Table X-12

THREE-FACTOR ANALYSES; HERBICIDE EXPOSURE, SYSTEMIC CANCER, AND X-RAY EXPOSURE AMONG FLYING OFFICERS

X-ray Exposure	Herbicide Exposure	Systemic Cancer Yes	No
Yes	low	1	23
	medium	1	23
	high	0	33
		P = 0.49	
No	low	0	87
	medium	0	104
	high	3	89
		P = 0.04	

* Three-way interaction P value = 0.04

Table X-13

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER, AND INDUSTRIAL CHEMICALS EXPOSURE AMONG ENLISTED GROUND PERSONNEL*

Industrial Exposure	Herbicide Exposure	Skin Cancer Yes	No
Yes	low	0	79
	medium	1	96
	high	3	73
		P = 0.12	
No	low	2	70
	medium	4	78
	high	1	71
		P = 0.45	

* Three-way interaction P value = 0.10

Table X-14

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER, AND DEGREASING CHEMICAL EXPOSURE AMONG ENLISTED FLYING PERSONNEL*

Degreasing Chemical Exposure	Herbicide Exposure	Skin Cancer Yes	Skin Cancer No
Yes	low	3	40
	medium	0	41
	high	0	51
		P = 0.04	
No	low	0	16
	medium	1	17
	high	0	15
		P = 0.42	

* Three-way interaction P value = 0.17

Table X-15

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER AND INSECTICIDE EXPOSURE AMONG ENLISTED FLYING PERSONNEL*

Insecticide Exposure	Herbicide Exposure	Skin Cancer Yes	Skin Cancer No
Yes	low	3	30
	medium	0	36
	high	0	41
		P = 0.03	
No	low	0	26
	medium	1	22
	high	0	25
		P = 0.32	

* Three-way interaction P value = 0.13

While these data show some confounding for exposure to x-ray, insecticides, industrial chemicals and degreasing chemicals, stratified analysis reveals no evidence of a dose-related effect for exposure to the herbicides used by the USAF in the RVN and the occurrence of cancer. The validity of the statistical

testing in the exposure index analyses is compromised by the extremely small numbers of cancers available for analysis. Therefore, any inferences based on these data must be made with caution.

6. Summary

The analysis of these data revealed significantly more skin cancer in the Ranch Hand group than in the subset of original comparisons who completed physical examination. This finding was of borderline significance in all original comparisons and in the total comparison population; however, these data are not fully corrected for exposure to the sun and other skin carcinogens. There were no significant group differences for the occurrence of systemic cancer. A small increase in oropharyngeal cancers and a total absence of digestive cancers were observed in the Ranch Hand group. The exposure index analyses did not demonstrate a dose-response effect for either skin or systemic cancer. Of interest was a borderline significant association between systemic cancer and smoking in both groups, demonstrating the sensitivity of the analyses to the effects of this known carcinogen.

Chapter XI

FERTILITY AND REPRODUCTIVE OUTCOMES

1. Introduction

The potential effects of Herbicide Orange exposure on reproduction, fertility, or the incidence of birth defects are highly emotional issues among Vietnam veterans and have received wide media coverage. Animal fertility studies in various species have shown variations in 2,4-D; 2,4,5-T and TCDD toxicity relative to age, dosage levels and routes of administration. TCDD exposed male mice when mated with unexposed females exhibited no abnormalities in mating behavior, fertility, sperm concentration, sperm motility, survival of offspring, or neonatal development (Lamb, 1980). Conversely, administering Herbicide Orange directly to pregnant mice resulted in three fetal effects: cleft palate, decrease in fetal weight, and fetal mortality (Courtney, 1970). The Australian Birth Defects Study of veterans serving in Vietnam showed no association between birth defects of children from veterans and their Vietnam experience (Case Control Study, Australia 1983). Reports from the Seveso, Italy accident, where 220,000 people were potentially exposed to TCDD in 1976, have shown that the incidence of congenital malformations and abortions in exposed women was below expected values for the region. Of 34 aborted fetuses examined for defects, no fetal malformations were attributed to exposure to TCDD. Additionally, developmental abnormalities in children have not been exhibited (Regianni, 1980). A reproductive study of the wives of DOW Chemical Company workers exposed to 2,4,5-T/TCDD found no differences in fertility patterns, fetal wastage, or birth defects (Townsend and Badner, 1981). In 1979 the Administrator of Environmental Protection Agency declared an emergency suspension of 2,4,5,-T based on the Alsea, Oregon study finding of an increased incidence of spontaneous abortion in 3 Oregon areas sprayed with the herbicides. This study's findings prepared by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, Office of Pesticide Programs, Office of Toxic Substances, and The Environmental Protection Agency remain controversial.

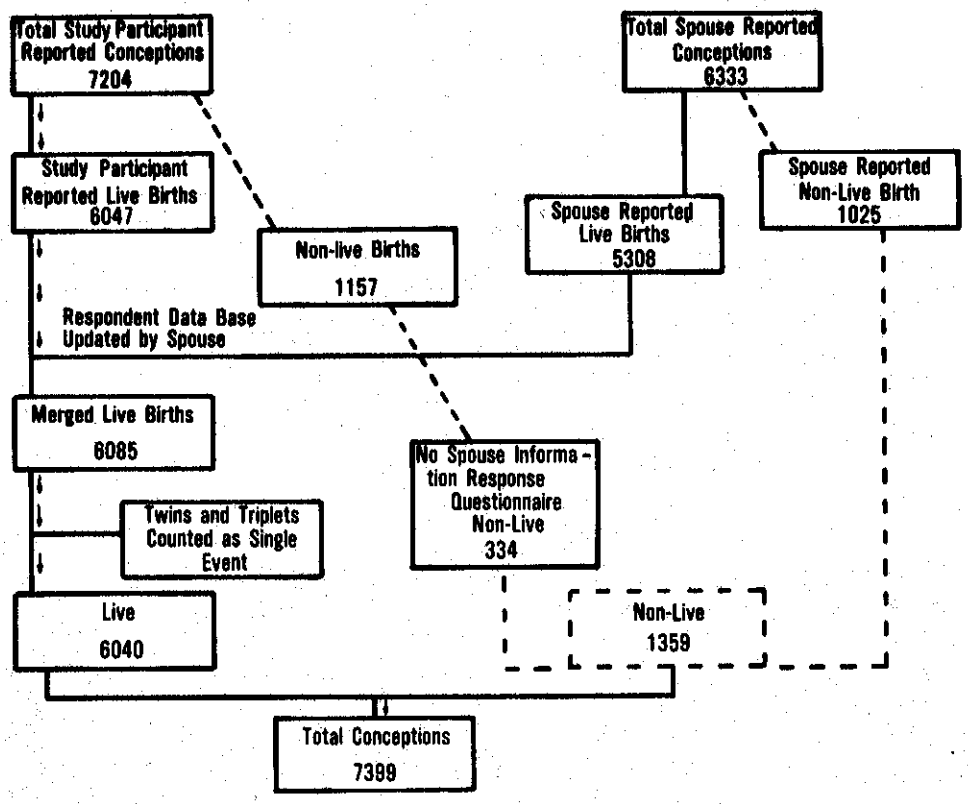
Data concerning fertility and reproductive events in this study were collected during the questionnaire and physical examination. Questions regarding reproduction, fertility/infertility, and offspring history were asked of study participants both in the in-home questionnaire and at the physical examination. In addition to the data collected from male respondents, questionnaires focusing on reproductive history were administered to all available spouses and partners. The data from the reconciliation of subject and spouse questionnaire responses constitute the data base described in this report. This reconciliation was based primarily on spouse data and study participant data only when spouse data was not collected. Analyses for this chapter are based on nonverified subjective questionnaire reporting. Analyses for this chapter are based on nonverified subjective questionnaire reporting. This report also contains data on children with defects and not defects per se. When a child was reported to have multiple birth abnormalities the most serious was analyzed. Sperm counts, and sperm abnormalities from the physical examination are also

analyzed. Verification of reported fertility events is presently ongoing and the analyses presented here are based on interim unverified data. Seven thousand three hundred ninety-nine conceptions are analyzed in this chapter. These represent 3293 Ranch Handers' or their spouses' reported conceptions and 4106 total comparison group or their spouses' reported conceptions. Comparison conceptions include 2669 original and 1437 shifted and replaced comparisons. The Ranch Hand and original comparisons' conceptions were analyzed considering 5 covariates: mother's smoking and drinking during each conception; mother's age; father's age; and the time of conception, i.e, before or after the father's military tour in Southeast Asia. Log-linear models were used to analyze the reproductive events of interest: miscarriages, still births, induced abortions, infant and neonatal deaths, and total numbers of live births. Live births were further analyzed for reported birth defects, learning disabilities and physical handicaps. Analyzed birth defects were those reported within a comprehensive range of ICD codes. Other reported birth defects included a broad range of pediatric conditions perceived by the parents as birth defects. Birth defects meeting ICD definition are further classified as to the severity of the defect. Fertility and reproductive outcomes were not analyzed by race for this report. These data will be presented in subsequent reports.

Questionnaire collection of fertility and reproductive information was linked to reproductive events that occurred while the participant was married, living with a partner, or reported in the questionnaire as other pregnancies. Fertility and reproductive events were keyed to the specific relationship in order to reconcile the information with similar data collected from all available spouses and partners. Figure XI-1 presents an algorithm for the development of the fertility data base.

Figure XI-1

ALGORITHM FOR THE DEVELOPMENT OF FERTILITY /REPRODUCTION DATA BASE



Of the 7204 total respondent reported conceptions shown in Figure XI-I 6047 (84%) were reported as live births and 1157 (16%) were reported as nonlive births. The spouses reported 6333 total conceptions. These are shown in the upper right portion of the figure. Of the total conceptions reported by spouses as attributable to the male respondent, 5308 (84%) were reported as live births and 1025 (16%) were reported as nonlive births. Figure XI-1 shows that the spouse-reported births were matched to the respondent reported live births and 38 children were added to the respondent data base. Six thousand eighty-five live births were thus identified. The first born of multiple births were maintained in the data base and the remaining children were deleted yielding 6040 live births. Three hundred thirty-four nonlive births were added to the nonlive birth study subject file as a result of the match of the male respondent and spouse files. Seven thousand three hundred ninety-nine total conceptions are contained in the merge of the live and nonlive birth files.

