALITY
FOR THREE COMPOUNDS RELATED TO PORPHYRIN METABOLISM

		Unadjusted Means	Adjusted Means	% Abnormal
Uroporphyrin	RH	30.5	*	6.5%
	COM	30.8	*	6.8%
Coproporphyrin	RH	31.2	*	0.2%
	COM	30.8	*	0.0%
d-aminolevulinic acid	RH	2328.9	2337.1	0.0%
	COM	2383.2	2371.4	0.0%

* adjusted means not represented due to interaction

Table XIV-9

SUMMARY OF RESULTS UNMATCHED ANALYSES
OF THREE COMPOUNDS RELATED TO PORPHYRIN METABOLISM
P-VALUES FOR MODELS WITH INTERACTION

VAR	Gp	ALC	BUN	CCL	IC	DC	Anti HBsAg	Gp x ALC	Gp x BUN	Gp x CCL	Gp x IC	Gp x DC	Gp x Anti HBsAg
URO	.227	-	<.001	<.001	-	-	-	-	.077	-	-	-	-
COPRO	.490	-	<.001	<.001	-	.049	-	.045	.097	-	-	-	-
ALA	.145	-	-	<.001	-	-	.014	-	-	-	-	-	-

Table XIV-9 displays the detailed analyses. No overall group differences are observed. With uroporphyrin a borderline significant group-by-BUN interaction (P = 0.077) was observed. In the Ranch Hand group, the uroporphyrin-BUN slope was -0.010 uroporphyrin logarithm units per BUN unit, while the comparison slope was steeper (-0.017). A borderline group-by-BUN interaction was also noted in the coproporphyrin data. In the Ranch Hand group, the coproporphyrin-BUN slope was -0.014 coproporphyrin logarithmic units per BUN unit, while the comparison slope was again steeper (-0.023). Lastly, a group-by-alcohol interaction was detected in the coproporphyrin data (P = 0.045). The Ranch Hand slope was positive (+0.013) while the comparison slope was negative (-0.008).

Table XIV-10

SUMMARY OF P VALUES FOR EXPOSURE INDEX ANALYSES OF THREE COMPOUNDS
RELATED TO PORPHYRIN METABOLISM

VAR	OCC CAT	EXP CAT	ALC	BUN	CCL	IC	DC	aHb	EXP × ALC	EXP × BUN	EXP × CCL	EXP × IC	EXP × DC	Exp × Anti HB$_s$Ag
URO	OFF	.207	-	-	<.001	-	-	-	-	-	-	-	.033	-
	ENL F.	.670	-	-	-	-	-	-	-	-	-	-	-	-
	ENL G.	.882	-	.010	.050	-	-	-	-	-	-	-	-	-
COPRO	OFF	.630	-	-	.022	.035	-	-	-	-	-	-	-	-
	ENL F.	.498	-	<.001	-	-	-	-	-	-	-	-	-	-
	ENL G.	.699	-	.016	.015	-	-	-	-	-	-	.016	-	-
ALA	OFF	.279	-	-	<.001	-	-	-	-	-	-	-	-	-
	ENL F.	.135	-	-	<.001	-	-	-	.028	-	-	-	-	-
	ENL G.	.312	-	-	<.001	.020	-	-	-	-	-	.040	.042	-

Table XIV-11

TABLE OF UNADJUSTED MEANS FOR THREE COMPOUNDS
RELATED TO PORPHYRIN METABOLISM

Variable	Occupational Category	N	Low Exposure	Medium Exposure	High Exposure
Uroporphyrin	Officers	212	28.9	26.9	31.3
	Enlisted Fly.	106	38.7	27.8	31.6
	Enlisted Gnd.	282	31.1	32.4	29.8
Coproporphyrin	Officers	212	32.4	26.7	29.9
	Enlisted Fly.	106	36.4	31.1	32.5
	Enlisted Gnd.	282	31.6	30.9	32.8
d-amino levulinic Acid	Officers	212	2221	2312	2211
	Enlisted Fly.	106	2460	2510	2381
	Enlisted Gnd.	282	2290	2441	2271

Table XIV-12

EXPOSURE-COVARIATE INTERACTIONS FOR THREE COMPOUNDS
RELATED TO PORPHYRIN METABOLISM

Variable	Occupational Category	Interaction	P Value for Interaction	Exposure Level	Slope
Uropophyrin	Officer	Exp x DC	.033	Low	-.000043
				Med	.000074
				High	.000190
Copro-porphyrin	Enlisted Ground	Exp x IC	.016	Low	.301 X 10^{-4}
				Med	-.540 X 10^{-4}
				High	.176 X 10^{-4}
d-amino levulinic acid	Enlisted Flying	Exp x ALC	.028	Low	.00045
				Med	-.02922
				High	.01445
d-amino levulinic acid	Enlisted Ground	Exp x IC	.040	Low	-.1450 X 10^{-4}
				Med	-.2944 X 10^{-4}
				High	.0315 X 10^{-4}
d-amino levulinic acid	Enlisted Ground	Exp x DC	.042	Low	-.0538 X 10^{-4}
				Med	.0398 X 10^{-4}
				High	.0394 X 10^{-4}

The literature indicates elevated porphyrin compound excretion resulting from sufficient dioxin exposure. The pattern found here is one of higher Ranch Hand uroporphyrin or coproporphyrin levels relative to comparisons when there are concomitantly higher BUN levels, or, in the case of coproprophyrin, when there is higher alcohol ingestion. No overall group differences are observed.

