

Chapter X

MALIGNANCY

1. Introduction

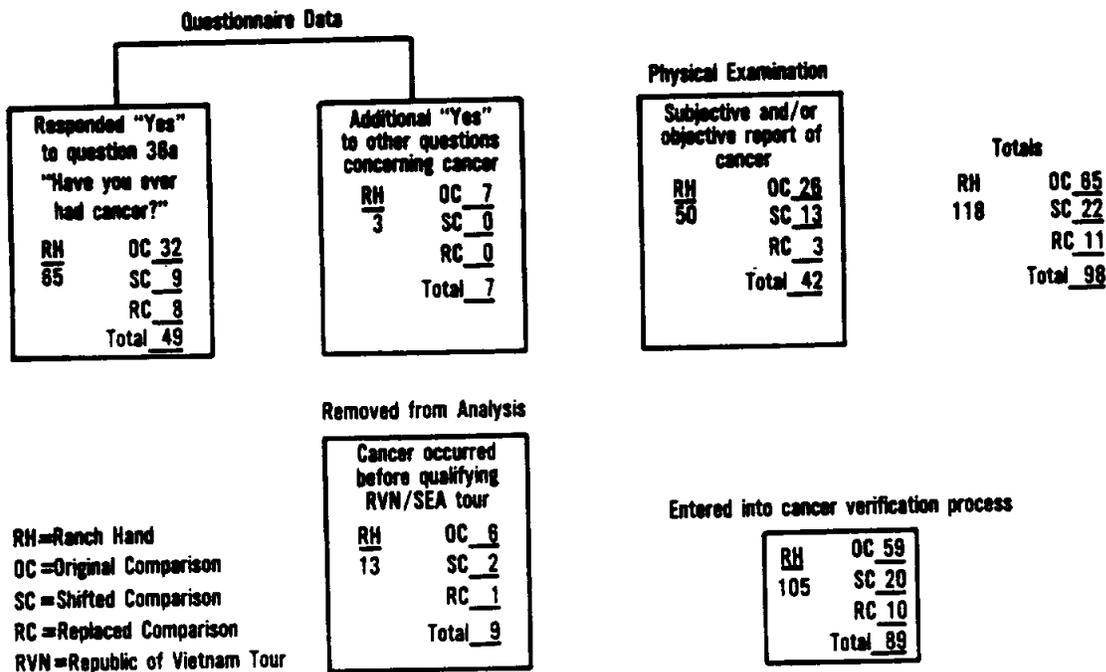
Of all the health effects being attributed to dioxin, cancer is one of the most feared in the minds of the veteran groups, the media and the general public. Dioxin has been identified as a carcinogen or cocarcinogen in some strains of rats and mice (Toth, et al, 1979; Kociba et al, 1978, 1979; Kouri, 1978); however, its carcinogenic effects in humans are unclear. Epidemiologic studies of carcinogenic effects in humans have been generally limited to investigations of phenoxy herbicide exposure among soft-tissue sarcoma patients in Sweden (Hardell and Sandstrom 1979; Axelson, 1977) and studies among industrial groups involved in the production of trichlorophenol and 2,4,5-T (Zack, 1980; Honchar, 1981). These studies have been contradictory and the issue is still being debated in scientific as well as public forums. The clarification of this important issue is a major focus of the Air Force Health Study.

Questions concerning a history of cancer or tumor were asked during both the in-person questionnaire and the physical examination. Question 36a of the study subject questionnaire concerned cancer alone while other areas of the questionnaire focused on tumors or other major medical conditions. In addition, the physical examination subjectively identified additional participants with a history of cancer in the past medical history and objectively identified participants with evidence of prior or newly diagnosed cancer. Figure X-1 shows the algorithm used for data collection for cancer in the study population, as well as those reported cancers that were entered into the cancer verification process.

In this algorithm 114 individuals (65 Ranch Handers and 49 comparisons) responded "yes" to question 36a, 10 other individuals (3 Ranch Handers and 7 comparisons) responded yes to other questionnaire questions concerning tumors or other major conditions, while 92 additional individuals (50 Ranch Handers and 42 comparisons) reported or were diagnosed as having cancer or tumors during the physical examination. A total of 22 reported cancers occurred prior to the individual's Southeast Asia tour of duty, and these cancers were removed from all analyses. A total of 194 individuals reporting cancer were entered into the verification process (105 Ranch Handers and 89 comparisons).