The data in Figure XI-1 are based on unverified data. The data in the fertility file has not been fully cleansed of keypunch, editing or other potential sources of errors. The study participant data collection stressed natural children; but, inadvertently, data collection resulted in information on multiple adopted, step and natural children. Additionally, there was no data link between spouse, male respondent and children. Following receipt of data, a USAF computer system was created to define this link, but precise definition of total conceptions, live births and nonlive births must await verification by receipt of birth certificates and medical records. This processing is presently ongoing and will be finalized in future reports. Of the 7399 conceptions analyzed in this report 3293 were reported by Ranch Handers or their spouses and 4106 were reported by the total comparison group or their spouses. Comparison conception included 2669 in the subset of originally selected comparison individuals and 1437 in the group of shifted and replacement comparisons.

2. Fertility/Infertility

Data on the number of conceptions, number of marriages, duration of marital and nonmarital relationships, and the number of couples with the desired number of children were gathered during the in-home questionnaire. Three reproductive indices were derived from these data; the Infertility Index (number of childless marriages per total number of marriages), the Married Fertility Index (number of conceptions per years of marriage) and the Total Fertility Index (number of conceptions per years together). The Total Fertility Index includes time spent in nonmarital relationships. The data on fertility/infertility outcomes are presented in Table XI-1.

Table XI-1

FERTILITY/INFERTILITY OUTCOMES
FOR QUESTIONNAIRE COMPLIANT INDIVIDUALS

Variable	Group RH	Group OC	Group AC	P value; RH versus Originals	P value; RH versus All
Number of participants	1174	956	1531	-	-
Number of Marriages	1456	1167	1860	-	-
Number of conceptions	3292	2668	4106	-	-
Number of participants with conceptions	1043	856	1359	-	-
Mean number of conceptions per participant	2.80	2.79	2.68	-	-
Mean number of marriages	1.24	1.22	1.21	-	-
Number of childless marriages	385	283	448	-	-
Infertility index	0.264	0.243	0.241	0.32	0.23
Number of couples with children, having the desired number of children	708	560	891	0.67	0.73
Married fertility index	0.165	0.155	0.158	>0.25	>0.25
Total fertility index	0.163	0.154	0.157	>0.25	>0.25

RH = Ranch Hand
OC = Original Comparisons
AC = All Comparisons

Although the crude numbers of conceptions and childless marriages differ between the Ranch Hand and comparison groups, the mean number of conceptions per participant and the proportion of marriages without children are not different. The percentages of couples with children who had the desired number of children, are not significantly different.

Two hundred eighty-three of the 1045 Ranch Handers (27.1%) and 211 of the 733 originally selected comparisons (27.3%) attending the physical examination had vasectomies (P = 0.92). Seven hundred fifty-eight of the Ranch Handers (72.5%) and 561 of the comparisons (76.5%) submitted semen specimens. Of those participants willing and able to provide semen specimens, 186 Ranch

Handers and 140 comparisons had vasectomies and/or orchiectomies (N = 6) and were therefore excluded from the statistical analysis of sperm counts. Six of these participants with a history of vasectomy were found to have sperm in their specimen and they were informed of these findings.

The semen specimens from the remaining 993 participants were analyzed by general linear model techniques, using continuous variables of sperm count and the percentage of each participant's sperm which had abnormal morphology. The means, standard deviations and median values for the sperm counts and percent of sperm with abnormal morphology are displayed in Table XI-2. These analyses were adjusted for age and exposure to industrial chemicals, and revealed no significant group differences in sperm counts (adjusted P = 0.77), or in the percentage of abnormal sperm morphology (adjusted P = 0.71). Twenty-seven Ranch Handers and 19 comparisons had abnormal sperm morphology out of 560 and 409 analyzed specimens, respectively. Unprotected exposure to industrial chemicals (ever, never) had no significant effect in these analyses. However, age had a significant effect on sperm count (P = 0.0001), with sperm count increasing with age. The relevance of this observation is unclear since the counts may be biased somewhat by the differential compliance observed with increasing age. Compliance differed significantly with age (P < 0.001) but not by group (P = 0.78). This in sperm count increase was the same in both the Ranch Hand and comparison groups, with a slope of 1.69 in the Ranch Hand/original analysis, and 1.85 in the Ranch Hand/all analysis. These slopes were significantly different from zero (P = 0.0001). There was no significant assooiation between age and abnormal sperm morphology (adjusted P = 0.57). The distribution of sperm counts in the two groups is presented in Figure XI-2, and the distribution of abnormal sperm morphology percentage is displayed in Figure XI-3. The patterns of compliance to semen specimen collection is shown in Figure XI-4.

Table XI-2

DESCRIPTIVE STATISTICS OF SPERM VARIABLES BY GROUP

	Mean	Standard Deviation	Median	P value
Count (in million/ml)				
Original Comparisons	111.864	108.833	80	0.77
Ranch Hand	111.469	102.782	86	
All Comparisons	111.025	108.475	78	0.99
Percent Abnormal Sperm				
Original Comparisons	9.614	5.182	9	0.71
Ranch Hand	9.705	5.525	9	
All Comparisons	9.643	5.946	8	0.79

Figure XI-2

DISTRIBUTION OF SPERM COUNTS BY GROUP

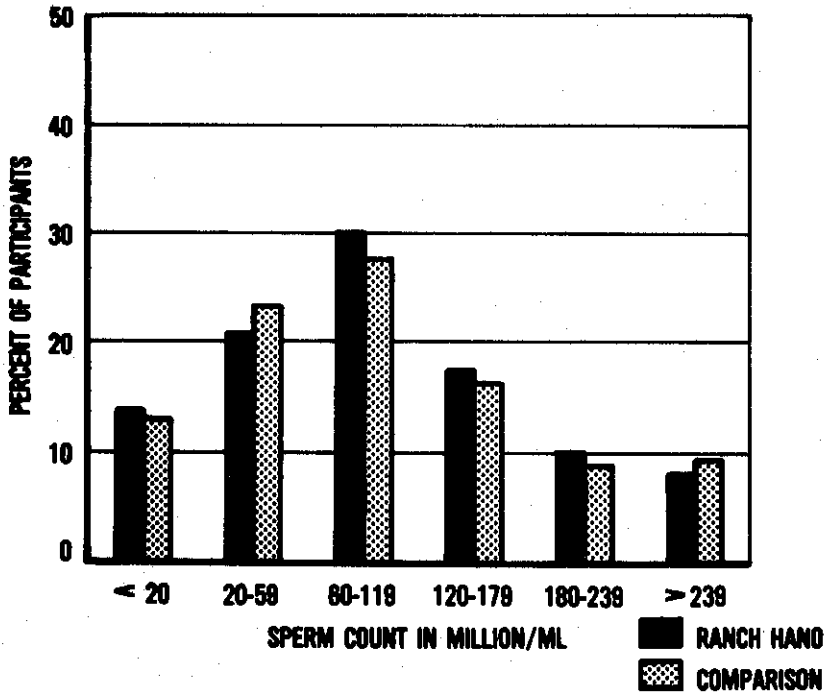


Figure XI-3

DISTRIBUTION OF ABNORMAL SPERM BY GROUP

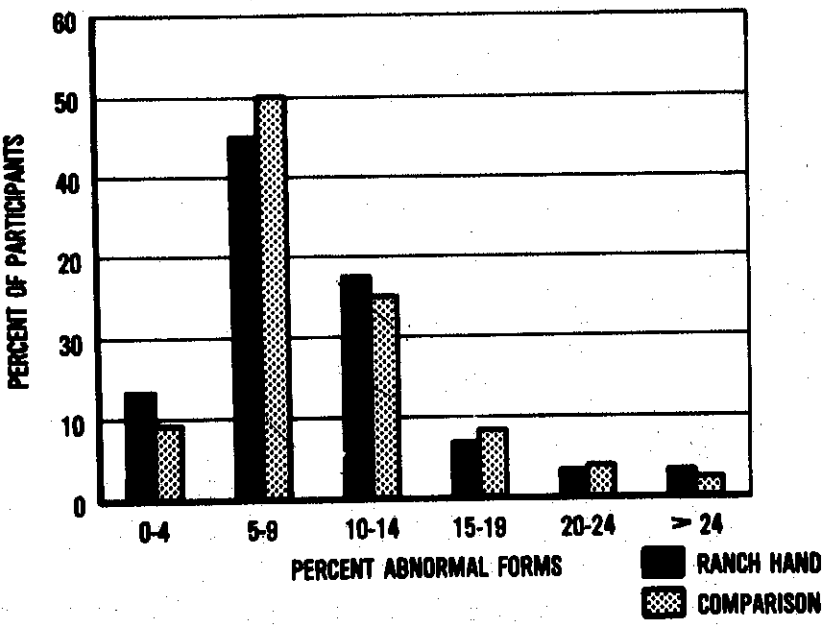
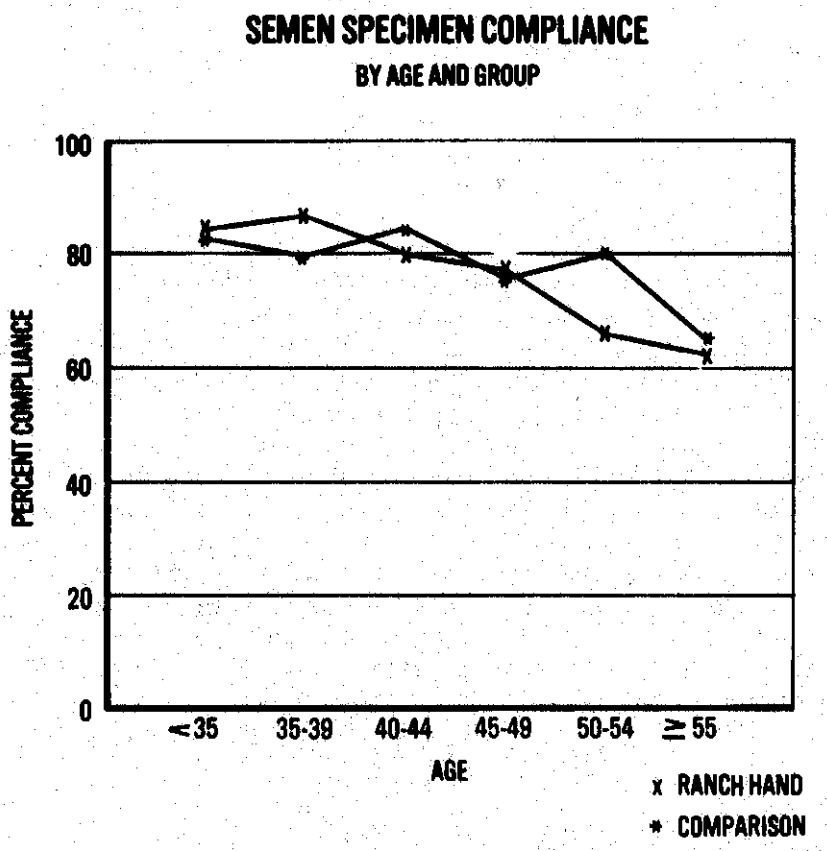


