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## AIR FORCE COMPLETES SECOND RANCH HAND HEALTH STUDY

The Air Force today released the second health study of its Herbicide Orange study. The study is an investigation of the possible health effects from herbicide exposure of Air Force members who conducted aerial spraying missions in Southeast Asia (Operation Ranch Hand).

Like the initial 1982 study, this follow-up concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and health affects in the Ranch Hand group at this time. A number of minor medical findings have been reported that require continued surveillance.

The Air Force is currently engaged in a collaborative study with the Centers for Disease Control to determine whether blood dioxin levels vary significantly in the Ranch Hand population. Initial serum analysis indicates clear and meaningful dioxin exposure did occur in the Ranch Hand group.

The follow-up study examined 2,309 participants (1,016 Ranch Hands and 1,293 comparisons). It was conducted under contract to the Air Force by Science Applications International Corporation, in conjunction with the Scripps Clinic and Research Foundation and the National Opinion Research Center.

This follow up study marks nearly 9 years of intensive Air Force research into the herbicide health question. Nearly 100 government, academic and industry scientists have guided and contributed to the study since its inception. The current advisory committee, (The Advisory Committee on Special Studies Related to the Possible Long-term Health Effects on Phenoxy Herbicides and Contaminants) comprised of renowned epidemiologists and chaired by Dr. Robert W. Miller of the National Cancer Institute, has reviewed and approved this report.

A detailed report on the study follows.

No significant differences between the Ranch Hand and comparison groups were seen in the 1982-1985 interval for skin or systemic cancers. However, when overall lifetime basal cell carcinoma rates were adjusted for risk factors involved in the cause of such cancers (e.g. sun exposure, skin color, skin reaction to sun), Ranch Hands had a significantly higher proportion of basal cell carcinoma (the most common neoplasm in the white population in the United States) than comparisons. Yet the degree of difference between the two groups is decreasing with the passage of time.

No group differences were observed for systemic cancer, although one soft tissue sarcoma and one suspected lymphoma were noted in the Ranch Hands. Two similar cases were previously found in the comparison group bringing the lifetime total to two of these cancers in each group. Overall, the cancer findings were not viewed as disturbing but as a reason for continued medical surveillance.

The neurological assessment of cranial nerve function, peripheral nerve function, and central nervous system coordination did not reveal any consistently significant group differences. There were fewer neurological abnormalities noted than in the baseline study. Age, alcohol, and diabetes had the medically expected effects on many neurological measures.

There were no group differences for current or past psychological or psychiatric illness. Age, educational level, and alcohol history showed strong and expected effects on the psychological measures.

In evaluating the gastrointestinal and hepatic functions, both groups had an equivalent history of liver disease and ulcers. The follow-up examination disclosed more statistically significant findings for tests of liver function than the Baseline examination, but they were equally divided between the two groups. There were no demonstrated clinical, statistical, or exposure patterns consistent with an herbicide-related health effect. No evidence was found to suggest an increased likelihood of porphyria cutanea tarda in the Ranch Hand group.

In the dermatological assessment, no cases of chloracne were diagnosed on examination, nor was there a history of acne that suggested past chloracne in the Ranch Hand group. Current and past non-malignant skin disease was equivalent in both groups.

Overall, there was similarity in the cardiovascular health between the Ranch Hand and comparison groups. The cardiovascular evaluation showed no significant group differences for reported or verified hypertension, reported heart disease, or reported or verified heart attacks. However, verified heart disease was significantly greater in the Ranch Hands than the Comparisons. This category included a wide variety of cardiac conditions.

Comparisons of the renal, and endocrine systems were very similar. Extensive study of the immune system revealed group equivalence in this important body function.

The pulmonary assessment, consisting of past history, physical examination, and x-ray results did not indicate any consistently different disease patterns in the two groups. Age and lifetime smoking history were important risk factors for most pulmonary measures.

The exposure index analyses, which were specific to each occupation, revealed sporadic differences between exposure levels; however, there were no consistent dose-response relationships that supported an herbicide effect for any clinical area.

These analyses found a subtle but consistent narrowing of medical differences between the Ranch Hands and comparisons since the baseline study in 1962. Continued close medical surveillance of these military populations is strongly indicated. At this time, there is not sufficient plausible or consistent scientific evidence to implicate a causal relationship between herbicide exposure and health effects in the Ranch Hand group.

### Exposure Index Refinements

Since the development of the study protocol and the analysis of the baseline data, there has been concern over the accuracy and validity of herbicide exposure estimates. The current herbicide exposure index is based on an estimate of the gallons of herbicide sprayed per month (1962-1971); the levels of dioxin contamination and the number of men assigned each month. A different index was established for each occupation group. It was recognized that a better method of determining exposure was needed.

In mid 1986, strong correlations between dioxin levels in fat tissue and blood were demonstrated by the Centers for Disease Control (CDC) and other institutions. The Air Force is currently engaged in a collaborative study with the CDC to determine whether serum dioxin levels vary significantly in the Ranch Hand population. Approximately 200 volunteers have supplied a pint of blood for analysis at the CDC laboratories. Initial serum dioxin analysis indicates clear and meaningful exposure did occur in the Ranch Hand group. The range of dioxin exposure in the Ranch Hand group (3-314 parts per trillion) is significantly higher than the control group (3-9 parts per trillion.) A part per trillion is equivalent to one second in 32 thousand years.

It is anticipated that serum dioxin testing will be expanded to all study participants and a more meaningful exposure index based on total current dioxin contamination may be developed for each participant. It may also be possible to calculate a precise half-life of dioxin in humans. These expanded studies will allow the estimation of dioxin in the participants since their departure from Southeast Asia. Study participants are providing blood for this dioxin test during the fifth year follow-up study currently underway.

Within the next two years, another morbidity report, mortality reports, and an expanded birth defects study will be completed. The Air Force Health Study is a planned twenty year research effort, concluding in 2002.

This follow-up morbidity report has been reviewed and approved by the Advisory Committee on Special Studies Related to the Possible Long-Term Health Effects on Phenoxy Herbicides and Contaminants.

# Air Force Health Study

## *An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides*

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## SUMMARY

### First Followup Examination Results

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## INTRODUCTION

### FIRST FOLLOWUP MORBIDITY STUDY

The Air Force Health Study is an epidemiological study conducted to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study consists of mortality and morbidity components, with followup studies. The Baseline study was conducted in 1982, and the first followup physical examinations were performed in 1985. The purpose of this report is to present the results of the first followup study.

In the Baseline study, each living Ranch Hand was matched to the first living and compliant member of a randomly selected Comparison group based on age, race, and military occupation. The Comparisons had served in numerous flying organizations that transported cargo to, from, and within Vietnam but were not involved in the aerial spray operations of Herbicide Orange. Recruitment for the first followup was in accordance with the Study Protocol: All previous participants and refusals, newly located study members, and replacements (matched to noncompliant Comparisons on self-perception of health) were invited. Of the living Baseline study participants, 99.2 percent were contacted to enroll in the followup on a strictly voluntary basis. Participation was very high, with 93 percent of both the Ranch Hands and the Comparisons who were fully compliant at Baseline also participating in the followup. Overall, the 2,309 followup participants (1,016 Ranch Hands and 1,293 Comparisons) represented a loss to the study of 159 individuals but a gain of 199 new participants since Baseline. Statistical analyses of selection and participation bias supported the use of the total Comparison group for the main analyses presented in this report.