Cancer verification was completed by review of the individual's medical records and available pathology reports. Although cancers reported by all participants were entered into the validation process, only the data from the Ranch Hand group and the subset of originally selected comparisons who completed physical examination were fully analyzed statistically. The rationale

Figure X-1
ALGORITHM OF COUNTS ON REPORTED CANCERS BY SOURCE OF DATA



for this restriction of the database is discussed in Chapter V, Study Selection and Participation Bias. Verification records were obtained with permission forms signed by the participants at the time the questionnaire was administered. The verification process was supported with a limited access computer software program. All reported cancers were classified as to behavior, type and morphology. In addition, cancers were classified as being skin or systemic due to the differing natures of these disease processes. The findings of the verification process are presented in Table X-1.

Table X-1

SUMMARY OF CANCER VERIFICATION PROCESS

Location	Behavior of Cancer	Ranch Hand	Comparison*			
			O	S	R	Total
Skin	Malignant	35	15	7	5	27
	Benign	17	14	3	1	18
	Diagnosis not supported	13	6	4	1	11
	Differential Diagnosis at physical examination; individual declined follow-up	13	3	3	0	6
	No record of treatment at facility as reported	1	1	0	0	1
	Medical record not available	<u>0</u>	<u>0</u>	<u>1</u>	<u>1</u>	<u>2</u>
	TOTAL	79	39	18	8	65
Systemic	Malignant	14*	10	2*	2	14
	Benign	8	10	0	0	10
	Not supported	4	0	0	0	0
	Medical record not available	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
	TOTAL	26	20	2	2	24

*Includes 1 Ranch Hander and 1 comparison who expired following interview

O = Original
S = Shifted
R = Replacement

2. Skin Cancer

Seventy-five percent (79/105) of all Ranch Hand and 73% (65/89) of all comparison-reported and verified neoplasms were cancer of the skin. Forty-four percent (35/79) of the Ranch Hand reported skin cancers were verified as malignant while 42% (27/65) of the reported total comparison skin cancers were verified as malignant (P = 0.74). All individuals with malignant skin cancer were non-Black. The occurrence of verified skin cancer in those participants who completed the questionnaire (regardless of their compliance to physical examination) was significantly higher in the Ranch Hand group when compared to the total comparison group (P=0.03) or to the subset of original comparisons (P=0.04). Table X-2 shows the distribution of verified malignant skin cancers by cell type.

Table X-2

VERIFIED MALIGNANT SKIN CANCERS BY CELL TYPE;
REPORTED BY FULLY AND PARTIALLY COMPLIANT PARTICIPANTS

<u>Cell Type</u>	<u>Ranch Handers*</u>	<u>Comparisons</u>			
		<u>O</u>	<u>S</u>	<u>R</u>	<u>Total</u>
Basal Cell	31	11	5	5	21
Melanoma	3	1	1	0	2
Squamous Cell	1	3	0	0	3
Fibrosarcoma	<u>0</u>	<u>0</u>	<u>1</u>	<u>0</u>	<u>1</u>
TOTAL	35	15	7	5	27

*1 Ranch Hander experienced 2 skin cancers, 1 melanoma and 1 squamous cell. He has been counted only once and placed under melanoma in this table.

O = Original
S = Shifted
R = Replacement

Nonmelanoma cancer accounts for 91% (32/35) of the Ranch Hand and 93% (25/27) of the comparison group skin cancers. This difference is not statistically significant (P = 0.87). These findings are consistent with reported data that nonmelanoma cancer of the skin is the most common malignant neoplasm in the white population of the United States (Schottenfeld and Fraumeni, 1982). The distribution of these verified skin cancers by anatomic site is presented in Table X-3.