Tables XIV-10, XIV-11 and XIV-12 display the results of exposure index analyses within the Ranch Hand group. Starting with Table XIV-10, no statistically significant overall group differences are seen and 5 statistically significant($P \leq 0.050$) group-covariate interactions are noted. Table XIV-11 displays unadjusted group means for the porphyrin metabolism related variables and, as indicated by the statistical testing of overall group differences, no trends with exposure index are observed.

The 5 exposure-by-covariate interactions are listed in Table XIV-12; however, only the exposure index by degreasing chemical interactions follow a classical dose-response pattern. Specifically, Ranch Hand officers with greater herbicide exposure, as measured by the exposure index, have greater increases in uroporphyrin output in response to degreasing chemical exposures than do Ranch Hand officers with less herbicide exposure. The same pattern is seen in the enlisted ground d-aminolevulinic acid data.

4. Clinical Variables

Sixteen of 1027 Ranch Handers (1.56%) were diagnosed as having hepatomegaly while 6 of 769 comparisons (0.78%) had that finding (P = 0.138) with an approximate 70% power. In the Ranch Hand group, the cases of hepatomegaly appear to be randomly distributed within the 3 exposure categories; however, due to the small number of cases statistical testing is not powerful. These data on hepatomegaly are shown in Table XIV-13 (febrile participants and individuals with HBsAg have been removed).

Table XIV-13

CASES OF HEPATOMEGALY IN THE RANCH HAND COHORT BY
OCCUPATION AND EXPOSURE CATEGORY

| Occupational Category | Exposure Index | | | | | |
| | Low | | Medium | | High | |
	Cases	N	Cases	N	Cases	N
Officers	2	110	2	124	2	123
Enlisted Flying	1	59	2	58	2	63
Enlisted Ground	0	148	3	176	1	147

Eighteen of 1027 Ranch Handers (1.75%) reported an enlarged liver during response to questionnaire inquiry while 13 of 760 comparisons (1.71%) reported the same.

The study questionnaire also inquired about a medical history of hepatitis, jaundice, cirrhosis, and a general category called other liver conditions. Ranch Hand and comparison responses to these questions are shown in Table XIV-14. Ranch Hand respondents differ from comparisons only in the other liver category. Thirteen of the 16 Ranch Handers reporting other liver conditions have had their report verified by medical record. One comparison has had his condition verified. A display of the verified findings is shown in Table XIV-15 (febrile individuals and HBsAg positive individuals were left in the analysis).

Table XIV-14

SPECIFIC LIVER DISORDERS REPORTED ON QUESTIONNAIRE

Reported Event	Ranch Hand		Comparison		P Value
	Yes	No	Yes	No	
Hepatitis	40	1005	32	741	>0.50
Jaundice	44	1001	35	738	>0.50
Cirrhosis	4	1041	3	770	>0.50
Other	16	1029	2	771	0.004

Table XIV-15

OTHER LIVER CONDITIONS REPORTED BY
STUDY PARTICIPANTS AND VERIFIED BY MEDICAL RECORDS

Ranch Hand:	ICD Code	Code Meaning	Number
	2724	Hyperlipidemia	1
	570	Liver necrosis	1
	5739	Unspecified	10
	7904	Enzyme elevation	1
Comparison:	5719	Chronic unspecified	1

Table XIV-16

REPORTED SKIN PATCHES, BRUISES OR SENSITIVITY
IN RANCH HAND PARTICIPANTS BY
OCCUPATION AND EXPOSURE CATEGORY

Occupational Category	Exposure Index								
	Low			Medium			High		
	Cases	%	N	Cases	%	N	Cases	%	N
Officers	36	32.4	111	48	37.5	128	44	35.2	125
Enlisted Flying	27	45.8	59	28	47.5	59	37	56.1	66
Enlisted Ground	74	49.0	151	82	45.8	179	76	51.4	148

Seeking historical evidence of porphyric symptoms, questions concerning skin changes that could have been associated with porphyria cutanea tarda were asked (specifically, skin patches, bruisibility or sensitivity). Of 1045 Ranch Hand respondents, 462 or 44.2% reported these skin symptoms while 278 of 773 comparisons or 36.0% reported these conditions. These reported cases indicate a statistically significant group difference (P <0.001); however, no regression with exposure index was noted (data given in Table XIV-16).

The historical and hepatomegaly data support an interpretation of some group difference. However, no positive association with herbicide exposure has been noted.