The followup study was conducted under contract to the Air Force by Science Applications International Corporation, in conjunction with the Scripps Clinic and Research Foundation and the National Opinion Research Center. Most of the data were collected through face-to-face interviews and physical examinations conducted at the Scripps Clinic in La Jolla, California. Other data sources included medical and military records and the 1982 Baseline data base. As a contract requirement, all data collection personnel were blind to exposure status, and all phases of the study were monitored by stringent quality control. The statistical analyses were based on analysis of variance and covariance, chi-square tests, Fisher's exact tests, general linear models, Kolmogorov-Smirnov tests, logistic regression, proportional odds models, t-tests, and log-linear models.

The release of this 1987 followup Morbidity Report marks more than 8 1/2 years of intensive Air Force research in the herbicide question. Since the commitment to Congress in October 1978 to conduct an epidemiologic investigation of Air Force personnel who aerially disseminated herbicides in the Vietnam War (code-named Operation Ranch Hand), the United States Air Force Surgeon General has issued the following publications: a Study Protocol, four annual mortality reports, the Baseline Morbidity Report, and this first followup morbidity report. Within the next 2 years, the second followup morbidity report, other annual mortality reports, and an expanded birth defects study are expected for publication. This level of commitment has used approximately \$40 million of contract research funds, excluding significant Air Force in-house expenditures.

Nearly 100 Government, academic, and industry scientists have guided and contributed to the Air Force Health Study (AFHS) since its inception. The Air Force's current advisory committee, chaired by Dr Robert W. Miller of the National Cancer Institute, is responsible for providing assistance on all scientific and medical matters pertaining to the AFHS.

The chief strength of the AFHS is its design. The interwoven study elements of multiple mortality assessments, a Baseline morbidity study, and five followup morbidity studies over 20 years provide a comprehensive approach to the detection of adverse health effects. The weakest feature of the design is the mortality assessment which cannot detect group differences for very rare conditions (e.g., soft tissue sarcoma) because of the inherent constraints of the limited size of the population. The strength of the mortality studies should increase with the aging of the study populations and the increase in death with the passage of time.

All four mortality assessments have shown that the Ranch Hand population is faring about the same as the Comparison group, with no unusual causes of death, increased frequency of death, or evidence suggesting death at younger ages. Because of the healthy veteran effect, both groups are surviving significantly longer than similarly aged civilians. The morbidity assessment, released in 1984, disclosed only minor differences between the Ranch Hands and the Comparisons, and these differences were not traditional indicators of dioxin-related disease. Both the content and the progress of the AFHS has been presented on many occasions to Congress, to the media, and to scientific meetings around the world. On the whole, the AFHS has been very well received in these circles, giving additional strength and credence to this work.

The questionnaire and physical examination data were analyzed by major organ system. The primary focus was on the assessment of differences between the Ranch Hand and Comparison groups based on data from the first followup. Additionally, dose-response relationships within the Ranch Hand group were examined, and longitudinal assessments of differences in the changes of the two groups between the examinations were conducted for selected variables. Reported significant findings in subsequent major organ systems are understood to be significant at the 0.05 level or less.

## GENERAL HEALTH

General physical health was evaluated by five measures, three of which were subjective (self-perception of health, appearance of distress, and appearance of relative age), and two of which were objective (percent body fat and sedimentation rate). Table 1 presents a summary of all the unadjusted and adjusted analyses of these five variables.

The mean age of the Ranch Hands was 46.9 years and the comparisons mean age was 46.8 years. The Ranch Hands rated their health as fair or poor more often than the Comparisons (9.1% versus 7.3%, respectively), but this difference was not significant by categorical testing. However, further analysis revealed a significant group-by-occupation interaction; differences were largely confined to the enlisted groundcrew category. Both the Ranch Hand and Comparison groups noticeably improved their perceptions of health since the 1982 Baseline examination.

Only 10 individuals were reported as appearing acutely ill or distressed at the followup examination, 4 were Ranch Hands and 6 were Comparisons. This difference was not statistically significant and the data were insufficient for adjusted analyses.

TABLE 1.  
Overall Summary Results of Unadjusted and Adjusted  
Analyses of General Health Variables

Variable	Unadjusted		Adjusted	
	Categorical	Mean	Categorical	Mean
Self-Perception of Health	NS	--	****	--
Appearance of Illness/Disstress	NS	--	--*	--
Appearance of Relative Age	NS	--	****	--
Sedimentation Rate	0.013	NS	0.011	NS
Percent Body Fat	NS	0.037	NS	0.035

--Analysis not performed.

\*\*\*\*Group-by-covariate interaction.

\*Analysis not possible due to sparse data.

Appearance of relative age, as determined by the examining physician, showed 1.6 percent of the Ranch Hands appearing younger than their stated age, 94.3 percent appearing the same, and 4.1 percent appearing older (as contrasted to 0.7%, 95.4%, and 3.9%, respectively, in the Comparison group). There was a significant group-by-occupational interaction, but none of the estimated relative risks for the occupational categories was significant. This observation at the followup examination contrasted with the significant tendency at the Baseline for a higher percentage of Ranch Hands than Comparisons to appear younger than their stated ages.

The geometric mean sedimentation rates (5.05 mm/hr Ranch Hand versus 4.93 mm/hr Comparison) did not differ significantly by group, either unadjusted or after adjustment for age, race, occupation, personality score, and an age-by-personality score interaction. However, in the dichotomous form, 5.8 percent of the Ranch Hands had sedimentation rate abnormalities as contrasted to 3.6 percent in the Comparison group. This difference was significant by

both unadjusted and adjusted tests. Also, this finding was opposite to that of the Baseline examination, where it was noted that younger Comparisons had significantly elevated sedimentation rates.

The mean percent body fat of the Ranch Hands was significantly lower than the Comparisons (21.10%±0.15, 21.54%±0.14, respectively,  $p=0.037$ ), and was of nearly the same magnitude after adjustment for age, race, and occupation. However, both unadjusted and adjusted categorical tests did not reveal significant group differences, although the percent obese was lower in the Ranch Hands than in the Comparisons. No group differences in percent body fat were noted at the Baseline examination.

Detailed exposure analyses were done on four general health variables (appearance of acute distress was too sparse for testing). Only one analysis demonstrated statistical significance, i.e., a positive association of sedimentation rate abnormalities with increasing exposure in the enlisted flyer cohort. Overall, no consistent pattern of exposure effects was discernible, and the exposure findings at the third-year followup were similar to the findings at Baseline.

Longitudinal differences between the 1982 Baseline and the 1985 followup examination were assessed by analyses of two discrete variables, self-perception of health and sedimentation rate. Perceived health showed no significant group differences over time, but both the Ranch Hand and Comparison groups paradoxically reported symmetrical improvements in their perceptions over the 3-year period. The sedimentation rate analysis revealed a highly significant group difference ( $p=0.002$ ), due to a reversal of findings between examinations, i.e., a significant detriment in the younger Comparisons at the Baseline versus a significant detriment in the Ranch Hands at the followup. The cause(s) and biological relevance of this observation are unclear.

In conclusion, a nonspecific assessment of general physical health has shown relatively close similarity between the Ranch Hand and Comparison groups, with the Ranch Hands continuing to perceive their health more negatively than the Comparisons, having a slightly more favorable percent body-fat proportion, but a higher proportion of abnormal sedimentation rates that reflects a marked change since the Baseline examination. These findings must be placed in context with the organ and system-specific evaluations found in the succeeding chapters.

## MALIGNANCY

The cancer analysis focused on cancer occurrences in the Baseline-followup interval, and also included analyses of the Baseline plus interval cancer history. A listing of systemic malignancies occurring in the study participants is shown in table 2 and a summary of the cancer findings is given in Table 3.