Table X-3

COUNTS OF SKIN CANCER BY ANATOMIC SITE

	Nonmelanoma skin cancer					Melanoma				
	RH	Comparison			Total	RH	Comparison			Total
O		S	R	O			S	R		
Face, head and neck	26	12*	5**	3	20	1	0	0	0	0
Upper extremities	1	1	1	0	2	0	1	0	0	1
Trunk	5+	1	0	2	3	2	0	1	0	1
Lower extremities	0	0	0	0	0	0	0	0	0	0
TOTAL	32	14	6	5	25	3	1	1	0	2

+Includes 1 Squamous cell

*Includes 3 squamous cell

**Includes 1 fibrosarcoma

RH = Ranch Hand

O = Original

S = Shifted

R = Replacement

Nonmelanoma skin cancers arose on the face, head and neck in 81% (26/32) of the Ranch Handers and in 80% (20/25) of all comparisons ($P = 0.91$). This distribution and the cell types of skin cancers is consistent with recently published information on the epidemiology of skin cancer (Schottenfeld and Fraumeni 1982). The occupational category of those individuals with verified skin cancer are presented in Table X-4. The counts of these individuals with cancer are relatively small and all occupational categories contribute to the Ranch Hand increase. Followup reports will contain additional analyses of these data with detailed considerations of sample size and age in each of the occupational strata.

Table X-4

COUNTS OF THE FACE, HEAD, AND NECK DISTRIBUTION OF
NONMELANOMA SKIN CANER; RANCH HAND VERSUS TOTAL COMPARISONS

Occupational Code	Ranch Hand		Total Comparisons	
	Cases	Rate/100	Cases	Rate/100
Officers	16	3.7	11	1.9
Flying Enlisted	3	1.5	1	0.4
Nonflying Enlisted	7	1.3	8	1.1
	26		20	

While medical literature implicates ultraviolet radiation from the sun as the dominant risk factor in the development of nonmelanomic skin cancer (Scott et al 1974), it was not possible to fully evaluate the effects of sun exposure in the initial phase of this study. Information required for this analysis will be obtained in the follow-up phases of the effort.

3. Systemic Cancer

A total of 50 systemic cancers (26 Ranch Handers and 24 comparisons) were reported and entered into the verification process (Table X-1). Of these, 14 Ranch Handers and 14 comparisons (10 Originals, 2 Shifted, and 2 Replacements) were verified as having had malignant systemic neoplasms. All individuals with systemic malignancy are non-Black. The site specific classification of these neoplasms is presented in Table X-5.

Table X-5

MORBIDITY SITE SPECIFIC VERIFIED SYSTEMIC MALIGNANT NEOPLASMS

<u>Site: ICD Code (9th Ed)</u>	<u>Ranch Hand</u>	<u>Comparison</u>			<u>Total</u>
		<u>O</u>	<u>S</u>	<u>R</u>	
Lip, oral cavity, pharynx (140-149)	4	2	0	0	2
Digestive organ, peritoneum (150-159)	-	4	0	1	5
Respiratory, intrathoracic (160-165)	3*	1	1*	0	2
Bone, connective tissue, skin, breast (170-175)	-	-	-	-	-
Genitourinary organ (179-189)	6	2	1	0	3
Other & unspecified sites (190-199)	1	1	0	0	1
Lymphatic & hematopoietic tissue (200-208)	-	0	0	1	1
TOTAL	14	10	2	2	14

*Includes 1 Ranch Hander and 1 comparison who expired following interview

O = Original
S = Shifted
R = Replaced

Four Ranch Handers and 2 original comparisons were found to have had neoplasms of the lip, oral cavity and pharynx, and all of these individuals reported a history of cigarette and/or cigar smoking.

Six Ranch Handers and 3 comparisons were found to have had malignancies of the genitourinary organs. The 6 Ranch Hand cancers included 1 prostate, 2 testicular, 2 bladder and 1 kidney neoplasm while the 3 comparison cancers included 1 of the prostate and 2 of the bladder. Both cases of testicular cancer were of a germ-cell morphology (one embryonal and one seminoma). Unadjusted statistical testing revealed no significant difference in total genitourinary cancer in the two groups ($P = 0.42$). Peak incidence rates of testicular cancer in the general population occur between the ages of 35 and 55, and bladder cancer has a peak age of onset between 50 and 70 years. All Ranch Hand bladder cancers occurred prior to age 50 and all verified comparison genitourinary cancer occurred at age 55 or later. The Ranch Hand testicular cancers occurred at 35 and 38 years of age. These are observational data, and are based on very small sample size.