5. Summary and Conclusion

Ranch Handers have slightly greater GGPT and LDH levels than the comparisons while having lower cholesterol levels. Also, Ranch Hand SGOT, SGPT and LDH levels are more highly correlated to (and therefore may be more influenced by) materials with an hepatic effect, namely, alcohol, degreasing compounds and industrial chemicals. No group differences were noted in alkaline phosphatase or bilirubin levels.

Borderline statistically significant group differences have been detected in uroporphyrin and coproporphyrin levels in association with BUN, and in coproporphyrin levels in association with alcohol ingestion. No overall group differences were detected in these compounds or delta aminolevulinic acid values.

Twice as many Ranch Handers as comparisons had enlarged livers on physical examination, but this difference was not statistically significant. Statistically significant group differences were noted in the occurrence of miscellaneous liver disorders exclusive of hepatitis, jaundice and cirrhosis, verified by

medical record review. Ranch Handers self reported 23% more skin changes of the type associated with porphyria cutanea tarda than did the comparison participants, and the group difference was statistically significant. Clinically apparent porphyria was not evident at physical examination.

The observed group differences in liver-related biochemical variables found in the blood, and in porphyrin metabolism compounds found in the urine are most likely of minor or negligible medical importance at the present time.   The verified reports of liver morbidity are of greater clinical interest.

The exposure index analyses do not support an interpretation of herbicide effect with respect to any of the group differences summarized.

Chapter XV

DERMATOLOGIC EVALUATION

A thorough dermatologic assessment was deemed essential because chloracne is the only recognized definitive clinical end point following exposure to chlorophenols and dioxin. Over one-half of all veteran complaints recorded in the Veterans Administration Herbicide Registry cited dermatologic symptoms. These facts, coupled with the knowledge that chloracne is transient following a single point exposure (Homberger, 1979), suggested that there is a significant potential to misclassify adolescent acne and chloracne. While the issue of correct diagnosis could be resolved by biopsies and histopathologic characterizations in all participants, this approach was rejected on ethical grounds, as well as concern for the adverse impact of biopsy procedures on future study participation. Consequently, the dermatologic assessment was carefully planned to collect historical and distributional dermatologic data by questionnaire, followed by a detailed corroborative physical examination, supplemented by voluntary biopsies when indicated. Most data reported in this chapter are from the 1045 Ranch Handers and the 773 originally selected comparison individuals enrolled in the study. Minor fluctuations from these denominators reflect missing dependent variable or covariate data. Relative risks and confidence intervals are shown for all dependent variables in Appendix XVIII.

1. Questionnaire Data

The in-home study questionnaire collected detailed medical histories on the occurrence of acne. These data are displayed in Table XV-1 and show that the Ranch Handers reported slightly more acne than their comparisons.

Table XV-1

REPORTED OCCURRENCE OF ACNE BY GROUP

Group	No Acne		Reported Acne		Total	
	Number	Percent	Number	Percent	Number	Percent
Ranch Hand	659	63.3	382	36.7	1041	100
Comparison	498	64.8	271	35.2	769	100

Reported acne group contrast: P = 0.52

Beginning and end dates of up to three sustained periods of acne activity were recorded for each individual on the questionnaire. Since only acne after 1961 could be possibly induced by herbicide exposure, cases of post-1961 acne were placed in time reference to each individual's RVN tour(s). This temporal distribution was not statistically different with respect to group membership. These data are reflected in Table XV-2.

Table XV-2

REPORTED POST-1961 ACNE BY TIME OF THE SOUTHEAST ASIA [SEA] TOUR(S) BY GROUP

Group	Pre-SEA Only		Post-SEA Only		Pre- and Post-SEA*	
	Number	Percent	Number	Percent	Number	Percent
Ranch Hand N = 179	62	34.6	31	17.3	86	48.0
Comparison N = 116	51	44.0	17	14.7	48	41.4

Reported acne by group by pre/post SEA: P = 0.27
Reported acne (Post SEA) relative risk: 1.18, 95% Conf. int. (.67, 2.18)

*Such acne could have been separate cases or the same case starting before his RVN tour and ending afterwards.

Durations of the cumulative acne episodes were distributed by 5-year intervals and contrasted by group and SEA category. These data are shown in Table XV-3.

Table XV-3

DURATION OF ACNE IN 5-YEAR CATEGORIES BY SEA TOUR AND GROUP MEMBERSHIP

	Duration in Years				
Pre-SEA ONLY	≤5	5 <Yr ≤10	10 <Yr ≤15	15 <Yr ≤20	Total
Ranch Hand	44	15	2	1	62
Comparison	38	12	0	1	51

$$P = 0.63$$

Post-SEA ONLY					
Ranch Hander	15	4	11	1	31
Comparison	9	2	4	2	17

$$P = 0.61$$

Thus, these SEA tour categories suggested that there were no group differences for the pre-SEA or post-SEA acne. Questionnaire information on whether the participant consulted a physician for his acne was used as an indirect measure of the clinical severity of the acne. Of 70 Ranch Handers with acne post-1961 who were asked this question, 29 (41.4%) responded as having visited a physician as contrasted to 15 of the 45 (33.3%) comparisons (P = 0.38), suggesting that there was not a statistically significant difference in the clinical severity of their acne.