No significant unadjusted differences were found between nonblack Ranch Hands and Comparisons in the Interval (Baseline-Followup) incidence rates of basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin cancers, sun-exposure related malignant neoplasms (comprising basal cell carcinoma, melanoma, and epithelial neoplasms NOS) or all malignant skin cancers as a group. The unadjusted group contrast of all skin neoplasms

TABLE 2.

**Summary of Followup Participants With Lifetime  
Incidence of Verified Malignant Systemic Neoplasms by Group**

Site	Group		Total
	Ranch Hand	Comparison	
Eye	1	0	1
Oral Cavity and Pharynx	3 <sup>a, b</sup>	0	3
Larynx	0	1	1
Thyroid Gland	0	2	2
Esophagus	0	1 <sup>c</sup>	1
Bronchus and Lung	2	0	1
Colon	0	5 <sup>d, e</sup>	5
Kidney and Bladder	4	3	7
Prostate	2	2	4
Testicles	3	0	3
Connective and Other Soft Tissue	1	1	2
Hodgkin's Disease	0	1	1
Ill-Defined Sites	1 <sup>f</sup>	1 <sup>g</sup>	2
<b>Total</b>	<b>17</b>	<b>17</b>	<b>34</b>

<sup>a</sup>Includes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

<sup>b</sup>Includes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

<sup>c</sup>Also has malignant neoplasm of bone.

<sup>d</sup>Includes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

<sup>e</sup>Includes one Comparison with secondary malignant neoplasm of liver.

<sup>f</sup>Malignant neoplasm of thorax.

<sup>g</sup>Malignant neoplasm of face, head, or neck.

TABLE 3.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval  
and Lifetime Skin and Systemic Cancer Incidence

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
<u>Malignant Skin Cancer (Nonblacks only)</u>				
Verified Basal Cell Carcinoma	NS	****	NS	S
Verified plus Suspected Basal Cell Carcinoma	NS	****	NS	****
Verified Melanoma	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified plus Suspected Melanoma	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified Squamous Cell Carcinoma	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified plus Suspected Squamous Cell Carcinoma	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified Sun Exposure Skin Cancers	NS	NS	NS*	S
Verified plus Suspected Sun Exposure Skin Cancers	NS	NS	NS	NS
All Verified Malignant Skin Cancers	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified plus Suspected Malignant Skin Cancers	NS	-- <sup>a</sup>	NS	-- <sup>a</sup>
Verified Skin Cancers of Any Type	NS*	--	S	--
Verified plus Suspected Skin Cancers of Any Type	NS	--	NS*	--

TABLE 3.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval  
and Lifetime Skin and Systemic Cancer Incidence (continued)

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
<u>Malignant Systemic Cancer (Blacks and Nonblacks)</u>				
Verified Systemic Cancer	NS	NS	NS	****
Verified plus Suspected Systemic Cancer	NS	****	NS	****
<u>All Neoplasms (Blacks and Nonblacks)</u>				
Any Type, Any Location <sup>b</sup> Verified	NS*	-- <sup>a</sup>	S	-- <sup>a</sup>

NS: Not significant ( $p > 0.10$ ).

\*\*\*\*Group-by-covariate Interaction.

--<sup>a</sup>Analysis not done.

NS\*: Borderline significant ( $0.05 < p \leq 0.10$ ).

<sup>b</sup>Comprises malignant, benign, uncertain behavior.

S: Significant ( $p \leq 0.05$ ).

(comprising malignant and benign neoplasms, and neoplasms of uncertain behavior or unspecified nature) was marginally significant, with a higher rate among Ranch Hands. When suspected malignant skin cancers (noted at Followup but not verified at the time of writing) were included in the analyses with the verified conditions, all the unadjusted group contrasts were nonsignificant.

The covariates used for the adjusted analyses of basal cell carcinoma and the sun exposure related skin malignancies were age, occupation, skin color, reaction of skin to sun, and average latitude, all of which were highly associated with skin cancer incidence. Other host factors were related to skin cancer incidence, but not as strongly as those included in the analysis. A borderline association with smoking history was noted, and was determined to be partly an age effect.

Analysis of the incidence of interval basal cell carcinoma revealed a significant group-by-occupation interaction, due to a significant group difference for enlisted flyers, but not for officers or enlisted groundcrew. Inclusion of suspected basal cell carcinoma resulted in a group-by-sun reaction index interaction. This was due to Ranch Hands with an intermediate reaction to sun having a higher relative risk than the corresponding Comparisons. The adjusted group contrast of the incidence rates of verified sun-exposure related skin cancers was not significant; inclusion of suspected conditions did not alter this lack of significance.

There was no significant group difference for Blacks and nonblacks in the unadjusted incidence rates of all interval verified malignant systemic neoplasms combined, nor was there a significant difference in the adjusted group rates. Analysis of the verified plus suspected interval systemic cancers showed a nonsignificant unadjusted group difference, but a group by occupation interaction was found in the adjusted analysis. This was due to a significant group difference of verified plus suspected systemic malignancies among the enlisted flyers with five occurrences among the Ranch Hands, but none among the Comparisons. Age and a race-by-packyear interaction were important adjusting factors.

The Baseline and Followup data were combined for the assessment of lifetime incidence of cancer; occurrences of cancer prior to Vietnam were excluded.

There were no significant unadjusted group differences in lifetime incidence rates among nonblacks for basal cell carcinoma, melanoma, squamous cell carcinoma, the sun-exposure related skin cancers, or all malignant skin cancers combined. The unadjusted group contrast of all lifetime skin malignancies was significant, with a higher rate among Ranch Hands. Inclusion of suspected cancers with the verified cancers reduced the difference between the groups for all these malignant skin contrasts, except for the sun-exposure related skin cancers, for which a marginally significant group difference was found. However, the contrast of all skin malignancies remained close to significance.

Adjusted analysis of the incidence rates of lifetime basal cell carcinoma revealed a significantly higher incidence rate among Ranch Hands (Adj. RR: 1.56,  $p=0.035$ ). Significant effects of an occupation-by-age interaction, a

skin color-by-sun reaction index interaction, and a sun reaction index-by-average residential latitude interaction were seen. The adjustment resulted in a significant relative risk that, moreover, was higher than the unadjusted relative risk. Average residential latitude, associated with both group and skin cancer, and skin color, which was associated with the disease and marginally associated with group, played a major part in the change from the unadjusted analysis due to confounding. Inclusion of suspected basal cell carcinoma in the adjusted analysis resulted in a group by sun reaction index interaction, as was noted for the interval analysis.

The adjusted group contrast in incidence rates of the sun-exposure related skin cancers was also significant (Adj. RR: 1.54,  $p=0.030$ ), which is not surprising since the majority are basal cell carcinoma. Inclusion of the suspected conditions resulted in a nonsignificant group contrast.

The unadjusted group contrasts of the incidence rates of all systemic cancers combined were not significant, both for verified and verified plus suspected conditions.

There was one new occurrence of a soft tissue sarcoma (Ranch Hand) and one suspected cancer of the lymphatic system (Ranch Hand), in addition to the one previously reported soft tissue sarcoma and one Hodgkin's disease in the Comparison group.

Adjusted analysis of all lifetime malignant systemic neoplasms as a group, however, revealed a group by occupation interaction, due to a significantly higher rate for Ranch Hand enlisted flyers as contrasted to Comparisons. The same result was found for verified plus suspected systemic cancers.

In conclusion, there were no adjusted or unadjusted differences between groups in basal cell carcinoma incidence in the Baseline-followup interval. At Baseline, a significantly higher rate of basal cell carcinoma was found for Ranch Hands when contrasted with Original Comparisons. When the Baseline data were combined with the interval data, adjusted analysis, but not the unadjusted analysis, revealed a significantly higher rate of basal cell carcinoma among the Ranch Hands than among all Comparisons. The relative risk of basal cell carcinoma appears to be declining over time.