Figure XI-4



3. Conception Outcomes

In the evaluation of the outcomes of pregnancies fathered by study participants, analyses were conducted on all reported pregnancies in which the date of conception was known, and repeated on a subset of those in which information on maternal age, maternal smoking, and drinking habits was available from spouse questionnaires (complete data subset). There were an additional 95 conceptions in which data were too incomplete for analysis, and thus were deleted from the data base.

There is no difference in the pattern of missing data between the two groups, as shown in Table XI-3.

Table XI-3

COMPLETENESS OF CONCEPTION INFORMATION

Group	Complete Data	Partial Data	Incomplete Data	P Values
Original Comparisons	2278 (85.4%)	348 (13.0%)	42 (1.6%)	0.59
Ranch Hand	2781 (84.5%)	459 (13.9%)	53 (1.6%)	
All Comparisons	3435 (83.7%)	599 (14.6%)	72 (1.8%)	0.64

The occurrence of miscarriage was determined for each conception in which a date was reported. Similarly, outcomes of induced abortion, stillbirth and live birth were also determined. Adjustments for maternal factors of age (< 35, ≥ 35), smoking (yes, no) and alcohol use (yes, no) and paternal age (< 35, ≥ 35) could not be performed on these pregnancies with partial data, and no analysis was possible on those with incomplete data. In the covariate adjusted analyses, the primary statistical relationship of interest is the complex relationship between group outcome and time. Use of the pre-SEA conception experiences allows the Ranch Hand pre-SEA conceptions to serve as a standard for comparison with post-SEA conceptions. This is of special importance since 63.2% of the Ranch Hand and 63.6% of the comparison conceptions were pre-SEA events. Table XI-4 presents the data and the results of the analysis of these outcomes. Similar analyses using data from the entire comparison group are presented in Appendix X. The results of these additional analyses were essentially the same as those in Table XI-4.

Table XI-4

ANALYSES OF CONCEPTION OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS); RANCH HANDERS VERSUS ORIGINAL COMPARISON

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	295	(14.4)	1754	190	(15.9)	1001
Comparison (0)	205	(12.3)	1467	130	(13.6)	825
	P = 0.06			P = 0.13		
Stillbirth						
Ranch Hand	13	(0.6)	2036	16	(1.3)	1175
Comparison (0)	13	(0.8)	1659	8	(0.8)	947
	P = 0.60			P = 0.27		
Induced Abortion						
Ranch Hand	13	(0.6)	2036	62	(5.2)	1129
Comparison (0)	14	(0.8)	1658	65	(6.8)	890
	P = 0.47			P = 0.12		
Live Birth						
Ranch Hand	1723	(84.1)	326	917	(77.0)	274
Comparison (0)	1435	(85.8)	237	744	(77.9)	211
	P = 0.15			P = 0.62		

These data demonstrate a borderline significant group difference in miscarriage (P = 0.06) prior to Southeast Asia duty and a suggestion of a difference (P = 0.13) post-SEA. However, inferences based on these analyses, unadjusted for key factors affecting pregnancy outcome, are of questionable value. Therefore, those conceptions in which full covariate information was known, were analyzed in greater detail.

The data reflecting outcomes for both pre- and post-SEA conceptions are shown in Table XI-5, and the results of the adjusted analyses are displayed in Table XI-6.

Table XI-5

CONCEPTION OUTCOMES (COMPLETE DATA SUBSET)
BY GROUP MEMBERSHIP AND TIME;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	239	(13.7)	1505	156	(15.0)	883
Comparison	172	(11.9)	1276	104	(12.5)	726
	P = 0.13			P = 0.12		
Stillbirth						
Ranch Hand	9	(0.5)	1735	12	(1.2)	1027
Comparison	8	(0.6)	1440	8	(1.0)	822
	P = 0.89			P = 0.69		
Induced Abortion						
Ranch Hand	8	(0.5)	1736	37	(3.6)	1002
Comparison	7	(0.5)	1441	33	(4.0)	797
	P = 0.92			P = 0.61		
Live Birth						
Ranch Hand	1487	(85.3)	257	833	(80.2)	206
Comparison	1258	(86.9)	190	682	(82.2)	148
	P = 0.19			P = 0.27		

Table XI-6

RESULTS OF THE ANALYSIS OF CONCEPTION OUTCOMES;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Relationship	P value
Miscarriage by Group by Pre/Post-SEA	0.76
Stillbirth by Group by Pre/Post-SEA	1.00
Induced Abortion by Group by Pre/Post-SEA	0.89
Live Birth by Group by Pre/Post-SEA	0.94

Although a group difference of 15% versus 12.5% in post-SEA miscarriage is observed ($P = 0.12$), both groups had similar post-SEA conception outcomes relative to their own pre-SEA baseline experiences ($P = 0.76$). Ranch Hand miscarriages increased from 13.7% pre-SEA to 15.0% post-SEA while comparison miscarriages increased from 11.9% to 12.5%. Thus, while more Ranch Hand conceptions resulted in miscarriages than the comparisons, they started from a higher level before their herbicide exposures occurred, and in the overall analyses, there was no significant difference. These rates of miscarriage are comparable to estimates of 10-20% for the general US population (Last, 1980). The rate of stillbirths in the US population is 0.98%, again comparable to the observed rates in this study. Similar analyses were conducted using data from all comparison individuals, and the results of these procedures were similar to those presented in Table XI-6. The data and analytic results of these additional analyses are shown in Appendix X.

The effect of increasing maternal age was evident in all of these measures, with highly significant increases in miscarriage and induced abortion and decreases in live births associated with increasing age ($P \leq 0.01$). The increase in induced abortions in both groups is unexplained, but is most likely the result of the altered legal status of induced abortion and its increased social acceptance.

Exposure index analyses were performed in each of the three occupational categories (Officers; Enlisted, Flying; and Enlisted, Ground). The degree of exposure in each of these categories was stratified as low, medium or high (see Chapter VIII). Since the stratification by occupational category and exposure level and patterns of missing covariate data resulted in smaller groups, analyses had to be conducted using each covariate separately. A single analysis using all covariates would have resulted in unacceptably small cell sizes for meaningful analysis. The number of conception outcomes by occupational category available for each covariate analysis are presented in Table XI-7, and results of each covariate analysis are shown in Table XI-8.

Table XI-7

NUMBER AND RESULT OF CONCEPTION OUTCOMES FOR EACH COVARIATE ANALYSIS BY OCCUPATIONAL CATEGORY

Parameter	Covariable	Category: Officers Yes	Officers No	Enlisted Flying Yes	Enlisted Flying No	Enlisted Ground Yes	Enlisted Ground No
Miscarriage	Maternal Smoking	34	225	19	100	102	542
	Maternal Alcohol	34	225	19	100	102	542
	Maternal Age	44	241	22	119	122	608
	Paternal Age	44	250	22	119	122	617
Stillbirth	Maternal Smoking	2	257	2	117	7	637
	Maternal Alcohol	2	257	2	117	7	637
	Maternal Age	3	282	2	139	8	722
	Paternal Age	4	290	2	139	9	730
Induced Abortion	Maternal Smoking	17	242	6	113	14	630
	Maternal Alcohol	17	242	6	113	14	630
	Maternal Age	18	267	9	132	23	707
	Paternal Age	24	270	9	132	29	710
Live Birth	Maternal Smoking	205	54	92	27	521	123
	Maternal Alcohol	205	54	92	27	521	123
	Maternal Age	219	66	108	33	576	154
	Paternal Age	219	75	108	33	576	163

Table XI-8

RESULTS OF THE CONCEPTION/EXPOSURE INDEX ANALYSES

Parameter	Occupational Category	Outcome/Exposure P Value, Adjusted for: Maternal Smoking	Maternal Alcohol	Maternal Age	Paternal Age
Miscarriage	Officers	0.04	0.04	0.07	0.06
	Enlisted, Flying	0.30	0.26	0.19*	0.20
	Enlisted, Ground	0.54	0.50	0.62	0.51
Stillbirth	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-
Induced Abortion	Officers	0.12	0.12	0.04*	<0.01*
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	0.25	0.25	0.48	0.43*
Live Birth	Officers	0.27	0.24	0.57*	0.59*
	Enlisted, Flying	0.60	0.55*	0.37*	0.45
	Enlisted, Ground	0.24	0.23	0.29	0.43

* Three-way covariate interaction is present.
- Data too sparse for valid statistical analysis

The only statistically significant findings observed are for miscarriage and for induced abortion among officers. Consistent patterns of increasing adverse outcomes of pregnancy with increasing herbicide exposure are not evident for other outcomes. In all four covariable analyses in the officer group, there was a significant association between miscarriage and exposure level (low, medium and high).