Since chloracne, following mild to moderate exposures, is classically found in skin areas on the temples, eyes/eyelids, and ears (eyeglass distribution), questions on rash locations and combinations of locations were presented to each participant reporting acne. Of the 117 post-SEA plus pre- and post-SEA cases of acne in Ranch Handers after SEA duty, 75 (64%) reported no acne at any of these locations, while 36 (55%) of the 65 post-SEA plus pre- and post-SEA comparisons reported none. These proportions are not significantly different (P = 0.25), and the occurrence of skin disease which could potentially be chloracne does not differ in the two groups. There were only four individuals, two in each group, with acne confined exclusively to the classical chloracne areas.

As further corroboration of these anatomically categorized data, a Venn diagram was constructed for post-1961 acne lesions on the temples, ears, and eyes for the Ranch Hand group and the entire comparison group. These data are shown in Figure XV-I and display remarkable visual concordance.

Figure XV-1

VENN DIAGRAM OF POST-1961 TEMPLE, EAR, AND EYE ACNE BY GROUP

RANCH HAND GROUP
(POST 1961)

ACNE, OTHER SITES: 157
N = 202 (ACNE REPORTED)

ENTIRE
COMPARISON GROUP
(POST 1961)

ACNE, OTHER SITES: 156
N = 198 (ACNE REPORTED)
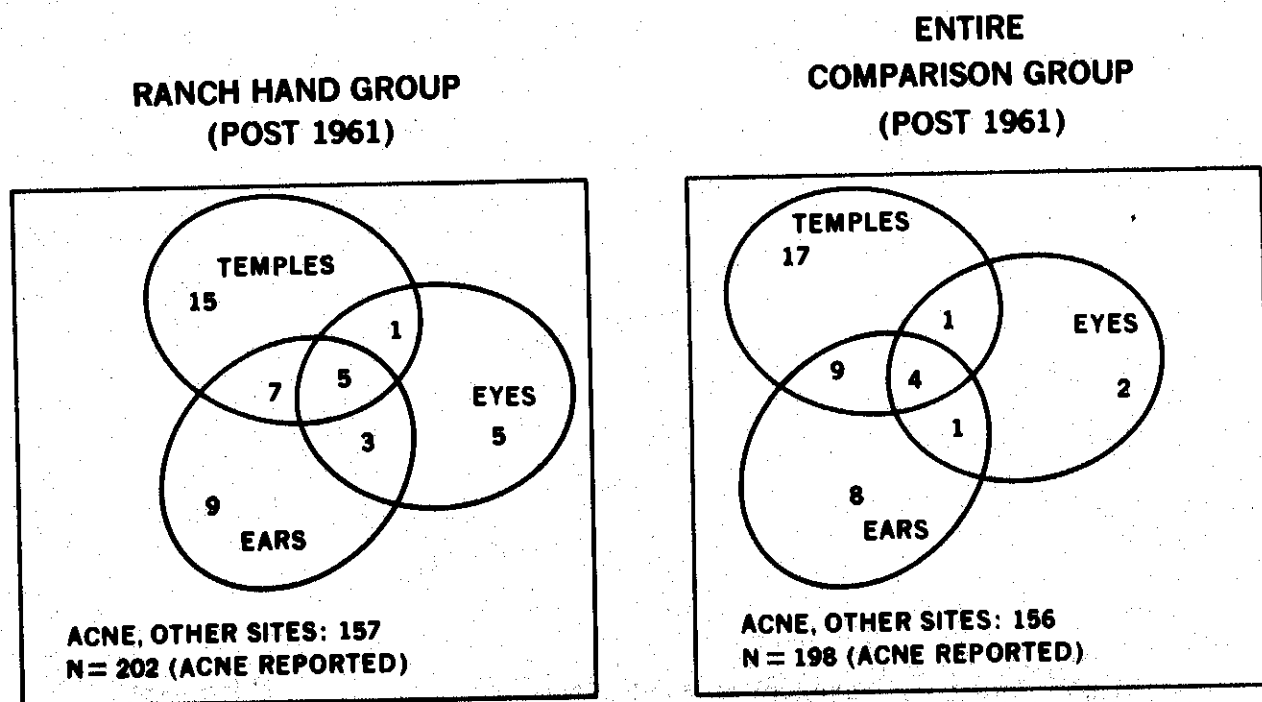
2. <u>Physical Examination Data</u>

All physical examination data were described using a diagnostic checklist, and abnormalities were annotated on a full body diagram. Color photographs were obtained at the dermatologist's discretion, and 14 lesions were biopsied. Of the 14 biopsies collected from 11 patients, none were suggestive of chloracne. No cases of chloracne were diagnosed. Histologic descriptions of these biopsies are presented in Table XV-4.