Relative risks of basal cell carcinoma and systemic cancer were found to be consistently larger than 1. Most of the skin cancers were basal cell carcinomas, upon which most of the skin cancer analysis focused, thus relative risks for sun-exposure related skin neoplasms and all malignant skin cancers as a group were very similar to those for basal cell carcinoma. The number of occurrences of systemic cancer was small, in part because the cohort is relatively young, and although the relative risks (lifetime and interval) are greater than 1, the difference between groups is not significant. Sufficient time may not have elapsed since Vietnam to enable a group difference in systemic neoplasms, if one exists, to be apparent.

## NEUROLOGY

Interval questionnaire data (1982 through 1985) on neurological illnesses, verified by medical records, revealed no significant group differences. These data were added to verified Baseline historical information to

assess possible differences in the lifetime experience of neurological disease. Again, there was no significant difference between the Ranch Hand and Comparison groups.

A detailed neurological examination evaluated neurological integrity in three broad areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) coordination. The summary analytic results for all measurement variables comprising these three functional areas are presented in Table 4.

Assessment of the 12 cranial nerves was based on the measurement of 14 variables. Two summary indices were constructed. Both the unadjusted and adjusted analyses did not disclose any statistically significant group differences, although two variables, speech and tongue position, were of borderline significance, with Ranch Hands faring worse than Comparisons. One of the two cranial nerve summary indices was marginally significant, again with the Ranch Hands at a slight detriment.

The unadjusted and adjusted analyses of peripheral nerve function, as measured by eight variables (four reflexes, three sensory determinations, and muscle mass), did not reveal significant group differences.

CNS coordination was evaluated by four measurements and a constructed summary variable. Hand tremor was found to be of borderline significance, with the Ranch hands faring slightly worse than the Comparisons. The CNS summary index showed a significant detriment to the Ranch Hands.

The exposure analyses for neurological variables with reasonable counts of abnormalities showed only occasional statistically significant results. No consistent pattern with increasing exposure was evident for any occupational category of the Ranch Hand group.

In a longitudinal analysis of the Romberg sign and the Babinski reflex, only the Babinski reflex revealed a significant difference between the Baseline and followup examination, with the Ranch Hands converting from significant adverse findings at Baseline to favorable nonsignificant findings at the followup examination.

Overall, the followup examination findings are quite similar to the Baseline findings. However, several distinct patterns were evident from the analyses: (1) The followup examination detected substantially fewer abnormalities for almost all measurement variables, (2) the decrease in abnormalities was equivalent in both groups, (3) most of the covariate effects were classical, although exceptions were evident, (4) the adjusted analyses were uniformly similar to the unadjusted analyses, (5) the constructed summary variables were generally statistically significant, or of borderline significance (however, some indices were created after the data were examined), and (6) although statistical significance at the pre-assigned  $\alpha$ -level of 0.05 was not achieved for any of the measurement variables, abnormalities tended to cluster in the Ranch Hand group.

Of the three group-by-covariate interactions in the adjusted analyses, only one, a borderline group-by-insecticide exposure interaction for hand tremor, where Ranch Hands exposed to insecticides had a marginally significant adverse effect, was of probable biologic (and operational) significance.

TABLE 4.

**Overall Summary Results of Unadjusted  
and Adjusted Analyses of Neurological Variables**

Variable	Unadjusted	Adjusted	Direction of Results**
<u>Questionnaire* Physical Examination</u>			
Neurological Disease (Interval)	NS <sup>b</sup>	--	
Neurological Disease (History)	NS	--	
<u>Cranial Nerve Function</u>			
Smell	NS	--	
Visual Fields	NS	--	
Light Reaction	NS	--	
Ocular Movements	NS	--	
Facial Sensation	NS	--	
Corneal Reflex	-- <sup>c</sup>	-- <sup>c</sup>	
Jaw Clench	NS	--	
Smile	NS	--	
Palpebral Fissures	NS	--	
Balance	NS	--	
Gag Reflex	NS	--	
Speech	NS*	--	RH>C
Tongue Position Relative to Midline	NS*	--	RH>C
Palate and Uvula Movement	NS	--	
Neck Range of Motion	NS	NS	
Cranial Nerve Function Index <sup>d</sup>	NS	NS	
Cranial Nerve Function Index <sup>d</sup> (excluding Neck Range of Motion)	NS*	NS*	RH>C
<u>Peripheral Nerve Function</u>			
Pin Prick	NS	****	
Light Touch	NS	NS	
Muscle Status	NS	NS	
Vibratory Sensation	NS	--	
Patellar Reflex	NS	--	
Achilles Reflex	NS	NS	
Biceps Reflex	NS	--	
Babinski Reflex	NS	--	

TABLE 4. (Continued)

Overall Summary Results of Unadjusted  
and Adjusted Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results**
<u>Central Nervous System Coordination</u>			
Tremor	NS*	NS*	RH>C
Coordination	NS	--	
Romberg Sign	NS	--	
Gait	NS	NS	
CNS Summary Index <sup>d</sup>	0.036	0.042	RH>C

\*\*RH>C: More abnormalities in Ranch Hand group than in Comparison group.

<sup>a</sup>Disease categories include: inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, disorders of the eye, disorders of the ear, and other disorders.

NS: Not significant ( $p > 0.10$ ).

<sup>b</sup>No inflammatory diseases noted; borderline significant ( $p = 0.069$ , RH>C) for other disorders; not significant for remaining categories.

--Analysis not performed because of sparse number of abnormalities.

<sup>c</sup>No abnormalities present.

NS\*Borderline significant ( $0.05 < p \leq 0.10$ ).

<sup>d</sup>Constructed variable.

\*\*\*\*Group-by-covariate interaction.

In conclusion, none of the 27 neurological variables demonstrated a significant group difference, although several showed an aggregation of abnormalities in the Ranch Hand group, which merits continued surveillance. Historical reporting of neurologic disease was equal in both groups. The clinical sensitivity in detecting neurological deficits varied substantially between the Baseline and the followup examinations, but the number of statistically significant variables remained about the same. None of the exposure analyses revealed dose-response patterns in the Ranch Hand occupational categories. The longitudinal analyses disclosed a favorable reversal of significant Babinski reflex abnormalities at Baseline to nonsignificant findings at the followup examination for the Ranch Hands. The similarity in results between unadjusted and adjusted statistical tests is evidence of group equality for the traditionally important neurological covariates of age, alcohol, and diabetes. Of three group-by-covariate interactions in the adjusted analyses, only the Ranch Hand insecticide interaction with hand tremor was biologically plausible.

## PSYCHOLOGY

Questionnaire data (verified by medical record reviews) for the lifetime events of psychotic illness, alcohol dependence, anxiety, or other neuroses disclosed no significant differences between groups for these conditions. (Table 5).

**TABLE 5**      **Distribution of Reported Psychological Illness**  
**By Group - Baseline and Followup Studies Combined**

Type of Illness	Abnormalities				Total	p-Value*
	Ranch Hands		Comparisons			
	Number	Percent	Number	Percent		
Psychoses	14	1.4	9	0.7	23	0.138
Alcohol Dependence	9	0.9	8	0.6	17	0.473
Anxiety	7	0.7	13	1.0	20	0.501
Other Neuroses	72	7.1	74	5.7	146	0.197

\*Fisher's Exact Test

Analyses of the followup psychological examination emphasized 14 scales from the Minnesota Multiphasic Personality Inventory (MMPI), 3 parameters of the Cornell Medical Index (CMI), and the Halstead-Reitan Battery (HRB) impairment index.