4. Live Birth Outcomes

Those conceptions resulting in a live birth were further analyzed to determine the frequency of adverse events in those infants and children. As in the assessment of conceptions, unadjusted analyses were conducted on all reported live births in which a date of conception was known or could be estimated from the known date of birth. Analyses were repeated on those live births for which information on maternal age, maternal smoking, and maternal use of alcohol were available. Table XI-9 presents the distribution of live births within the subsets with complete and partial data. The difference in the proportion of the groups with only partial data are not statistically significant. Those births with inadequate data are omitted.

Table XI-9

COMPLETENESS OF LIVE BIRTH DATA

	Complete Data	Partial Data	Total	P Values
Original Comparisons	1940 (89.0%)	239 (11.0%)	2179	0.21
Ranch Hand	2320 (87.8%)	320 (12.2%)	2640	
All Comparisons	2922 (87.2%)	429 (12.8%)	3351	0.43

Based on in-home questionnaire responses and respondent definitions of gestational age, there were no differences in the occurrence of prematurity, and postmaturity in the Ranch Hand and comparisons groups (P=0.85). Further analyses of the incidence of prematurity based on objective criteria of birth weight will be conducted after birth certificate verification.

Information concerning learning disabilities, physical handicaps, birth defects and the occurrence of neonatal and infant death was collected for each live birth. The information was obtained as a "yes" response primarily from the spouse questionnaire. Study subject responses were used when spouse data were unavailable. Data collection questions included: "Did (child) have any birth defects?"; "Does/Did (child) have a diagnosed learning disability?"; and "Does/Did (child) have any physical, mental, or motor impairments?" Yes responses to all 3 questions had been coded by the USAF from the ICD-9-CM based on the mother's or father's statement concerning the kind of birth defect, learning disability or physical, mental or motor impairment. For each defect reported for each child, the interviewer had the opportunity to document 3 statements within the question regarding the kind of birth or developmental problem. Therefore, each yes response had in some cases 3 ICD-9-CM codes. A computer program was written to select defined birth defects, learning disabilities and physical, mental and motor impairments. For the child with multiple reported birth defects, he/she was counted only once for analysis. For children with multiple reported birth defects the most serious condition was analyzed. This report contains data on children with reported defects and not all reported defects; analyses of total reported defects will occur in a future report. A thorough review of the birth defect codes including key punch and code verification was accomplished prior to analysis of the merged data file. This review was not accomplished for reported learning disabilities or physical, mental and motor impairments, neonatal or infant death. The comprehensive definition of those reported defects within the definition for this report are presented in Appendix V. Reported birth defects not within the acceptable definition are presented in Appendix XIX.

Counts of the total-reported and within-definition birth defects are presented in Table XI-10. Fifty-nine percent of the Ranch Hand and 64% of the total comparison reported defects were within the acceptable defined range of birth defect.

Table XI-10

COUNT AND PERCENT OF TOTAL REPORTED
WITHIN-DEFINITION BIRTH DEFECTS

	Total Reported	Within Definition	P Values
Original Comparison	218	137 (63%)	0.37
Ranch Hand	292	172 (59%)	
All Comparisons	334	212 (64%)	0.24

The 5-6% difference in the perception of conditions which constitute a birth defect is not statistically significant. However, differential reporting of birth defects is of concern because media attention to hypothesized effects from exposure to the herbicide may affect parental reporting. In addition literature suggests the possibility that parents could perceive post-SEA births as "vulnerable" children (McCormick, 1982). Because of the above factors, all reported defects within range were categorized as severe, moderate, and limited (those of minor medical consequence) birth defects. This approach is based on a recent study (Christianson, 1981) which demonstrated that the incidence of reported congenital anomalies increased as children aged. Living children with reported defect average 23 years of age at the present time, with an age range of 2 through 39 years, and therefore, many years of parental observation have elapsed. The definition used for the collapsing of data into this system are as follows:

Severe: Conditions which are life threatening or produce severe handicaps (e.g., physical, mental, motor).

Moderate: Conditions which are not life threatening and handicaps which with medical care will not interfere with the individual's overall health or socio-economic progress.

Limited: All conditions which without medical care would not interfere with the individual's health or socio-economic progress. Those reported birth defects without type of defect data were included in the limited category.

Responses to birth defects which were unclear, incomplete or could be classified into more than one category were classified in the highest category applicable to the condition.

Table XI-11 summarizes the reported birth defects categorized by level of severity system.

Table XI-11

SUMMARY OF CHILDREN REPORTED WITH BIRTH DEFECTS BY LEVEL OF SEVERITY (SEVERE, MODERATE, LIMITED) RANCH HAND AND COMPARISON, PRE AND POST SEA TOUR

Nature of Reported Defect	Ranch Hand Counts	Ranch Hand %	Original Comparisons Counts	Original Comparisons %	Total Comparisons Counts	Total Comparisons %
			PRE-SEA			
Severe	51	56.5	50	57	62	51
Moderate	32	35.5	27	31	40	33
Limited	7	8	10	12	20	16
TOTAL	90	100	87	100	122	100
			POST-SEA			
Severe	32	40	18	37.5	34	40
Moderate	22	27.5	20	41.5	34	40
Limited	26	32.5	10	21	18	20
TOTAL	80	100	48	100	86	100
			TOTAL (PRE AND POST-SEA)			
Severe	83	49	68	50	96	46
Moderate	54	32	47	35	74	36
Limited	33	19	20	15	38	18
TOTAL	170	100	135	100	208	100

This table shows that overall, 19% of the Ranch Hand, 15% of the original and 18% of the total comparison group reported birth defects were classified as "limited." Ranch Handers reported 8% limited pre-SEA and 32.5% post-SEA. Original comparisons reported 12% pre-SEA and 21% post-SEA and total comparisons reported 16% and 20%, respectively. These observations will be analyzed more fully in subsequent reports.

Table XI-12 presents the analysis of the live birth outcomes for the partial and complete data subsets unadjusted for maternal factors of smoking, age and alcohol use.

Table XI-12

ANALYSES OF LIVE BIRTH OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS); RANCH HANDERS VERSUS ORIGINAL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Learning Disability						
Ranch Hand	61	(3.5)	1662	77	(8.4)	840
Comparison	62	(4.3)	1373	51	(6.9)	693
	P = 0.26			P = 0.24		
Physical Handicaps						
Ranch Hand	144	(8.3)	1579	132	(14.4)	785
Comparison	112	(7.4)	1323	85	(11.4)	659
	P = 0.57			P = 0.07		
Infant Death						
Ranch Hand	8	(0.5)	1715	4	(0.4)	913
Comparison	3	(0.2)	1432	3	(0.4)	741
	P = 0.23			P = 0.92		
Birth Defects						
Ranch Hand	90	(5.2)	1633	80	(8.7)	837
Comparison	87	(6.1)	1348	48	(6.5)	696
	P = 0.31			P = 0.08		
Neonatal Death						
Ranch Hand	25	(1.5)	1698	14	(1.5)	903
Comparison	17	(1.2)	1418	3	(0.4)	741
	P = 0.51			P = 0.02		

Live birth outcomes were not statistically different in the 2 groups prior to the participants tour of military duty in SEA. However, 3 of the 5 measures of outcomes after SEA duty demonstrated borderline or statistically significant differences between the Ranch Hand and comparison groups. The significant findings in neonatal deaths (P = 0.02), and the borderline significant

finding for birth defects (P = 0.08) and physical handicaps (P = 0.07) were not adjusted for the effects of key covariables. Therefore, the data from those live births with full covariate information (complete data subset) concerning the maternal covariables were analyzed. Table XI-13 displays the pre-SEA and post-SEA data from this subset of births.

Table XI-13

LIVE BIRTH OUTCOMES (COMPLETE DATA SUBSET);
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Parameter	Group	Pre-SEA			Post-SEA		
		Yes	(%)	No	Yes	(%)	No
Learning Disability	RH	57	(3.8)	1430	75	(9.0)	758
	Comp	57	(4.5)	1201	47	(6.9)	635
Physical Handicap	RH	134	(9.0)	1353	126	(15.1)	707
	Comp	103	(8.2)	1155	77	(11.3)	605
Infant Death	RH	7	(0.5)	1480	3	(0.4)	830
	Comp	2	(0.2)	1256	1	(0.1)	681
Birth Defects*	RH	78	(5.2)	1409	76	(9.1)	757
	Comp	80	(6.4)	1178	44	(6.5)	638
Neonatal Death	RH	20	(1.3)	1467	14	(1.7)	819
	Comp	17	(1.4)	1241	3	(0.4)	679

*Analysis includes 2 Ranch Hand birth defects which were double counted.

Log-linear analyses, simultaneously considering all covariates (maternal age, maternal smoking, and maternal alcohol use, and paternal age) were accomplished. Table XI-14 confirmed the differences in birth defects initially seen in the unadjusted analyses of post-SEA live births. This finding was statistically significant (P = 0.04) after adjusted analysis. Suggestive associations were noted in learning disabilities (P = 0.19) and in neonatal deaths (P = 0.20). Incidence rates of neonatal death and infant death in the general US population are estimated to be 0.99% and 1.4%, respectively (Last, 1980). The incidence rate of major birth defects in the general population is estimated to be 3-5%, but varies, depending upon the criteria used to define the "defects."