Table XV-4

BIOPSY RESULTS

Number	Histologic Description
3	Active degeneration
2	Inclusion cysts
2	Epidermal cysts
1	Basal cell carcinoma
1	Intradermal melanosis
1	Seborrheic keratosis
1	Pigmented nevus
1	Psoriasiform dermatitis
1	Chronic inflammation
1	Insect bite

The five most common diagnoses and the P value for group differences are shown in Table XV-5. Abnormal skin findings were prevalent but almost identical in both groups (i.e., 45.0% in Ranch Handers, and 44.9% in the comparisons; P = 0.97). Only for the miscellaneous diagnoses of "Other Abnormalities" (which included 15 diagnostic categories) was there a statistically significant group difference, with the comparisons having more disease than the Ranch Handers.

Table XV-5

PREVALENCE OF DERMATOLOGIC DIAGNOSES IN PERCENT

Diagnoses	Ranch Hand N = 1045	Comparison N = 773	P Value	Relative Risk	95% Conf int
Comedones	21.7	20.7	0.60	1.05	(.87,1.26)
Acneiform lesions	18.3	17.5	0.66	1.05	(.85,1.29)
Acneiform scars	11.2	10.4	0.57	1.08	(.82,1.43)
Cysts	11.6	10.5	0.46	1.10	(.84,1.46)
Hyperpigmentation	8.3	7.1	0.35	1.17	(.84,1.65)
Other abnormalities	12.6	16.3	0.03	.77	(.81, .98)
Any abnormality	45.0	44.9	0.97	1.00	(.90,1.11)

Based upon the four most prevalent diagnoses in Table XV-5 (comedones, acneiform lesions, acneiform scars, and dermal cysts), all of which should encompass the diagnostic possibility of chloracne, a dermatologic index was constructed for each study participant. A score of zero was given if none of the four lesions were noted, and a score of 1 was assigned if one lesion was diagnosed, etc. These data are displayed in Table XV-6.

Table XV-6

DERMATOLOGIC INDEX SCORE BY GROUP

	Scores									
	0		1		2		3		4	
Group	Number	%	Number	%	Number	%	Number	%	Number	%
Ranch Hand (N = 1045)	633	60.6	234	22.4	124	11.9	42	4.0	12	1.1
Comparison (N = 773)	487	63.0	157	20.3	95	12.3	27	3.5	7	0.9

P = 0.74

The distributions of these scores did not differ significantly, suggesting a similar crude clinical severity between the groups.

3. Questionnaire - Examination Correlations

The dermatologic index was contrasted to the historical occurrence of acne by group. These data are shown in Table XV-7.

Table XV-7

DERMATOLOGIC INDEX IN PERCENT BY QUESTIONNAIRE HISTORY OF ACNE BY GROUP

History	Group	Score					P Value
		0	1	2	3	4	
No Acne	Ranch Hand	66.3	21.4	9.4	2.4	0.5	0.72
	Comparison	69.1	18.1	9.6	2.6	0.6	
Acne ≤1961	Ranch Hand	55.3	25.1	13.4	4.5	1.7	0.84
	Comparison	55.1	21.8	17.7	4.1	1.4	
Acne >1961	Ranch Hand	47.3	23.2	17.7	8.9	3.0	0.82
	Comparison	48.4	26.6	16.9	6.4	1.6	

These data show that the dermatologic index does not differ significantly by group for any historical subset. And, as can be observed in Table XV-7, there is a positive association between the history (and time) of acne and the dermatologic index, regardless of group membership. An additional analysis of the dermatologic index for each individual who reported acne after his SEA tour (post-SEA only) did not reveal significant Ranch Hand-comparison differences ($P = 0.50$).

4. Exposure Index Analyses

Several comparisons were made using the exposure index and both historical and examination findings in the Ranch Hand group. Two historical parameters (incidence of acne and severity of acne) and the dermatologic examination findings were contrasted to the exposure index after stratifying for occupational categories by log-linear models. The historical-exposure analyses were essentially negative. Major dermatologic lesions from the examination were contrasted to the exposure index by occupational category. This analysis is presented in Table XV-8.