The similarity of the group distribution for the 14 MMPI variables, each stratified by the 3 occupational categories, was examined, and only 2 of the 42 tests approached statistical significance. The group distributions of the total CMI score were similarly contrasted, with separate analyses performed with stratification by the five covariates of age, race, occupation, education, and current drinking status. For one stratum of each of these covariates, a significant difference in the distribution of the Ranch Hand and Comparison scores was found. In all cases for the CMI, the Ranch Hand mean was greater than the Comparison mean. Distributional analyses using Original Comparisons generally reflected the same results as those involving the total Comparison group.

Results of unadjusted and adjusted analyses on all of the 18 psychological variables are given in Table 6.

The unadjusted analyses showed a significant difference for the MMPI scales of denial ( $p < 0.001$ ) and masculinity/femininity ( $p = 0.017$ ), the total CMI ( $p < 0.001$ ), and the Section A-H area subscore ( $p = 0.003$ ). A borderline significant difference was observed for the MMPI scales of hysteria ( $p = 0.067$ ) and social introversion ( $p = 0.069$ ). Comparisons had a greater percentage of abnormal scores for the denial and masculinity/femininity scales, whereas Ranch Hands showed adverse findings for the other four variables. The overall MMPI results have been interpreted in light of the significant increased denial in the Comparison group.

The covariates age, education, drink-years, current alcohol use, and occupation had pronounced effects on the psychological variables, with a significant association or a borderline significant association with at least two-thirds of the 18 psychological variables. Many dependent variables in this chapter were affected by age in an expected pattern. Very few variables exhibited this pattern of consistency with drink-years. The intermediate category of greater than 0 to 50 drink-years often had the smallest proportion of abnormalities. The post-traumatic stress disorder (PTSD) variable, derived from a subset of the MMPI, was strongly associated with the CMI measures, but not with the HRB Impairment Index. Race and the Vietnam combat index (used for the MMPI subscales) had significant associations with a lesser amount of the psychological variables (6 of 18 variables and 3 of 14 variables, for race and combat index, respectively).

The adjusted analyses were generally quite similar to the unadjusted analyses with respect to group differences, although a direct comparison of these analyses was often clouded by the presence of a substantial number of interactions (six group-by-covariate interactions were significant, and three interactions approached significance [ $0.05 < p < 0.10$ ]). The MMPI scales of denial and masculinity/femininity were statistically significant in both the adjusted and unadjusted analyses, where Comparisons showed an adverse effect over Ranch Hands. The A-H area subscore of the CMI (suggesting diffuse medical problems) was also significant, where the Ranch Hands had higher mean scores than the Comparisons, suggesting the Ranch Hands had more illness. Education was often involved in significant group interactions with high

TABLE 6.

**Overall Summary Results of Adjusted and Unadjusted  
Analyses of Psychological Variables**

Variable	Unadjusted	Adjusted	Direction of Results <sup>a</sup>
<u>Questionnaire:</u>			
Psychological Illness	NS	--	
<u>Psychological Examination:</u>			
<u>MMPI</u>			
Anxiety	NS	NS	
Consistency	NS	****	
Defensiveness	NS	NS	
Denial	<0.001	<0.001	C>RH
Depression	NS	NS	
Hypochondria	NS	NS	
Hysteria	NS* <sup>b</sup>	NS* <sup>b</sup>	RH>C
Mania/Hypomania	NS	NS	
Masculinity/Femininity	0.017	0.020	C>RH
Paranoia	NS	****	
Psychopathic/Deviate	NS	NS	
Schizophrenia	NS	****	
Social Introversion	NS* <sup>b</sup>	****	RH>C
Validity	NS	****	
<u>CMI</u>			
Total CMI	<0.001	****	RH>C
M-R Subscore	NS	NS	
A-H Area Subscore	0.003	0.040	RH>C
<u>HRB</u>			
Impairment Index	NS	NS	

<sup>a</sup>RH>C - more abnormalities in Ranch Hands; C>RH - more abnormalities in Comparisons.

<sup>b</sup>Illnesses include psychosis, alcohol dependence, anxiety, and other neuroses.

--Analysis not performed.

NS: Not significant.

NS\*: Borderline significant ( $0.05 < p < 0.10$ ).

\*\*\*\*Interaction involving group.

school-educated Ranch Hands demonstrating a higher percentage of abnormal scores than high school-educated Comparisons. No group differences were observed in the college-educated stratum. The M-R subscore of the CMI, a broad indicator of emotional health, was not statistically different between the two groups.

The HRB impairment index, a measure of central nervous system (CNS) functional integrity, did not differ significantly between the Ranch Hand and Comparison groups. Strong covariates in the adjusted analysis were age, race, and education.

Because of alternate statistical models and slightly different psychological testing parameters, a direct contrast between the psychological results of the Baseline and followup examinations was not always possible. However, several broad patterns were observed: (1) the discordance between distributional tests and results from traditional statistical models of the MMPI variables was noted with data from both examinations; (2) there was a narrowing of group differences at the followup examination for most subjective variables, either by a decrease in Ranch Hand reporting, or by an increase in Comparison reporting; and (3) as at the Baseline, functional CNS testing, as measured by the HRB impairment index, showed no group differences, and did not support an organic basis for differences in self-reported symptomatology. The longitudinal analysis of two MMPI scales, depression and denial, showed a significant reversal of depression seen at Baseline in the high school-educated Ranch Hands.

The determination of PTSD in both Air Force cohorts by a relatively new MMPI scale showed a prevalence rate of less than 1 percent. This low rate is strongly influenced by characteristics of the study population (e.g., age, education, and officer ratio).

Unadjusted exposure index analyses did not reveal any patterns consistent with a dose-response relationship. For the adjusted exposure analyses, approximately one-third presented exposure interactions with the covariates of race, education, and age, but no consistent pattern could be identified.

In conclusion, some test measures of psychological health (MMPI and CMI) did not show substantial adverse effects for either group. Significant test results were present in both groups or were noted in specific subgroups of a covariate. Educational level, age, and alcohol use showed strong effects on the psychological scales and scores in this psychological assessment. There was a subtle but consistent trend for more favorable subjective test results at the followup examination for the Ranch Hands relative to the Comparisons. Testing of the CNS by the HRB demonstrated an almost identical prevalence of pathology in both groups.

#### DIGESTIVE SYSTEM

The interval questionnaire revealed sparse reporting of liver disorders from 1982 to 1985 that was not significantly different between groups. Historical liver disease was verified by medical records, and these data were added to the verified Baseline history to assess possible lifetime differences. No significant differences were found. The medical record verifica-

tion process showed that the historical data were generally correctly reported and classified between groups, except for the category of enlarged liver which showed a higher verification rate in the Comparison group.

Digestive system mortality showed an overall nonsignificant excess in the Ranch Hands, but a relative nonsignificant excess of malignant neoplasms in the Comparisons.

No differences were found for past or current peptic ulcer disease for the Ranch Hand and Comparison groups, adjusted for standard covariates as well as blood type.

The physical examination disclosed a borderline significant increase of hepatomegaly in the Ranch Hand group. Emphasis was placed on nine laboratory test variables measuring liver function, i.e., serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), gammaglutamyl transpeptidase (GGTP), alkaline phosphatase, total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, and triglycerides. In addition, uroporphyrin and coproporphyrin measurements were obtained to assess liver function and the likelihood of porphyria cutanea tarda (PCT). The nine hepatic variables were subjected to continuous and categorical statistical tests, and were adjusted for the covariates age, race, occupation, current alcohol consumption, and unprotected exposure to both industrial chemicals and degreasing chemicals. Final statistical models used only the significant covariates and two-way interactions for adjustment. The two porphyrin measurements were analyzed only in the continuous form. The overall summary results of the analyses of these 11 variables are given in Table 7.