Table XI-14

RESULTS OF THE ANALYSIS OF LIVE BIRTH OUTCOMES;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Relationship	P Value
Learning Disability by Group by Pre/Post SEA	0.19
Physical Handicap by Group by Pre/Post SEA	0.45
Infant Death by Group by Pre/Post SEA	0.81
Birth Defects by Group by Pre/Post SEA	0.04
Neonatal Death by Group by Pre/Post SEA	0.20

The distribution of reported post-SEA birth defects is presented in Table XI-15. This table clarifies the reported birth anomalies by level of medical consequence. Twelve congenital anomalies of the skin (ICD code 757) are present in the Ranch Hand data. This category of skin anomalies is quite broad, and includes simple birth marks, pigmentary changes, and more serious conditions. Reanalysis of the data concerning birth defects among live births in which full covariate data were available was aocomplished with skin anomalies deleted. The birth anomalies included in the ICD category 757 are generally of minor medical consequences and their removal from analysis can be expected to provide a clearer understanding of group differences in birth defects of major health significance. This analysis revealed no significant group difference between Ranch Hand and comparison group live births for the remaining nonskin birth anomalies ($P = 0.14$). However, this weak association is still of interest. All reported birth defects are presently being validated by medical record reviews. Significant associations were noted ($P < 0.05$) between maternal smoking during pregnancy and learning disabilities, physical handicaps, infant deaths and birth defects. Maternal alcohol use during pregnancy was also associated with physical handicaps ($P < 0.001$). Future analyses of the birth defect data will also make use of the severity level classification. Live birth analyses using data from all of the comparisons were also conducted, and are contained in Appendix X. These analyses identified significant group differences in physical handicaps, birth defects and neonatal deaths. However, the influences of increased sample size and potential replacement group bias (differential reporting) have not been taken into consideration in these analyses.

Table XI-15

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	M	L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	M	L
228	1			Blood tumor on nose		1	
				Hemagioma on left portion of head and face			
5240				Micrognathia	1*		
5531				Umbilical hernia		1	
741	1*			Spina bifida			
	1*			Open spine (severe case of Spina bifida)			
742	1*			Spinal cord and brain not connected			
	1*			Brain damage			
743			1	Slightly, eye coordination			
744	1			Deaf in left ear (nerve under-developed)			
				Malformed ear		1	
		2		Bump on ear			
		1		Missing small part of right earlobe			
745	1			Septal defects	2		
	1*			Double outlet right ventricle			
				Heart murmur	1		
	1			Foramen ovale was not totally closed			
746	1			A congenital heart			
	1			Heart valve			
	1			Heart SV node, two nodes in heart			
				Heart condition		1	
	1			Blue baby	1		
747	3			Patent ductus			
			1	Varicose vein in right groin			
748	2*			Underdeveloped lungs, Premature			
			1	Spot on lung			

Table XI-15 (Cont)

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	M	L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	M	L
749	2			Cleft lip	2		
	1			Cleft palate			
750				Pyloric stenosis	1		
				Skin growing across his esophagus	1		
		1		Large bubble or abscess on throat			
	1			TE fistula			
			4	Tongue tied			
751	1*			Couldn't eat her food			
752				Undescended testicle		3	
		1		Hypospadia			
		1		Opening for urinating lower than normal			
				Vagina fused, had operation		1	
753	1			Defective kidney			
	1			Malformation of right kidney			
		1		Infantile polycystic kidney disease			
754				Talipes	2		
				Club foot	2		
				Dislocated hips		3	
				Leg bowed in at birth required cast and then braces		1	
		1		Chest cavity deformity			
				Ankle bones deformed		2	
			5	Foot turned in			
				Toes turned in			1
755				Left hand had no fingers, has thumb	1		
				Crooked femur bone	1		
	1			Possible hip or feet or both developed later			
				Deformed feet		2	
		1		Two toes joined together			
				Hip and foot defect, wore a brace		1	
		1		Extra finger and toe			

Table XI-15 (Cont)

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	M	L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	M	L
		1		Leg turned in, wore a cast for 3 months			
		1		Bones from knees to ankles grew inward			
			1	Webbed finger on hand			
				Delta phalanges of index fingers			1
			3	Crooked foot or legs			
			1	Leg problem, knees hurt as infant			
756	1			Unusually tiny head			
	1			Premature fusion of sagittal sutures			
				Skull slightly deformed		1	
		1		Bone deformity			
				Small neck muscles from being in breach position		1	
			1	Feet curved in at birth			
757				Ichthyosis	1		
		1		No finger or toe nails			
		2		Skin pigmentation			
			1	Skin discoloration			
			1	Yellow color, disappeared in a week			
			5	Birthmarks			1
			1	Two nipples on breast			
			1	Skin tags			1
758	2			Down's Syndrome	3		
TOTAL	30	18	26 = 74		19	19	6 = 44

*Child deceased.

Table XI-15 relates the ICD codes to the level of severity to the reported statement of the spouse or study participant. Of the 74 post-RVN Ranch Hand reported birth defects, 30 are of a severe and 18 of a moderate level of severity. Counts of reported birth defects pre-RVN and post-RNV by occupational category are presented in Table XI-16. Inspection of this table shows that the increase in reported birth defects post-RVN are predominately from personnel in

the Ranch Hand and total comparison enlisted ground occupational category. However, these data have not yet been adjusted by the number of live births in each occupational category.

Table XI-16

COUNTS OF REPORTED BIRTH DEFECTS PRE- AND POST-SEA BY OCCUPATIONAL CATEGORY (OFFICER, ENLISTED-FLYING, ENLISTED-GROUND)

Occupational Category	Ranch Hand		Original Comparisons		Total Comparisons	
	Pre-SEA Counts	Post-SEA Counts	Pre-SEA Counts	Post-SEA Counts	Pre-SEA Counts	Post-SEA Counts
Officer	44	15	40	16	52	22
Enlisted - Flying	13	12	15	5	21	10
Enlisted - Ground	21	49	25	23	40	45
TOTAL	78	76	80	44	113	77

Exposure analyses were performed using the covariates of maternal age, maternal smoking, maternal alcohol use, and paternal age. Each covariable was analyzed separately. The number and result of live birth outcomes by occupational category available for each covariate analysis are presented in Table XI-17 and the results of each covariate analysis are shown in Table XI-18.

Table XI-17

NUMBER AND RESULT OF LIVE BIRTH OUTCOMES FOR EACH COVARIATE ANALYSIS BY OCCUPATIONAL CATEGORY

Parameter	Covariable	Category: Officers Yes	Officers No	Enlisted Flying Yes	Enlisted Flying No	Enlisted Ground Yes	Enlisted Ground No
Learning Disability	Maternal Smoking	15	190	8	84	52	469
	Maternal Alcohol	15	190	8	84	52	469
	Maternal Age	16	203	8	100	53	523
	Paternal Age	16	203	8	100	53	523
Physical Handicap	Maternal Smoking	26	179	12	80	81	440
	Maternal Alcohol	26	179	12	80	81	440
	Maternal Age	26	193	13	95	86	490
	Paternal Age	26	193	13	95	86	490
Infant Death	Maternal Smoking	1	204	1	91	2	519
	Maternal Alcohol	1	204	1	91	2	519
	Maternal Age	1	218	1	107	3	573
	Paternal Age	1	218	1	107	3	573
Birth Defects	Maternal Smoking	12	193	11	81	50	471
	Maternal Alcohol	12	193	11	81	50	471
	Maternal Age	12	207	12	96	53	523
	Paternal Age	12	207	12	96	53	523
Neonatal Death	Maternal Smoking	3	202	4	88	6	515
	Maternal Alcohol	3	202	4	88	6	515
	Maternal Age	3	216	4	104	6	570
	Paternal Age	3	216	4	104	6	570

Table XI-18

RESULTS OF THE LIVE BIRTH/EXPOSURE INDEX ANALYSES

Parameter	Occupational Category	Outcome/Exposure P Value, Adjusted for: Maternal Smoking	Maternal Alcohol	Maternal Age	Paternal Age
Learning Disability	Officers	0.47	0.46	0.31	0.34
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	0.92	0.94	0.89	0.85
Physical Handicap	Officers	0.07	0.07	0.06	0.05
	Enlisted, Flying	0.89	0.69	0.47	0.56
	Enlisted, Ground	0.78	0.79*	0.76*	0.79
Infant Death	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-
Birth Defects	Officers	0.02	0.02	0.02	0.02
	Enlisted, Flying	0.03	0.06	0.03	0.03
	Enlisted, Ground	0.39	0.35	0.46	0.41
Neonatal Death	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-

- Data too sparse for valid statistical analysis.
* Significant three-factor interaction is present.

These results demonstrate consistency across all covariates for each of the live birth outcomes; however, as noted in Table XI-18, the data are sparse in many instances, espeoially for officer and enlisted flying personnel. Birth defects are found to have a statistically significant association with herbicide exposure level in the officer and enlisted flying groups. However, there is not a consistent increase in defects with increasing exposure in the officer category. In the enlisted flying group the adverse outcome did increase consistently with increasing exposure. The pattern in the officer group demonstrated a two-fold rise in the medium level but the highest exposure group had the lowest proportion of children with defects (1.2%). Physical handicaps in children of officers demonstrated borderline significance.

5. Summary

A summary of the findings of the fertility and reproductive analyses are displayed in Table XI-19.