Five comparisons were found to have had verified malignancies of the digestive organs. There were no Ranch Hand cancers of this organ system. These cancers included 1 of the appendix, 1 of the pancreas, and 3 colon cancers. The annual incidence rate for colon cancer increases dramatically with increasing age after the age of 30. The ages at the onset of the colon cancers in the comparison group were 35, 43, and 50 years. The occurrence of genitourinary, oropharyngeal and digestive cancers in the study population was compared to the experience of the Surveillance, Epidemiology and End Results program (SEER). Based on these tumor registry data, there is a 30% probability of observing two or more testicular cancer in the Ranch Hand group, and a 29% probability of two or more bladder cancers. Similar contrasts revealed only a 3% chance of observing the 4 oropharyngeal cancers and a 2% chance of seeing a total absence of digestive cancers in the Ranch Hand group. The probabilities of finding the observed numbers of these malignancies in the comparison group were 32% or greater.

Table X-6 shows the known morbidity and mortality of the Ranch Handers and comparisons from cancer to date. Appendix VIII shows the site specific distribution of both the morbidity and mortality study cancers. The mortality sections of these tables include only the first cohort of the comparison population from the Baseline Mortality Study (Lathrop, 1983).

Table X-6

TOTAL MORTALITY AND MORBIDITY STUDY
MORPHOLOGY OF SYSTEMIC NEOPLASM

ICD-0 CODES	NOMENCLATURE	MORTALITY		MORBIDITY*			
		RANCH HAND	COMPARISON	RANCH HAND	COMPARISON		
					O	S	R
M800	Neoplasm not other- wise specified (NOS)						
	Bronchus and Lung	0	1	0	0	0	0
	Intestinal Tract	0	1	0	0	0	0
M801-804	Epithelial neoplasms						
	Appendix	0	0	0	1	0	0
	Bladder	0	0	0	1	0	0
	Bronchus and Lung	1	1	1	0	0	0
	Kidney	1	0	0	0	0	0
	Lip	0	0	1	0	0	0
	Nasopharynx	0	1	0	0	0	0
	Tongue	0	0	1	0	0	0
	Unspecified site	1	1	0	0	0	0
	Vocal Cord	0	0	0	1	0	0
M805-808	Papillary and Squamous Cell						
	Lip	0	0	2	2	0	0
	Lung	0	0	1	0	0	0
M812-813	Transitional Cell Papillomas and Carcinomas						
	Bladder	0	0	2	0	1	0
M814-838	Adenomas and Adeno- carcinomas						
	Bronchus and Lung	0	1	0	0	0	0
	Colon	0	0	0	2	0	1
	Kidney	0	1	1	0	0	0
	Prostate	0	0	1	1	0	0
	Pancreas	0	0	0	1	0	0
M850-854	Ductal, lobular, and medullary neoplasms						
	Thyroid	0	0	0	1	0	0
M872-879	Nevi and melanomas						
	Mediastinal	1	0	0	0	0	0
M905	Mesothelioma						
	Bronchus and Lung	0	1	0	0	0	0
M906-909	Germ cell neoplasms						
	Testicle	0	0	2	0	0	0
M938-948	Gliomas						
	Frontal Lobe	0	1	1	0	0	0

Table X-6 (Cont)

TOTAL MORTALITY AND MORBIDITY STUDY
MORPHOLOGY OF SYSTEMIC NEOPLASM

ICD-O CODES	NOMENCLATURE	MORTALITY		MORBIDITY*			
		RANCH HAND	COMPARISON	RANCH HAND	COMPARISON		
					O	S	R
M965-966	Hodgkins disease Hodgkins (NOS)	0	0	0	0	0	1
M986	Myeloid Leukemias Acute myelocytic leukemia	$\frac{0}{4}$	$\frac{1}{10}$	$\frac{0}{13}$	$\frac{0}{10}$	$\frac{0}{1}$	$\frac{0}{2}$

O = Original
S = Shifted
R = Replaced

*Two morbidity study participants (1 Ranch Hand, 1 comparison) expired following interview. They are included in the mortality column of this Table because of their date of death.