The results showed a significantly lower mean SGPT level, a greater mean alkaline phosphatase level, a lower mean uroporphyrin level for Ranch Hands as contrasted with Comparisons, and a marginally significant greater mean coproporphyrin level. Only in the instance of alkaline phosphatase did the discrete analysis approach statistical significance. No group differences were noted for SGOT, GGTP, total and direct bilirubin, LDH, cholesterol, or triglycerides. However, an analysis using only the Original Comparisons revealed a significantly greater mean cholesterol level in the Comparison group. A review of the covariate effects in the adjusted statistical models revealed that all covariates behaved as expected with the exception of alcohol consumption for the alkaline phosphatase analysis, which showed an inverse relationship with wine consumption.

Exploration of group-by-group covariate interactions for alkaline phosphatase, direct bilirubin, triglycerides, SGOT, and uroporphyrins revealed significant group differences within specific covariate strata. In particular, Ranch Hands exposed to industrial chemicals had a significantly higher adjusted mean level of alkaline phosphatase and a significantly higher abnormal prevalence rate of direct bilirubin than similarly exposed Comparisons. For triglycerides, Ranch Hands born in or before 1922 had a significantly higher adjusted mean level than similar aged Comparisons, while Ranch Hand officers exhibited a significantly higher abnormal prevalence rate than Comparison officers. For SGOT, Ranch Hand moderate current drinkers (more than one to four drinks per day) had a significantly higher mean level than corresponding Comparisons. In the opposite direction, Comparisons with a mean BUN level less than or equal to 14 (median participants) were found to have a

TABLE 7.

**Overall Summary Results of Unadjusted  
and Adjusted Analyses of Nine Hepatic Function Variables  
and Two Porphyrin Metabolite Tests**

Variable	Unadjusted		Adjusted*			Direction of Results**
	Mean	Categorical	Mean		Categorical	
			CC	CD		
<u>Questionnaire</u>						
<u>Liver Disease</u> (Lifetime History)						
Hepatitis	--	NS	--	--	--	
Jaundice	--	NS	--	--	--	
Cirrhosis	--	NS	--	--	--	
Enlarged Liver	--	NS	--	--	--	
Miscellaneous Liver Disorders	--	NS	--	--	--	
Peptic Ulcer Disease	--	NS	--	--	NS <sup>a</sup>	
<u>Physical Examination</u>						
Hepatomegaly	--	NS*	--	--	--	RH>C
<u>Laboratory Testing</u>						
SGOT	NS	NS	NS	****	NS	
SGPT	NS*	NS	0.048	0.029	NS	C>RH
GGTP	NS	NS	NS	NS	NS	
Alkaline Phosphate	0.009	NS	0.008	****	NS*	RH>C
Total Bilirubin	NS	NS	NS	NS	NS	
Direct Bilirubin	NS	NS	NS	NS	****	
LDH	NS	NS	****	NS	NS	
Cholesterol	NS	NS	NS	NS	NS	
Triglycerides	NS	NS	****	NS	****	
Uroporphyrin	0.048	--	****	--	--	C>RH
Coproporphyrin	NS*	--	NS*	--	--	RH>C
<u>Questionnaire-Laboratory Correlation</u>						
Skin Bruises, Patches, and Sensitivity	--	0.001	--	--	--	RH>C

\*C: Continuous

D: Discrete

\*\*RH&gt;C: more abnormalities, or higher mean value, in Ranch Hands.

C&gt;RH: more abnormalities, or higher mean value, in Comparisons.

<sup>a</sup>Adjusted for blood type.NS: Not significant ( $p > 0.10$ ).NS\*: Borderline significant ( $0.05 < p \leq 0.10$ ).

--Analysis not performed.

\*\*\*\*Group-by-covariate interaction.

significantly higher adjusted mean uroporphyrin level than similar Ranch Hands. These results did not disclose any common pattern detrimental to the Ranch Hand group.

These findings were generally consistent with the 1982 Baseline data, which disclosed a significantly increased mean cholesterol level in the Comparisons and nonsignificant Ranch Hand mean elevations for GGTP and LDH. Slight differences in analytic results are probably due to the use of more fully adjusted models used for the followup examination data.

Overall, the followup examination laboratory data showed no adverse clinical or exposure patterns in either group. Further, the detection of significant mean shifts (still within normal range) by the continuous statistical tests, not mirrored by the categorical tests, suggests a circumstance of statistical power rather than findings of biological relevance.

Of the five significant or marginally significant results that were found in the adjusted exposure index analyses, four exhibited a trend suggestive of an increasing dose-response relationship. In the enlisted flyer cohort, the percentages of SGPT abnormalities were significantly different and increased from the low to the high exposure categories. The corresponding mean values were marginally significantly different among exposure levels. Also, the mean levels of total bilirubin were marginally significantly different among exposure levels, increasing with exposure level. For enlisted groundcrew, the percentage of SGOT abnormalities significantly differed among exposure levels. Within the enlisted flyer cohort, all nine laboratory tests of hepatic function had the lowest percentage of abnormalities in the low exposure category; correspondingly, six of the nine mean levels were lowest for the low exposure category. Of the ten group-by-covariate interactions that were found, three (SGOT, SGPT, and GGTP) supported a dose-response relationship in the enlisted groundcrew cohort. Exploration of these interactions revealed a trend that showed an increasing association between current alcohol consumption and the dependent variables for increasing exposure levels.

Longitudinal analyses for SGOT, SGPT, and GGTP disclosed no statistically significant group differences in the mean shifts from the Baseline to the followup examination.

Interval reporting of PCT-like symptoms of skin patches, bruises, and sensitivity was significantly increased in the Ranch Hands ( $p=0.001$ ). However, when these historic data were contrasted to both uroporphyrin and coproporphyrin abnormalities, no correlation was apparent, nor were there any significant group differences. Since an elevation in the uroporphyrin level is required for a diagnosis of PCT, the historic data were retabulated with only uroporphyrin abnormalities; again, no group differences were apparent, and, in fact, uroporphyrin abnormalities in both groups were higher in those participants without a history of skin disorders than in those participants with such a history. The likelihood of bona fide PCT among study participants, and particularly among the Ranch Hands, appears to be remote.

In conclusion, the followup examination disclosed more statistically significant findings for tests of liver function than the Baseline examination, but they were equally divided between the two groups and did not demon-

strate clinical, statistical, or exposure patterns consistent with an herbicide-related effect on health. No evidence was found to suggest an increased likelihood of PCT among the Ranch Hand group.

## DERMATOLOGY

Interval questionnaire data on the occurrence, time, and location of acne were analyzed to assess the possible historical diagnosis of chloracne. No significant difference was observed between groups for reported occurrence of acne, although the Ranch Hand cohort reported slightly more acne. The occurrence of acne relative to 1961 was comparable between groups. A marginally significant difference in the occurrence of post-1961 acne was found, with more Ranch Hands than Comparisons reporting acne strictly post-SEA. The duration of post-1961 acne was not significantly different between the two groups.

For participants with post-SEA acne, the spatial eyeglass distribution of acne (suggesting chloracne) was observed to be similar for the Ranch Hand and Comparison groups, both for individual sites and the combination of acne on the eyelids, ears, and temples. This analysis suggested that the occurrence of skin disease compatible with chloracne was not different in the two groups.

Analyses of the followup physical examination data, as with the Baseline examination, placed primary emphasis on six dermatologic disorders: comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation. Secondary emphasis was given to 16 other minor conditions (generally not associated with chloracne) recorded at the physical examination. No significant findings occurred in any variable, as reflected in Table 8.