Table XI-19

SUMMARY OF FERTILITY AND REPRODUCTIVE ANALYSES

	P Values						
					Exposure Analyses by Occupational Group		
	Unadjusted		Adjusted				
Parameter	O	A	O	A	Officers	Enlisted Flying	Enlisted Ground
Infertility	NS	NS					
Sperm Count			NS	NS			
Sperm Abnormality			NS	NS			
Conception Outcomes							
Miscarriage	0.13	0.15	NS	NS	0.04	0.19	NS
Stillbirth	NS	0.10	NS	NS			
Induced Abortion	0.12	NS	NS	NS	0.12		NS
Live Birth	NS	NS	NS	NS	NS	NS	NS
Live Birth Outcomes							
Prematurity	NS						
Learning Disability	NS	0.05	0.19	0.12	NS		NS
Physical Handicap	0.07	<0.01	NS	0.02	0.05	NS	NS
Infant Death	NS	NS	NS	NS			
Birth Defects	0.08	0.04	0.04	0.02	0.02	0.03	NS
Defects Excluding Skin Anomalies			0.14	0.07			
Neonatal Death	0.02	<0.01	0.20	0.03			

NS = Nonsignificant
O = Original Comparisons
A = All Comparisons

The analyses in this chapter did not reveal any significant differences in fertility/infertility and sperm counts between the Ranch Hand and either comparison group. Conception outcomes of miscarriage, stillbirth, induced abortion and live births also were not found to differ significantly. Analyses unadjusted for known risk factors of pre-SEA conception history, maternal age, maternal smoking, and maternal alcohol use, and paternal age revealed a suggestive association for increases in miscarriage after the father's SEA service in the Ranch Hand group. However, this association and a borderline increase in post-SEA induced abortion in the original comparison group were not evident after consideration of these other risk factors. Analyses of these conception outcomes with the herbicide exposure index also did not reveal any evidence of herbicide effects. A statistically significant association between increasing herbicide exposure and miscarriage was identified in the officer group but this

effect was not observed in the other occupational categories. Borderline significance was noted in officers for stillbirth and induced abortion, but these findings did not increase in occurrence with increasing exposure.

Significant differences were reflected in the analyses of live birth outcomes. These differences were observed for birth defects after the analyses were adjusted for parental covariates. There appeared to be a clustering of birth anomalies of the skin in children of the Ranch Handers. There were no significant group differences for other birth defects, but a suggestive association remained ($P = 0.14$) after reanalysis with the skin anomalies excluded. Suggestive group differences between the Ranch Handers and original comparisons were also observed after adjusted analysis for learning disability and neonatal death. Exposure analysis identified several findings of statistical and borderline significance; however, the patterns were not consistent across occupational strata. Overall, birth defects demonstrated statistical significance in the adjusted intergroup analysis, and 2 of the 3 occupational group exposure analyses.

A larger number of live birth outcome differences were observed in analyses comparing the Ranch Handers to the total comparison group; however, it is unclear whether these differences are true group differences, or are due to changes in sample size or replacement bias (differential reporting). The value of these analyses in making inferences is therefore limited at this time.

The findings in this chapter do require further evaluation of the possible link between herbicide/dioxin exposure and birth defects. The analyses have relied heavily on unverified spouse reports, and the effect of differential reporting of conception and birth outcomes in pregnancies and in children who the parent might perceive as "special" or "vulnerable" has not been evaluated. This evaluation will be conducted using birth certificates and medical records so that an analysis of verified fertility/reproductive data can be included in the report of the first follow-up physical examination.

Chapter XII

NEUROLOGICAL ASSESSMENT

1. Introduction

Neurological abnormalities have long been recognized as acute toxic effects following the exposure of humans to phenoxy herbicides and dioxin (Goldstein, 1959; Wallis, 1970; Berkley, 1963; Boeri, 1978). Signs and symptoms, such as hyporeflexia, a decrease in nerve conduction velocity, general muscular weakness and decreased sensation in the extremities have been noted. One study documented demyelination as a result of 2,4-D exposure (Dudley, 1972). While these effects have only been demonstrated acutely following heavy exposures, complaints of peripheral neuropathy are prominent among Vietnam veterans who have participated in the Veterans Administration Agent Orange Registry Program. Twelve percent of the 110,000 patients in the Registry had complaints compatible with symptoms of peripheral neuropathy. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans were primary factors in the decision to place a major emphasis on the neurological evaluation of participants in this study.

During the administration of the questionnaire, each subject was asked to provide information on any major health conditions he may have experienced. All reported neurological conditions were coded using the ICD-9-CM and group analysis of the distribution of the conditions was performed. As revealed in Table XII-1, there were no statistically significant differences in reported neurological diseases between the Ranch Hand and comparison groups.

Table XII-1

DISTRIBUTION OF REPORTED NEUROLOGICAL DISEASES BY GROUP MEMBERSHIP

Disease Category	Original Comparisons	Ranch Hand	All Comparisons
Inflammatory Diseases	2	3	3
Hereditary and Degenerative Diseases	2	1	3
Peripheral Disorders	7	7	11
Disorders of the Eye	15	14	21
Disorders of the Ear and Mastoid	14	23	21
	P = 0.73		P = 0.69

There were 1045 Ranch Handers, and 773 originally selected comparisons included in the analyses in this chapter. Where analyses were accomplished using the total comparison group, the data from 1194 comparisons were used. Some variation in numbers did occur due to missing data. In the analyses of the data obtained from the neurological evaluation, only those participants with a negative serological test for syphilis were included since chronic neurological disease can result from inadequately treated syphilis (5 Ranch Handers and no comparisons were found to have positive serological tests for syphilis.) In addition, data from 15 individuals found to have edema of the extremities on physical examination (8 Ranch Handers and 7 comparisons) were deleted from the analyses of the peripheral sensory nerve evaluation and nerve conduotion velocities since edema can interfere with these clinical evaluations. Several covariables were considered in the analysis. The use of alcohol (dichotomized to ever/never); years of unprotected exposure to industrial chemicals (yes, no), insecticides (yes, no), and degreasing chemicals (yes, no); and 2-hour postprandial glucose levels equal to or greater than 120 mg/dl were used as covariates.

2. Cranial Nerve Status

The functional integrity of all 12 cranial nerves was assessed during the neurological examination. The specific cranial nerves and the examination parameters used in their evaluation are listed in Table XII-2.

Table XII-2

CRANIAL NERVE EVALUATION

Cranial Nerve		Parameter
I	Olfactory	Sense of smell
II	Optic	Visual fields
III	Oculomotor	Pupillary reaction to light Ocular movement
IV	Trochlear	Ocular movement
V	Trigeminal	Facial sensation Corneal reflex Clenching jaw
VI	Abducens	Ocular movement
VII	Facial	Smile Palpebral fissure
VIII	Acoustic	Balance (Romberg Sign)
IX	Glossopharyngeal	Gag reflex
X	Vagus	Speech Tongue position
XI	Spinal Accessory	Palate and uvula movement Neck movement
XII	Hypoglossal	Neck range of motion

Analysis of the examination data revealed no statistically significant differences in cranial nerve function between the Ranch Hand and comparison groups. No significant three-way interactions between the examination parameters, group membership and the covariables of glucose and alcohol were noted. These results are summarized in Table XII-3. Data from the entire comparison group are also presented.

Table XII-3

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand Versus Original Comparisons	P Values; Ranch Hand Versus All Comparisons
I	Smell, left	RH	1025	19	0.67	0.68
		OC	759	12		
		AC	1172	19		
	Smell, right	RH	1027	17	0.73	0.70
		OC	760	11		
		AC	1174	17		
II	Visual fields, left	RH	1037	3	0.91*	0.87*
		OC	768	2		
		AC	1186	3		
	Visual fields, right	RH	1038	2	0.43*	0.51*
		OC	768	3		
		AC	1186	4		
III	Light reaction	RH	1031	8	0.52	0.43
		OC	763	4		
		AC	1180	6		
III-IV, VI	Ocular movement	RH	655	349	0.82	0.49
		OC	486	265		
		AC	746	423		
V	Sensation, left	RH	1035	7	0.68	0.26
		OC	769	4		
		AC	1190	4		
	Sensation, right	RH	1038	4	0.99*	0.58*
		OC	770	3		
		AC	1191	3		
	Corneal reflex	RH	1043	2	0.75*	0.49*
		OC	772	1		
		AC	1193	1		
	Jaw clench	RH	1042	1	-	-
		OC	773	0		
		AC	1194	0		

Table XII-3 (Cont'd)

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand versus Original Comparisons	P Values; Ranch Hand versus All Comparisons
VII	Smile	RH	1035	4	0.65*	0.85*
		OC	767	2		
		AC	1186	4		
	Palpebral fissure	RH	986	59	0.84	0.70
		OC	731	42		
		AC	1131	63		
VIII	Balance	RH	833	207	0.69	0.26
		OC	625	148		
		AC	813	228		
IX	Gag reflex	RH	1030	15	0.67	0.58
		OC	760	13		
		AC	1180	14		
X	Speech	RH	1041	3	-	0.26*
		OC	770	0		
		AC	1190	1		
	Tongue in mid-line	RH	879	4	0.63*	0.51*
		OC	662	2		
		AC	1085	3		
XI	Palate and uvula movement	RH	1042	3	0.48*	0.26*
		OC	771	1		
		AC	1192	1		
XI, XII	Neck range of motion	RH	1004	41	0.44	0.24
		OC	748	25		
		AC	1158	36		

*P values are of limited validity due to small cell sizes in these analyses
RH = Ranch Hand
OC = Originally selected comparison
AC = All comparisons
- = Cells containing zeros; P values not valid

The 18 neurological parameters listed in Table XII-3 were again analyzed with regard to occupational group and exposure level. The exposure index, stratified into 3 occupational groupings and 3 levels of exposure, was applied to these cranial nerve data. These results are summarized in Table XII-4. Fully adequate cell sizes were obtained in only 13 instances. In these analyses, in which no individuals in either group had abnormalities, statistical testing for significance was invalid, and P values are not given.