Table XV-8

PERCENTAGE OF SPECIFIC SKIN LESIONS IN RANCH HANDERS
BY EXPOSURE LEVEL BY OCCUPATIONAL CATEGORY
(POST 1961 DATA ONLY)

| | | Exposure Level | | | |
| | | Low % | Medium % | High % | P Value |
Condition	Occupational Group				
All skin abnormalities	Officers	57.1	22.2	21.4	0.20
	Enlisted Flying	14.3	16.7	60.0	0.17
	Enlisted Ground	39.5	35.8	25.0	0.40
Comedones	Officers	14.3	22.2	21.4	0.91
	Enlisted Flying	57.1	50.0	20.0	0.42
	Enlisted Ground	18.6	24.5	31.2	0.45
Acneiform Lesions	Officers	0	33.3	50.0	0.08
	Enlisted Flying	57.1	16.7	20.0	0.23
	Enlisted Ground	37.2	22.6	37.5	0.21
Acneiform Scars	Officers	28.6	11.1	21.4	0.68
	Enlisted Flying	71.4	50.0	40.0	0.53
	Enlisted Ground	10.9	28.3	31.2	0.57
Inclusion Cysts	Officers	14.3	0	14.3	0.49
	Enlisted Flying	14.3	50.0	20.0	0.32
	Enlisted Ground	18.6	18.6	27.1	0.53
Hyperpigmentation	Officers	0	11.1	7.1	0.72
	Enlisted Flying	14.3	16.7	0	0.64
	Enlisted Ground	9.3	15.1	3.1	0.20

Thus, of the 18 exposure analyses, none were statistically significant
(although based upon small sample sizes). Similarly, the relationship between
the dermatologic index and exposure index was explored. For all three occupa-
tional categories, the dermatologic index showed no significant correlation to
the exposure index, as reflected in Table XV-9.

Table XV-9

RANCH HAND DERMATOLOGIC INDEX IN ALL OCCUPATIONAL CATEGORIES
BY THE EXPOSURE INDEX
(POST 1961 DATA ONLY)

| | Dermatologic Index | | | |
| | 0 | | ≥ 1 | |
Exposure Level	Number	Percent	Number	Percent
Low	26	45.6	31	54.4
Medium	28	41.2	40	58.8
High	20	39.2	31	60.8

P = 0.78

5. Summary

A comprehensive dermatologic assessment was conducted by questionnaire and physical examination. The questionnaire data revealed that the incidence of past acne, its time of occurrence relative to the individual's SEA tour(s), its severity and duration, and its anatomic location did not significantly differ between the Ranch Hand and comparison groups. No cases of chloracne were diagnosed at physical examination or by biopsy. No group differences were noted for the five most prevalent dermatologic diagnoses. The category, other abnormalities (containing 15 dermatologic conditions), was significantly larger for the comparison group than for the Ranch Hand group. However, when all skin abnormalities were considered, the group rates were essentially identical. A dermatologic index was constructed to account for the number of skin abnormalities per individual (severity index) that might encompass a diagnosis of chloracne. The index was not associated with group membership but showed some correlation with a total history of past acne in both groups. There were no associations between historical or dermatological examination findings and exposure level in any occupational category of the Ranch Hand group.

CARDIOVASCULAR EVALUATION

1. Introduction

The effects of Herbicide Orange and its dioxin contaminant on the cardio-vascular system are not well defined. Both bradycardia and tachycardia have been suggested in acute heavy exposures to the 2,4-D and 2,4,5-T components, but the cardiovascular effects following chronic low dose exposure are essentially unknown. The thrust of this cardiovascular evaluation has been to collect important data by questionnaire, physical examination, and laboratory testing, that would identify Ranch Hand-comparison group differences after accounting for the effects of confounding variables. Of the well-established risk factors for cardiovascular disease, smoking, cholesterol level or cholesterol to high density lipoprotein (HDL) ratio, and age were selected as covariates in most analyses (Brand et al, 1976). The covariates were categorized as follows: age, ≤ 40, 40 years 1 month - 59 years 11 months (abbreviated 40 < > 60), and 60 years or more; smoking, 0 pack-years, 1-10 pack-years, and 11 or more pack-years; cholesterol, ≤ 180 mg/dl, 181-279 mg/dl, and ≥ 280 mg/dl; and cholesterol-HDL ratio, <5.3, ≥ 5.3. In complex analyses with sparse data, trichotomous covariates were reduced to dichotomous ones. The cutpoint for cholesterol-HDL ratio was derived from data on rated Air Force personnel referred for cardiovascular diagnostic examination; it is an unweighted average of means of flyers verified at cardiac catheterization as having or not having occlusive coronary atherosclerosis. A more optimal approach, based upon a median HDL value of the comparison group, will be used in subsequent reports. Statistically significant interactions between these covariates were not explored in detail when there was no effect on group membership and when the interactions were consonant with the classical epidemiology of cardiovascular disease. Analyses of weak risk factors in the data will be presented in subsequent reports. Because of the low proportion of Black participants in both groups, covariate adjustment by race was not possible. Consequently, a variety of dependent variable analyses by race, unadjusted for age, smoking, and cholesterol, are discussed throughout this chapter. In addition, where adjusted group differences were found to be statistically significant, other covariates (e.g., percent body fat, current smoking, history of intermittent claudication, testosterone level, differential cortisol level, etc.) have been used to reanalyze all data in an attempt to clarify the clinical significance of the finding.