No significant difference was found for any of these variables in the unadjusted analyses. The variable consisting of the 16 secondary conditions, labeled "other abnormalities," had the largest difference in the prevalence of abnormalities for the Ranch Hand cohort over the Comparison group (Est. RR: 1.08, 95% C.I.: [0.92,1.28],  $p=0.349$ ), but the difference was clearly nonsignificant. The covariate effects of age, race, occupation, and the presence of pre-SEA acne were often profound with respect to the recorded dermatologic conditions.

The adjusted analyses closely mirrored the unadjusted analyses, with no significance noted between groups for any variable. Only one group-by-covariate interaction was observed in the adjusted analysis of the dermatology index, with a group-by-presence of pre-SEA acne interaction noted. However, further analysis of this interaction did not show an adverse effect in the Ranch Hand group.

Exposure index analyses did support dose-response relationships for some of the variables in certain occupational strata, but did not reveal a strong pattern of results suggesting a relationship between skin disease and herbicide exposure.

Overall the followup examination results paralleled the Baseline findings. Although the followup examination detected more dermatologic abnormalities than those present at Baseline, slightly more abnormalities were found in

TABLE 8:

**Overall Summary Results of Unadjusted and Adjusted Analyses  
of Questionnaire and Physical Examination Dermatological Variables**

Variable	Unadjusted	Adjusted
<u>Questionnaire</u>		
Incidence of Acne		
Occurrence	NS	--
Relative to 1961	NS	--
Relative to SEA (Post-1961 Cases)	NS*	--
Duration of Acne	NS	NS
Location of Acne	NS	--
<u>Physical Examination</u>		
Comedones	NS	NS
Acneiform Lesions	NS	NS
Acneiform Scars	NS	NS
Depigmentation	NS	NS
Inclusion Cysts	NS	NS
Hyperpigmentation	NS	NS
Other Abnormalities	NS	NS
Dermatology Index	NS	****

NS: Not significant ( $p > 0.10$ ).

-- Analyses not performed.

NS\*: Borderline significant ( $0.05 < p \leq 0.10$ ).

\*\*\*\*Group-by-covariate interaction.

the Comparisons, and most relative risks approached unity. The longitudinal analysis for the dermatology index showed no statistically significant differences between groups in the change in results from the Baseline to the follow-up examination.

In conclusion, none of the questionnaire results disclosed an increased likelihood of past chloracne in the Ranch Hands. The physical examination did not diagnose a current case of chloracne. The dermatological data were similar between the Ranch Hand and Comparison groups, and the longitudinal analysis of the dermatology index suggested equivalence between the Baseline and followup examination results.

## CARDIOVASCULAR SYSTEM

The cardiovascular health of both cohorts was assessed by collection of reported and record-verified heart disease events; measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and electrocardiograph (ECG) findings; and evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Table 9 presents the overall summary of the unadjusted and adjusted results. Where possible, the analyses used the covariates of age, race, occupation, percent body fat, cholesterol, high density lipoprotein (HDL) cholesterol, cholesterol-HDL ratio, smoking history (pack-years and current smoking level), alcohol history (drink-years and current drinking level), personality score, and differential cortisol.

The cardiovascular variables did not reveal significant group differences, with the exception of verified heart disease, for which the proportions of recorded cardiac events were 24 and 20 percent in the Ranch Hand and Comparison groups, respectively, ( $p=0.054$  unadjusted,  $p=0.036$  adjusted). This finding was not reinforced by results of individual questionnaire or examination variables showing impairment in the Ranch Hands. There was a remarkable balance in relative risks above and below unity between the groups.

Other related analyses showed an absence of significant group differences in reported or verified hypertension, reported or verified heart attacks, and reported heart disease. There was good correlation between the verified cardiovascular history and the central and peripheral cardiovascular abnormalities detected at the physical examination, supporting accuracy and validity of the cardiovascular measurements.

The adjusted analyses of central cardiac function disclosed a significant group-by-age interaction involving systolic blood pressure in the Black cohort, with a mean systolic blood pressure greater in the Ranch Hands than the Comparisons at younger age levels, but a lower mean pressure at the older ages; the group-by-age interaction was not significant in the nonblack cohort. Additionally, there was a significant group-by-pack-years of smoking interaction for the overall ECG findings, and significant group-by-pack-years of smoking and group-by-percent body fat interactions for arrhythmia, but they all generally pointed to lower adjusted relative risks in the Ranch Hands.

TABLE 9.

**Overall Summary Results of Unadjusted and Adjusted Analyses  
Cardiovascular Variables**

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
<b>Historical and Verified Heart Disease</b>			
Reported Hypertension		NS	NS
Verified Hypertension		NS	NS
Reported Heart Disease*		NS	NS
Verified Heart Disease*		NS*	S <sup>b</sup>
Reported Heart Attack		NS	NS
Verified Heart Attack		NS	NS
<b>Central Cardiac Function</b>			
Systolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	****
Heart Sounds		NS	NS
Electrocardiogram (Overall)		NS	****
ECG: RBBB		NS	NS
ECG: LBBB		---	N/A
ECG: Nonspecific T-Wave Changes		NS	NS
ECG: Bradycardia		NS	NS
ECG: Tachycardia		---	N/A
ECG: Arrhythmia		NS	****
ECG: Other Diagnoses		NS	NS

TABLE 9. (Continued)

Overall Summary Results of Unadjusted and Adjusted Analyses  
Cardiovascular Variables

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
<b>Peripheral Vascular Function</b>			
Diastolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	NS
Funduscopy Examination		NS	NS
Carotid Bruits		NS	NS
Radial Pulses	Manual	NS	NS
	Doppler	NS	NS
Femoral Pulses	Manual	NS	NS
	Doppler	NS	NS
Popliteal Pulses	Manual	NS	****
	Doppler	NS	NS
Dorsalis Pedis Pulses	Manual	NS	****
	Doppler	NS	NS
Posterior Tibial Pulses	Manual	NS	****
	Doppler	NS	NS
Leg Pulses	Manual	NS	****
	Doppler	NS	NS
Peripheral Pulses	Manual	NS	****
	Doppler	NS	NS
All Pulses	Manual	NS	****
	Doppler	NS	NS

NS:Not significant ( $p>0.10$ ).

NS\*:Borderline significant ( $0.05<p\leq 0.10$ ).

\*\*\*\*Group-by-covariate interaction.

\*Excluding hypertension.

<sup>b</sup>RH>C (Est. RR: 1.25; 95% C.I.: [1.02, 1.54],  $p=0.054$ ).

In the analysis of peripheral vascular function, no significant group differences were observed for abnormalities involving radial, femoral, popliteal, posterior tibial, dorsalis pedis, or three anatomic aggregates of these pulses, either by manual palpation or Doppler techniques. This overall finding was in distinct contrast to the 1982 Baseline examination, which by the manual palpation method, showed significant peripheral pulse deficits in the Ranch Hands. This favorable pulse reversal over the two examinations is primarily attributed to the rigid 4-hour tobacco abstinence applied prior to Doppler testing, although other factors may be related. The lack of group differences for pulse abnormalities was noted even though the manual and Doppler techniques differed significantly ( $p < 0.05$ ,  $p < 0.001$  for most) in the detection of abnormalities for all but one of the pulses or pulse combinations.

For manually-determined pulse abnormalities, there was a significant group-by-race interaction for the popliteal pulses, a significant group-by-percent body fat interaction for the leg pulses, and significant group-by-occupation interactions for the posterior tibial, dorsalis pedis, and the three pulse aggregates (leg, peripheral, and all pulses). No interactions were encountered in the adjusted analyses of the Doppler results, and none showed significant group differences.