4. Covariate Analysis

Group Membership

The previous sections of this chapter contained descriptions of the cancer data on the occurrence of skin cancer and systemic cancer in the Ranch Hand and originally selected comparison groups. Except where noted, the remaining analyses in this chapter are based on the Ranch Hand and comparison population that had verified cancer and had completed the physical examination. Covariates used in these analyses included smoking habits and exposure to asbestos, industrial chemicals (yes, no), insecticides (yes, no), degreasing chemicals (yes, no), and nonmedical x-ray sources (yes, no). The results of the basic two-factor analysis are shown in Table X-7.

Table X-7

VERIFIED CANCER AND GROUP MEMBERSHIP

		Original Comparisons (N=773)	Ranch Hand (N=1045)	Total Comparisons* (N=1194)
Skin Cancer	Yes	11	35	25
	No	762	1010	1169
		P = <0.01		P = 0.07
Systemic Cancer	Yes	8	13	11
	No	765	1032	1183
		P = 0.68		P = 0.46

* This total does not include the 30 participants interviewed by USAF interviewers.

The group differences in skin cancer are statistically significant, in the original subset that completed physical examination, ($P = < 0.01$) and borderline in the total comparisons ($P = 0.07$), with an excess in the Ranch Hand group. The relative odds of skin cancer in the Ranch Handers are 2.35 and are 1.20 for systemic cancer, with confidence intervals of 1.16 to 4.90, and 0.47 to 3.15 respectively. These broad intervals are due to the small numbers of cancers available for analysis.

The analysis of skin cancer in the Ranch Handers and the original comparisons was repeated with months of agricultural/forestry/fisheries work as a covariable. Seventy-one (6.8%) of the Ranch Handers and 66 (8.5%) of the original comparisons had worked in these occupations; however, these statistical adjustments did not alter the significant difference between the groups. The P value after adjustment remained 0.01. These analyses are as yet incomplete since they have not accounted for the relationship between skin cancer and geographic area of residence or exposure to other potential skin carcinogens. Geographic area of current residence in a mobile military population may not discriminate differences in ultraviolet radiation exposure. An attempt to collect data that will support analyses for geographic and ethnic background will be made at the time of the first follow-up examination.

Three-factor analytic techniques were used to account for the possible confounding effects of the covariables listed above. Exposure to industrial chemicals, degreasing chemicals and smoking habits were not different in the Ranch Hand and comparison groups. The analyses of systemic cancer demonstrated an association between cancer and smoking which approached statistical significance ($P = 0.07$). However, there were no significant differences or suggestive trends between the groups for systemic cancer.

Significant group differential in exposure to x-ray (P <0.001), insecticides (P <0.001), and asbestos (P = 0.05) were also identified. More comparisons than Ranch Handers were exposed to asbestos and x-ray but more Ranch Handers had previously been exposed to insecticides, many during their tours of duty in RVN. Three-way interactions between variables were significant only for the systemic cancer by group by insecticide analysis (P = 0.01) and suggestive for the systemic cancer by asbestos by group analysis (P =0.16). The results of these analyses are displayed in Table X-8.

Table X-8

RESULTS OF THREE-FACTOR LOG-LINEAR ANALYSES OF SYSTEMIC CANCER,
GROUP MEMBERSHIP AND CHEMICAL EXPOSURE (P VALUES)

<u>Exposure</u>	<u>Statistical Relationship</u>			
	Group by Cancer	Group by Exposure	Cancer by Exposure	Cancer by Exposure by Group
Asbestos	0.72	0.04	0.33	0.16
Degreasing Chemicals	0.68	0.33	0.71	0.23
Industrial Chemicals	0.71	0.25	0.34	0.84
Insecticides	0.72	<0.001	0.89	0.01
Smoking	0.50	0.46	0.07	0.53
X-Ray	0.63	<0.001	0.46	0.86

Table X-9

RESULTS OF THREE-FACTOR LOG-LINEAR ANALYSES OF SKIN CANCER,
GROUP MEMBERSHIP AND EXPOSURE (P VALUES)

<u>Exposure</u>	<u>Analysis</u>			
	Group by Cancer	Group by Exposure	Cancer by Exposure	Cancer by Exposure by Group
Asbestos	0.009	0.04	0.24	0.11
Degreasing Chemicals	0.009	0.37	0.20	0.47
Industrial Chemicals	0.009	0.30	0.03	0.58
Insecticides	0.02	<0.001	0.19	0.79
Smoking	0.01	0.44	0.70	0.22
X-Ray	0.008	<0.001	0.86	0.51