Most analyses herein are based upon Ranch Hand contrasts to the "originals" of the comparison group. Where group associations are statistically significant or of general interest, other comparison group denominators have been used (e.g., matched originals only and the entire comparison group). Further, for specific analyses, participants with diabetes and pedal edema have been deleted. Small denominator fluctuations are also inherent in these analyses because of missing covariate or dependent variable information. Thus, tabular data may not be directly comparable between analyses because of the type of

covariate adjustment, or the denominator of the comparison group, or the dele-
tion of certain medical conditions thought to confound a specific clinical
diagnosis. In general, covariates having a nonsignificant association with the
dependent variable were removed from the analysis. The statistical analyses
are based on log-linear models (BMDP-4F), logistic regression (BMDP-LR), and
generalized linear models, chi-square, t tests, and matched covariate analyses
(Breslow, 1982). Relative risks and confidence intervals, computed using the
hypergeometric distribution (Thomas, 1971) and the normal approximation
(Fleiss, 1981), are shown for all dependent variables in Appendix XVIII.

2. Central Cardiovascular System

   a. Systolic Blood Pressure

        Abnormal systolic blood pressure was defined as pressure in excess of
140 mmHg by standard observer auscultation. All blood pressures were obtained
in a sitting position. Second or third readings were recorded on those indi-
viduals who manifested an initial elevation. There was no significant differ-
ence in systolic blood pressure (P = 0.248) between the non-Black Ranch Hand
and the non-Black original comparison group after adjusting for age, smoking,
and cholesterol level. These data are reflected in Tables XVI-1-1 and XVI-1-2.
Diabetics (2-hour postprandial glucose ≥120 mg/dl) were removed from the analy-
ses.

Table XVI-1-1

SYSTOLIC BLOOD PRESSURE
RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	36	10.4	309	32	14.3	192	68	11.9	501
≥40	113	23.1	377	94	24.6	288	207	23.7	665

Systolic pressure between groups: P = 0.248   Age versus systolic
Relative risk under 40: .73, 95% Conf int (.46,1.18) pressure (unadjusted
Relative risk over 40: .94, 95% Conf int (.73,1.20) for smoking and chol-
                                                    esterol): P <0.0001

        The unadjusted systolic blood pressure by smoking history association,
presented in Table XVI-1-2, is not significant (P=0.179) in these data.

Table XVI-1-2

SYSTOLIC BLOOD PRESSURE PARTICIPANTS BY SMOKING HISTORY
(NON-BLACKS ONLY)

Smoking History in Pack-Years	Abnormal	% Abnormal	Normal
0	70	17.8	324
1-10	44	16.1	230
>10	161	20.8	612

$P = 0.179$

Ranch Handers and original comparisons reflected in these tables were also compared on systolic blood pressure as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was no significant difference between the groups on systolic blood pressure ($P = 0.976$). The Ranch Hand and original comparison adjusted means were 133.12 and 133.15, respectively. The covariates of age and body fat were both significantly associated with systolic blood pressure ($P = 0.0001$).

Additional categorical analyses comparing Non-Black Ranch Handers with the total non-Black comparison group adjusted for age, smoking, and cholesterol showed comparable nonsignificant intergroup differences ($P = 0.366$) for systolic blood pressure. The effects of age and smoking were statistically significant, $P < 0.0001$ and $P = 0.04$, respectively. In addition, a chi-square analysis of Black Ranch Handers and Black individuals from the entire comparison group (diabetics removed) showed no group difference ($P = 0.265$) in systolic pressure.

b. Diastolic Blood Pressure

Diastolic blood pressure in excess of 90 mmHg was categorized as abnormal. No significant intergroup difference was noted after adjustment for age, smoking, and cholesterol level. These data are based upon non-Black, nondiabetic denominators and are presented in Table XVI-1-3.

Table XVI-1-3

DIASTOLIC BLOOD PRESSURE
IN RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

| | Ranch Hand | | | Original Comparisons | | | Total Both Groups | | |
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	18	5.2	327	12	5.4	212	30	5.3	539
≥40	57	11.6	433	53	13.9	329	110	12.6	762

Diastolic blood pressure P = 0.351
between groups:
Relative risk under 40: .97,95% Conf. int. (.45,2.18)
Relative risk over 40: .84,95% Conf. int. (.58,1.21)

Age versus diastolic
pressure (unadjusted
for smoking and chol-
esterol): P <0.0001

The Ranch Handers and original comparisons (as represented in Table XVI-1-3) diastolic blood pressure was also compared as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was a borderline significant diastolic blood pressure by group by age interaction (P = 0.0585), indicating a change in the blood pressure by group association with level of age (<40, ≥40). However, separate analyses at each level of age revealed no significant group differences. In the under-40 age group, the diastolic blood pressure by group association was not significant (P = 0.435); the adjusted group means were 78.2 and 77.02 for Ranch Handers and comparisons, respectively. In the 40-and-over age group, the diastolic blood pressure by group association was not significant (P = 0.904); the Ranch Hand and comparison adjusted means were 80.7 and 81.7, respectively.