Table XII-4

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
I	Smell, left	O/F	0.79
		E/F	0.67
		E/G	0.16
	Smell, right	O/F	0.01
		E/F	0.84
		E/G	0.31
II	Visual fields, left	O/F	0.05
		E/F	0.40
		E/G	0.44
	Visual fields, right	O/F	0.06
		E/F	0.40
		E/G	0.11
III	Light reaction	O/F	0.32*
		E/F	-
		E/G	0.28
III, IV, VI	Ocular movement	O/F	0.21*
		E/F	0.33*
		E/G	0.47*
V	Sensation, left	O/F	0.32
		E/F	0.12
		E/G	0.72
	Sensation, right	O/F	0.64
		E/F	0.34
		E/G	0.35
	Corneal reflex	O/F	-
		E/F	-
		E/G	0.55

Table XII-4 (Cont'd)

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
	Jaw clench	O/F	0.64
		E/F	-
		E/G	-
VII	Smile	O/F	0.64
		E/F	0.57
		E/G	-
	Palpebral fissure	O/F	0.97*
		E/F	0.14
		E/G	0.12*
VIII	Balance	O/F	0.89*
		E/F	0.25*
		E/G	0.44*
IX	Gag reflex	O/F	0.99
		E/F	0.84
		E/G	0.20
X	Speech	O/F	0.38
		E/F	0.34
		E/G	0.11
	Tongue in midline	O/F	0.07*
		E/F	0.30*
		E/G	0.40*
XI	Palate and uvula movement	O/F	0.64
		E/F	-
		E/G	0.43
XI, XII	Neck range of motion	O/F	0.67*
		E/F	0.78
		E/G	0.46

O/F = Officer, flying E/F = Enlisted, flying E/G = Enlisted, ground
* = Cell sizes of 5 or less
- = Cells containing zeros; P values not valid

3. Peripheral Nerve Status

The variables used in the assessment of peripheral nerve function were analyzed with the covariates of 2-hour postprandial glucose in excess of 120 mg%, history of alcohol use and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. There were statistical interactions between group membership (Ranch Hand and comparison) and insecticide exposure, and between insecticide exposure and the other covariables. Since these relationships have no impact on the primary question being addressed by this study, further statistical analyses of these interactions will not be undertaken at this time.

Analysis of the data pertaining to the peripheral nervous system is summarized in Table XII-5. Data from the entire comparison group are also presented. With the exception of a borderline association between group and Babinski reflex in the originals and a significant association in the entire comparison group, these analyses did not demonstrate statistically significant differences in neurological functions between the 2 groups. Matched pair analyses were performed on the Babinski reflex and the vibration sense data, using the Breslow matched logistic regression technique. A P value of 0.18 was found for the Babinski reflex and a nonsignificant P value of 0.47 was found for vibration sense. Significant interactions were, however, detected between postprandial glucose levels and several of the examination parameters. The association between abnormal glucose metabolism and peripheral neurological disease is well recognized (Scientific American, 1983) and its demonstration in this study reflects a degree of confidence in the quality of the neurological data collection process. These glucose by neurological disease associations are shown in Table XII-6. A positive history of alcohol use had borderline significance with pin prick ($P = 0.07$). In this analysis, a continuing effect of abnormal glucose is seen for vibration ($P = 0.0005$), patellar reflex ($P = 0.03$), Achilles reflex ($P = 0.04$), and light touch ($P = 0.03$). Alcohol use also had a borderline significant effect on pin prick ($P = 0.07$).

Table XII-5

ANALYSIS OF THE PERIPHERAL NERVOUS SYSTEM

Parameter	Group	# Normal	# Abnormal	P value; Ranch Hand versus Original Comparisons	P value; Ranch Hand versus All Comparisons
Pin prick	RH	934	97	0.94	0.76
	OC	691	73		
	AC	930	101		
Light touch	RH	958	73	0.78	0.67
	OC	707	57		
	AC	953	78		
Muscle Status (strength, bulk)	RH	1003	37	0.94	0.62
	OC	745	28		
	AC	1009	32		
Vibration	RH	954	78	0.38	0.30
	OC	698	67		
	AC	941	91		
Patellar Reflex	RH	1034	4	0.45	0.74
	OC	766	5		
	AC	1003	5		
Achilles Reflex	RH	995	39	0.62	0.62
	OC	746	26		
	AC	1005	35		
Biceps Reflex	RH	1030	8	0.53	1.00
	OC	767	4		
	AC	1032	8		
Babinski Reflex	RH	1024	9	0.10	0.03
	OC	770	2		
	AC	1039	2		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Table XII-6

POSTPRANDIAL GLUCOSE ABNORMALITIES VERSUS NEUROLOGICAL FINDINGS
(RANCH HANDERS VERSUS ORIGINAL COMPARISONS)

Parameter	Examination Status	Glucose Status # Normal	Glucose Status # Abnormal	P Value
Light Touch	Normal	1406	259	0.03
	Abnormal	100	30	
Vibration	Normal	1402	250	0.0005
	Abnormal	106	39	
Patellar Reflex	Normal	1514	286	0.03
	Abnormal	5	4	
Achilles Reflex	Normal	1463	273	0.04
	Abnormal	48	17	
Pin prick	Normal	1369	256	0.23
	Abnormal	137	33	

The data from the Ranch Hand group were also analyzed against the exposure index. As shown in Table XII-7, there were no three-way interactions between occupational group, herbicide exposure and the neurological parameters evaluated. No statistically significant results were found in the analysis of exposure versus examination parameters. Borderline associations were noted for vibration in the enlisted flying group ($P = 0.10$) and for Babinski Reflex in the enlisted ground personnel ($P = 0.09$). The relevance of these findings, in the face of the other negative results, is unclear at this time. There were no distinct patterns of increasing abnormality with increasing exposure.

Table XII-7

PERIPHERAL NEUROPATHY BY EXPOSURE ANALYSES: SUMMARY OF P VALUES

Parameter	Occupational Group: Officer	Occupational Group: Enlisted Flying	Occupational Group: Enlisted Ground
Pin prick	0.78	0.99	0.47
Light Touch	0.40	0.83	0.81
Muscle Status	0.43	0.96	0.65
Vibration	0.94	0.10	0.96
Patellar Reflex	0.50	0.57	1.00
Achilles Reflex	0.35	0.53	0.60
Biceps Reflex	0.49	0.57	0.91
Babinski Reflex	0.57	0.53	0.09

4. Evaluation of Central Functioning

A brief evaluation of central nervous system coordination processes was accomplished, focusing on the presence of muscle tremor, finger-to-nose coordination, gait and balance as assessed by the modified Romberg Sign. These analyses are shown in Table XII-8. As in the analysis of the peripheral nerves, there were no significant interactions of these findings with chemical exposures or group membership; however, abnormal glucose metabolism was associated with abnormal balance (P = 0.0002) and the presence of tremor (P = 0.004). Alcohol also had a significant effect on the presence of tremor (P = 0.05) and a borderline effect on balance (P = 0.09). Breslow matched pair analysis of the tremor and coordination data revealed nonsignificant P values of 0.21 and 0.31 respectively.

Table XII-8

ANALYSIS OF CENTRAL FUNCTION

				P values; Ranch Hand versus	
				Original	All
Parameter	Group	# Normal	# Abnormal	Comparisons	Comparisons
Tremor	RH	985	55	0.19	0.36
	OC	742	31		
	AC	995	46		
Coordination	RH	992	48	0.44	0.59
	OC	743	30		
	AC	998	43		
Romberg Sign	RH	833	207	0.64	0.26
	OC	625	148		
	AC	813	228		
Gait	RH	1014	24	0.47	0.76
	OC	758	14		
	AC	1018	22		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Exposure analysis was performed on these parameters as well. Three-factor analysis of parameter by exposure level by occupational group again demonstrated no significant interactions. In these analyses, the herbicide exposure/coordination analysis yielded a suggestive association (P = 0.10). Again, there was a statistically significant association between an abnormal Romberg Sign and abnormal glucose metabolism (P = 0.002). Two-way analysis results are shown in Table XII-9.

Table XII-9

HERBICIDE EXPOSURE VERSUS ABNORMALITY OF CENTRAL FUNCTIONING
SUMMARY OF P VALUES

Parameter	P Values		
	Officers	Enlisted Flying	Enlisted Ground
Tremor	0.50	0.76	0.20
Coordination	0.07	0.16	0.63
Romberg Sign	0.89	0.25	0.44
Gait	0.54	0.38	0.11

5. Nerve Conduction Velocity

Nerve conduction was evaluated using a continuous measurement and analyzed using a general linear model technique for maximal statistical power. Velocities were measured from 2 locations in the ulnar nerve and from 1 position in the peroneal nerve. Covariables in these analyses included history of alcohol use (measured in drink-years), abnormalities in postprandial glucose levels (equal to or greater than 120 mg/dl), and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. No associations between the chemical exposures and conduction velocities were identified on covariate analysis; however, highly statistically significant associations were noted in both the Ranch Hand and comparison groups between alcohol use and glucose and conduction velocity. This association held for both measurements of the ulnar nerve ($P \leq 0.01$) with the velocity decreasing as the drink-years of alcohol increased. Glucose was found to be associated with conduction velocity in the peroneal nerve ($P = 0.002$) and both ulnar velocities ($P = 0.001$) with velocity decreasing as glucose level increased. These analyses did not demonstrate any significant intergroup differences in velocities in either nerve. The unadjusted and adjusted means and their respective P values are presented in Table XII-10. Similar analyses, using data from the entire comparison group, were performed with similar means and results.

Table XII-10

NERVE CONDUCTION VELOCITY (M/SEC) AND GROUP MEMBERSHIP

Nerve	Group (N)	Unadjusted Mean	P Value	Adjusted Mean	P Value
Ulnar (above the elbow)	R (1035)	55.88	0.30	55.89	0.38
	C (769)	56.15		56.12	
Ulnar (below the elbow)	R (1042)	60.50	0.39	60.52	0.48
	C (771)	60.73		60.71	
Peroneal	R (1041)	48.22	0.74	48.23	0.66
	C (769)	48.14		48.93	

Herbicide exposure analyses were performed using the covariates of occupational group serum glucose and history of alcohol use. These results are shown in Table XII-11.