As shown in Table X-9, analyses of skin cancers demonstrated a significant difference between the Ranch Hand and the original comparison group that completed physical examination. These data again demonstrate the significant group differential in skin cancer. Even after covariate adjustment (asbestos, industrial chemicals, smoking, x-ray, insecticide and degreasing chemical exposure) the significant group difference in the occurrence of skin cancer remained. Significant between group differentials were noted for x-ray and, asbestos exposure, as previously seen in the systemic cancer analyses. A significant association between skin cancer and exposure to industrial chemicals was found ($P = 0.03$). Associations between the occurrence of skin cancer and exposure to degreasing chemicals and insecticides are also of interest, with suggestive P values of 0.20 and 0.19 respectively.

5. Exposure Index Analyses

The group difference in cancer occurrence was further evaluated using the exposure index, divided into low, medium, and high degrees of exposure. These analyses used only data gathered on the Ranch Hand group. Table X-10 contains the data and results from the basic two-factor analysis (herbicide exposure versus cancer).

Table X-10

HERBICIDE EXPOSURE VERSUS CANCER

<u>Occupational Group</u>	<u>Exposure Level</u>	<u>Systemic Cancer</u>		<u>Skin Cancer</u>	
		<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Flying Officers					
	Low	1	110	7	104
	Medium	1	127	5	123
	High	3	122	8	117
		P = 0.48		P = 0.62	
Flying Enlisted					
	Low	0	59	3	56
	Medium	2	57	1	58
	High	1	65	0	66
		P = 0.35		P = 0.14	
Ground Enlisted					
	Low	2	149	2	149
	Medium	3	176	5	174
	High	0	148	4	144
		P = 0.31		P = 0.63	

These analyses did not reveal a dose-response effect between herbicide exposure and the occurrence of either skin or systemic cancer in the Ranch Hand group; however, the number of cancers within each exposure level are very small. A "suggestive" negative association between herbicide exposure and skin cancer was noted among the enlisted flying group (P = 0.14) with decreasing occurrence of cancer with increasing exposure; however, cell sizes were quite small. Three-factor analysis suggested the presence of interactive effects from insecticide and x-ray exposure, in the flying officers for systemic cancer, and industrial chemicals, degreasing chemicals, and insecticides among the enlisted ground personnel for skin cancer. The results of these analyses are shown in Tables X-11, and X-12, X-13, X-14, and X-15.

Table X-11

THREE-FACTOR ANALYSIS: EXPOSURE, SYSTEMIC CANCER, AND
INSECTICIDE EXPOSURE AMONG FLYING OFFICERS*

<u>Insecticide Exposure</u>	<u>Herbicide Exposure</u>	<u>Systemic Cancer</u>	
		<u>Yes</u>	<u>No</u>
Yes	low	1	74
	medium	1	79
	high	0	72
		P = 0.62	
No	low	0	36
	medium	0	48
	high	3	50
		P = 0.09	

* Three-way interaction P value = 0.10

These data demonstrate confounding by insecticide exposure, with a borderline association between systemic cancer and herbicide (P = 0.09) in the noninsecticide-exposed group of officers. However, the validity of statistical testing in this instance is compromised due to the extremely small number of cases in the analysis. Similarly, this effect is seen with x-ray exposure (Table X-12).

Tables X-13, X-14 and X-15 present the data for the herbicide exposure, cancer, industrial chemical, degreasing chemical and insecticide three-factor analyses for enlisted personnel. Confounding is again seen.

Table X-12

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

<u>X-ray Exposure</u>	<u>Herbicide Exposure</u>	<u>Systemic Cancer</u>	
		<u>Yes</u>	<u>No</u>
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*

<u>Industrial Exposure</u>	<u>Herbicide Exposure</u>	<u>Skin Cancer</u>	
		<u>Yes</u>	<u>No</u>
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*

<u>Degreasing Chemical Exposure</u>	<u>Herbicide Exposure</u>	<u>Skin Cancer</u>	
		<u>Yes</u>	<u>No</u>
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*

<u>Insecticide Exposure</u>	<u>Herbicide Exposure</u>	<u>Skin Cancer</u>	
		<u>Yes</u>	<u>No</u>
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.