An intergroup log linear analysis of diastolic blood pressure for Blacks and non-Blacks using original comparisons showed comparable nonsignificant results (P = 0.573). Age was a significant covariate (P <0.0001) while the history of past smoking was not. An unadjusted contrast of Black Ranch Handers and Black individuals from the entire comparison group also showed similar nonsignificant group differences (P = 0.533).

c. Electrocardiograms (ECG's)

ECG's were obtained on all participants, following a minimum fast of 4 hours and abstinence from tobacco for 4 hours. The vast majority of ECG's were obtained by 1 or 2 technicians on dedicated and calibrated machines. The tracings were read by a contract clinic cardiologist and categorized into normal and abnormal groups, the latter consisting of right bundle branch block, left bundle branch block, nonspecific T wave changes, bradycardia, tachycardia, and

other diagnoses.   Grave findings were immediately discussed with the partici-
pant's family physician and appropriate follow-up was arranged.   As shown in
Table XVI-1-4,   abnormal ECG findings were   not associated with group member-
ship (P = 0.987).   For both the non-Black Ranch Hand and original comparison
groups, there was a highly statistically significant (P <0.0006) association
between abnormal ECG's and increased age.

Table XVI-1-4

ECG FINDINGS IN RANCH HANDERS AND THE ORIGINAL COMPARISONS
BY AGE, ADJUSTED FOR SMOKING HISTORY AND HDL RATIO
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	69	20.1	274	51	23.1	170	120	21.3	444
≥40	148	30.2	342	107	28.4	269	255	29.4	611

Abnormal ECG findings between groups: P = 0.987   ECG findings in both
Relative risk under 40: .87,95% Conf. int. (.62,1.23) groups by age (un-
Relative risk over 40: 1.06,95% Conf. int. (.86,1.32) adjusted for smoking
      and HDL ratio):
      P = < 0.0006

When the ECG data in Table XVI-1-4 were redistributed into the catego-
ries of tachycardia, bradycardia, other abnormalities, and normal, an unad-
justed analysis showed no significant differences between the Ranch Hand and
original comparison group (P = 0.881).

An additional cardiac assessment was made on all past or present flying
personnel in both groups. Participants' names and social security numbers were
computer matched to the USAF ECG Repository, the world's largest ECG repository
on flying personnel (Lancaster and Ord, 1972; Hiss and Lamb, 1962). Three
hundred and fifty-four Ranch Handers and 282 original comparisons had between
one and 10 previous tracings on file which had been diagnostically coded by
stringent criteria. Accordingly, USAF cardiologists reviewed all 636 physical
examination ECG's (without knowledge of group membership) and coded them by the
standardized USAF criteria. The physical examination ECG was contrasted to the
past ECG's and categorized as no change or degraded (no ECG's were improved in
either group). These data analyzed by group membership and age are shown in
Table XVI-1-5. Blacks and diabetics were removed from the analysis. This
analysis is not adjusted for elapsed time between ECG readings.

Table XVI-1-5

CLINICAL COMPARISON OF CURRENT ECG'S TO PAST ECG'S IN FLYING PERSONNEL
BY GROUP MEMBERSHIP AND AGE
(NON-BLACKS ONLY)

	Ranch Hand			Comparison			Total		
	No Change	Degraded		No Change	Degraded		No Change	Degraded	
Age	Number	Number	Percent	Number	Number	Percent	Number	Number	Percent
<40	45	2	4.2	29	2	6.4	74	4	5.1
≥40	226	20	8.1	182	17	8.5	408	37	8.3
	271	22		211	19		482	41	

Because of sparse data in the under-40 age group, an analysis adjusted for both age and smoking was not possible; the unadjusted ECG change by group association was not significant (P = 0.652). In the 40-and-over age group, the ECG change by group association was not significant (P = 0.939), adjusted for smoking history. The smoking history covariate was borderline significant, P = 0.0852. In both the Ranch Hand and comparison groups combined, the age by ECG association (P = 0.412) was not significant. The unadjusted ECG change by smoking history association was significant (P = 0.018).

An overall analysis of systolic/diastolic blood pressures and ECG abnormalities was performed by group membership and adjusted for smoking (0, 1-10, >10 pack-years), cholesterol-HDL ratio (<5.3, ≥5.3), age (<40, ≥40) and differential cortisol level (continuous); Blacks and diabetics were omitted. The differential cortisol level is defined as the 7:30 AM cortisol measurement minus the 9:30 AM cortisol measurement. A logistic regression analysis showed similar nonsignificant results (as in Sections a-c above) that are presented in Table XVI-1-6.

Table XVI-1-6

RANCH HAND AND ORIGINAL COMPARISON GROUP CONTRAST FOLLOWING ADJUSTMENT
FOR AGE, SMOKING, CHOLESTEROL-HDL RATIO, AND DIFFERENTIAL CORTISOL RESULTS
(NON-BLACKS ONLY)

Dependent Variable	P Value
Systolic Blood Pressure	0.195
Diastolic Blood Pressure	0.351
ECG Abnormality	0.999