Table XII-11

ADJUSTED MEAN NERVE CONDUCTION VELOCITY (M/SEC) AND EXPOSURE

Nerve	Exposure			
	Low	Med-High	High	P Value
Officers				
Ulnar (above elbow)	55.77	55.66	55.97	0.90
Ulnar (below elbow)	60.54	60.60	61.10	0.70
Peroneal	47.69	47.76	47.87	0.96
Enlisted Flying				
Ulnar (above elbow)	54.54	55.72	55.35	0.53
Ulnar (below elbow)	58.31	60.68	60.83	0.03
Peroneal	48.22	48.28	48.29	0.99
Enlisted Ground				
Ulnar (above elbow)	55.53	56.60	56.33	0.24
Ulnar (below elbow)	59.96	60.74	60.69	0.96
Peroneal	48.34	48.31	49.00	0.14

These exposure analyses have not demonstrated any consistent trends in conduction velocity and increasing exposure either within or between occupational categories. A single significant result ($P = 0.03$) was found in the distal ulnar nerve velocity in flying enlisted personnel, but there was no corresponding finding in the same nerve when measured over a larger distance above the elbow ($P = 0.53$). The borderline significance in the peroneal nerve velocity of ground enlisted personnel ($P = 0.14$) was not evident in the other occupational categories. Again, significant associations with glucose were noted, with P values falling between 0.06 and 0.005.

6. Summary

As summarized in Table XII-12, detailed analyses of the neurological examination data pertaining to the status of the cranial nerves, peripheral nerves and central functioning were performed.

Table XII-12

SUMMARY OF NEUROLOGICAL STATUS

	Analysis (P Values)			
		Exposure		
Parameter	Group	Off	Enl Fly	Enl Gnd
Cranial Nerves				
1	NS	0.01	NS	0.16
2	NS	0.05	NS	0.11
3	NS	NS	NS	NS
4	NS	NS	NS	NS
5	NS	NS	0.12	NS
6	NS	NS	NS	NS
7	NS	NS	0.14	0.12
8	NS	NS	NS	NS
9	NS	NS	NS	NS
10	NS	0.07	NS	0.11
11	NS	NS	NS	NS
12	NS	NS	NS	NS
Peripheral Nerves				
Pin Prick	NS	NS	NS	NS
Light Touch	NS	NS	NS	NS
Muscle Status	NS	NS	NS	NS
Vibration	NS	NS	0.10	NS
Patellar Reflex	NS	NS	NS	NS
Achilles Reflex	NS	NS	NS	NS
Biceps Reflex	NS	NS	NS	NS
Babinski Reflex	0.10	NS	NS	0.09
Control Function				
Tremor	0.19	NS	NS	NS
Coordination	NS	0.07	0.16	NS
Romberg	NS	NS	NS	NS
Gait	NS	NS	NS	0.11
Conduction Velocity				
Proximal Ulnar	NS	NS	NS	NS
Distal Ulnar	NS	NS	0.03	NS
Peroneal	NS	NS	NS	0.14

NS = Nonsignificant

With the exception of a borderline increase in the proportion of Ranch Handers with a positive Babinski reflex, there were no significant differences detected between the Ranch Hand and comparison groups with respect to neurological parameters. The Babinski reflex, however, did not show a significant relationship to past herbicide exposure. There were no consistent findings of increasing abnormality with increasing herbicide (dioxin) exposure. The relative risks and confidence intervals for the dependent variables analyzed in this chapter are included in Appendix XVIII. Thus, it appears at this time, that there are no neurological abnormalities in the Ranch Hand group that can be attributed to herbicide exposure in Vietnam.

The evaluation of neurological status among the participants in this study has demonstrated the ability to identify classical interactions between abnormal glucose metabolism and alcohol use and evidence of neurological abnormalities. These findings lend confidence to the validity of the negative findings of a chronic herbicide (dioxin) effect on the neurological system.

Chapter XIII

PSYCHOLOGICAL ASSESSMENT

Since 1961, psychological abnormalities have been ascribed to acute phenoxy herbicide exposure (Bauer, 1961). Subsequently, a wide range of psychological symptoms, including anxiety, depression, emotional instability, and asthenia have been reported following exposure (Monarca and di Vito, 1961; Kramer, 1974; Poland et al, 1971). Since many Vietnam veterans have expressed concern that their exposure to the defoliants during the war caused them to experience psychological and behavioral problems, the psychological functioning of the study participants was assessed in both the questionnaire and physical examination phases of the study. Overall, the responses of 1045 Ranch Handers, 1230 comparisons, and a subset of 773 originally selected comparisons were analyzed. Slight variations in these numbers occurred in some analyses due to missing data. Except where indicated, all analyses reported in this chapter used the data from the subset of originally selected comparisons. Each participant was asked whether he had ever experienced psychological illness. Additionally, six specific psychological dimensions were explored in detail in the questionnaire: depression, anxiety, erosion of skills, social isolation, fatigue, and aggressive or impulsive behavior. The questions used were selected from an extensive test battery, previously developed and validated (Robbins, 1982). More standardized measurements of psychological performance were obtained during the physical examination by the use of several standardized tests. The Cornell Index, the Minnesota Multiphasic Personality Inventory (MMPI), the Halstead-Reitan Battery and the Wechsler Adult Intelligence Scale (WAIS) were the primary testing instruments. Throughout much of this chapter, educational level (high school versus college) and rank (officer versus enlisted status) received special attention in all analyses. These variables are widely recognized as having major influences on psychological testing performance (Dalstrom, 1960) and their importance in the setting of the Air Force Health Study was very apparent. Dependent variables were stratified by education and rank, and in log-linear techniques, they were used as covariables. Table XIII-1 displays the education and rank distributions of the Ranch Hand and original comparison groups.

Table XIII-1

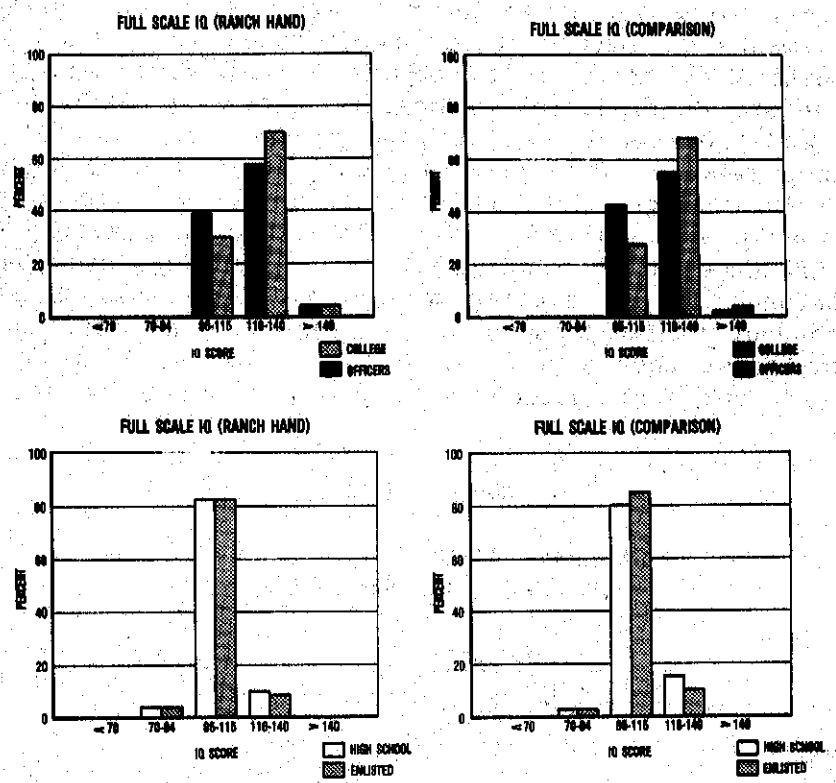
EDUCATION AND RANK DISTRIBUTION OF RANCH HAND AND ORIGINAL COMPARISON GROUPS

	Ranch Hand		Original Comparisons	
	High School	College	High School	College
Officers	54 (14.3%)	324 (85.7%)	53 (18.2%)	239 (81.8%)
Enlisted	521 (80.8%)	124 (19.2%)	377 (79.4%)	98 (20.6%)

Regardless of statistical technique or procedure, the analytic results of all psychological testing from the high school group closely mirrored those of the enlisted group, and college results matched those of the officer group, since, in general, the attainment of a college degree is a prerequisite for commissioning as an officer. However, 124 of the Ranch Hand enlisted and 98 of the original comparison enlisted personnel have college degrees as well. The similarities between these groups are graphically demonstrated in Figure XIII-1, where full scale IQ scores are compared. Since the variables of rank and education had identical impact on the analyses of psychological data, only the data from the educational analyses will be presented. The results of the rank analyses parallel those of education, and their presentation in this report would not further clarify the herbicide/dioxin issue.

Figure XIII-1

COMPARISON OF EDUCATIONAL ACHIEVEMENT AND RANK



1. Analysis of Questionnaire Data

a. Past History of Emotional or Psychological Illness

Detailed information concerning reported emotional or psychological illnesses was sought and, wherever possible, these illnesses were coded to the ICD-9-CM, 1980 edition. The unadjusted chi-square analyses of these data are presented in Table XIII-2. It is evident from these analyses that there were no statistically significant differences in the type of reported psychological illnesses between the Ranch Hand and either the entire comparison group or the subset of original comparison individuals.

Table XIII-2

DISTRIBUTION OF REPORTED PSYCHOLOGICAL ILLNESS BY TYPE OF ILLNESS

Type of Illness	Original Comparisons	Ranch Hand	Entire Group Comparison
Psychoses	4	6	4
Alcohol Dependence	2	5	7
Anxiety	4	9	5
Other Neuroses	6	16	9
	P = 0.91	P = 0.59	

b. Psychological Indices

A further comparison of the responses to the psychological subsections of the questionnaire was performed. Responses to the questions addressing each psychological dimension were combined in an index equal to the number of positive responses for each dimension. Group differences in the distribution of questionnaire responses were tested by the Kolmogorov-Smirnov two-sample test, and the results are tabulated in Table XIII-3 and XIII-4. The isolation index was analyzed in a discrete fashion, adjusted for educational level. The data for this index are presented in Table XIII-5. When the responses to the isolation scale are dichotomized as equal or greater than 14 or less than 14, a relative risk of 1.97 is seen, with a 95% confidence interval of 1.14 to 3.58. The number of individuals analyzed in the depression index is reduced, since this is primarily an index of severity, and those individuals not reporting depression were excluded from the analysis.