Statistical analyses involving the Original Comparisons also showed no significant differences in the cardiovascular measurements between groups, although slightly different interactions were detected in some of the adjusted analyses.

For the exposure analyses, the only statistically significant effects were those pointing to less bradycardia and less reported and verified heart disease in the medium exposure level category, as contrasted to the low exposure category, among the enlisted groundcrew. In many cases there were too few abnormalities within the occupational categories to permit formal statistical tests. Overall, the exposure analyses were deemed as unresponsive of any meaningful dose-response relationships.

The longitudinal analysis of the pulse index confirmed the significant difference in the change in the pattern of results from the Baseline examination to the followup examination, largely due to a relatively greater increase of pulse abnormalities in the Comparison group than in the Ranch Hand group. There was no significant change in pattern between the two groups in overall ECG findings between examinations.

There was a similar distribution of the covariates between groups, except for a slightly higher level of current Ranch Hand smoking (also observed at Baseline), and a corresponding slightly lower mean percent body fat. The general covariate effects were strong and showed expected, classical associations with the cardiovascular measurements. However, unexpected effects were consistently noted for personality score, with higher proportions of various cardiovascular abnormalities associated with scores in the Type B direction, a finding possibly attributable to the method of personality determination. Although smoking was positively associated with many of the cardiovascular measurements, negative associations were seen between current smoking and reported and verified essential hypertension and between pack-years of smoking and verified hypertension.

In conclusion, of 27 cardiovascular variables, only one, verified heart disease, showed a significant excess in the Ranch Hands, but this finding was largely unsupported by other cardiac measurements. Both manual palpation and Doppler recordings of five peripheral pulses were similar in both groups, in marked contrast to the 1982 Baseline examination which found significant pulse deficits in the Ranch Hand group. This change at the followup examination was most likely due to required tobacco abstinence prior to the pulse measurements. Exposure index analyses did not support a consistent dose-response relationship for any variable. Overall, there was remarkable similarity in the cardiovascular health between the Ranch Hand and Comparison groups.

## HEMATOLOGY

The functional integrity of the hematopoietic system was assessed by the measurement of eight peripheral blood variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). These variables were analyzed in the discrete form to detect differences in the percentages of values outside the designated laboratory range, as well as in the continuous form to detect shifts in mean values between the two groups. A summary of all of these analyses, unadjusted and adjusted for the covariates of age, race, occupation, and smoking, is presented in Table 10.

The unadjusted discrete analysis of the percent abnormal values, both low and high, showed no statistically significant differences between the Ranch Hand and Comparison groups for any of the hematological variables. Similarly, the adjusted categorical analysis disclosed that none of the adjusted relative risks was significant for either group, and that no significant group-by-covariate interactions were present.

The unadjusted continuous analysis did not detect any significant differences in group means for any of the eight variables. The adjusted continuous analysis found no significant group differences for HGB, HCT, MCV, MCH, and MCHC, but encountered significant three-factor interactions for WBC (group-by-race-by-age, group-by-age-by-smoking history, and group-by-race-by-occupation), for PLT (group-by-race-by-smoking history and group-by-race-by-current level of smoking), and a borderline interaction for RBC (group-by-occupation-by-smoking history). Ranch Hand versus Original Comparison analyses revealed further significant interactions for HGB, HCT, MCV, and MCH. As no group strata demonstrated consistent patterns of hematologic impairment, biologic relevance was not assigned to the interactions. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the hematological variables.

The effect of race was particularly profound for all variables except PLT. There was fair consistency in the covariate effects upon the RBC-related variables. Generally, decreasing hematologic values were associated with increasing age and the Black race, and increasing hematologic values were associated with increasing smoking. The detection of these classical covariate effects lends credence to the overall finding of nonsignificant group differences for all of the hematological variables. Significant group differences found for MCV and MCH at the Baseline examination were not significant at the first followup. Other differences (e.g., covariate effects, interactions)

TABLE 10.

Overall Summary Results of Unadjusted  
and Adjusted Analyses of Hematological Variables

	Unadjusted		Adjusted	
	Mean	Categorical	Mean	Categorical
RBC	NS	NS	NS*	NS
WBC	NS	NS	****	NS
HGB	NS	NS	NS	NS
HCT	NS	NS	NS	NS
MCV	NS	NS	NS	NS
MCH	NS	NS	NS	NS
MCHC	NS	--	NS	--
PLT	NS	NS	****	NS

NS: Not significant ( $p > 0.10$ ).

NS\*: Borderline significant group-by-covariate interaction ( $0.05 \leq p < 0.10$ ).

--Analysis not performed due to sparse data.

\*\*\*\*Group-by-covariate interaction.

Note: Significant group-by-covariate interaction, Ranch Hands versus Original Comparisons only, for HGB, HCT, MCV, and MCH.

between the Baseline and followup examinations may be due to small numeric shifts in the cohorts under study (see Chapter 2) and the selection of alternate statistical models, or due to chance.

Unadjusted continuous exposure analyses in the Ranch Hand group revealed only one significant effect (RBC in enlisted groundcrew) and one borderline effect (HCT in enlisted groundcrew) but neither was consistent with a plausible dose-response relationship. The adjusted continuous exposure analyses found only one significant contrast (HCT, medium exposure versus low exposure, enlisted groundcrew). However, seven exposure level-by-covariate interactions were noted for four of the hematological variables. Discrete outcome analyses of the exposure level index revealed a significant result only for WBC in the enlisted flyers.

The longitudinal analyses of MCV, MCH, and PLT found significant differences only for PLT values between the Baseline and followup examinations, with the Baseline group difference in mean values closing to near equivalence at the followup examination.

In conclusion, none of the eight hematological variables were found to differ significantly between the Ranch Hand and Comparison groups. In fact, group equivalence was more apparent at the followup examination than at the Baseline examination. The classical effects of age, race, and smoking were demonstrated with most of the hematological variables. The longitudinal analyses also suggested that neither group manifested an impairment of the hematopoietic system. Exposure index analyses did not support a plausible dose-response relationship for any of the hematological variables.

## RENAL

A summary of all renal variables, including unadjusted and adjusted analyses, is displayed in Table 11.

A historical assessment of kidney disease/kidney stones by a review-of-systems questionnaire showed no significant differences between the Ranch Hand and Comparison groups (see Table 12). An adjusted analysis did not alter this conclusion as an adjusted relative risk of 0.95 (95% C.I.: [0.71,1.25],  $p=0.693$ ) was demonstrated. These statistics appeared to be in marked contrast to the Baseline historical findings. Differences vis-a-vis the Baseline were most likely due to a difference in questionnaire techniques.

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

The unadjusted analysis of proteinuria showed no group differences (Est. RR: 1.18, 95% C.I.: [0.75,1.86],  $p=0.485$ ), but the adjusted analysis showed an interaction of group and diabetic class; appropriate stratified analyses revealed that the prevalence of proteinuria was lower in the Ranch Hands than in the Comparisons in the diabetic and impaired strata, but higher in the normal strata for the Ranch Hands. These results were in contrast to the

TABLE 11.

Overall Summary Results of Unadjusted and  
Adjusted Analyses for Renal Variables

Variable	Unadjusted	Adjusted
Reported Kidney Disease	NS	NS
Urinary Protein	NS	****
Urinary Occult Blood	NS	****
Urinary Leukocytosis	NS	****
BUN	NS	****
Urine Specific Gravity	NS*	****

NS: Not significant ( $p > 0.10$ ).

NS\*: Borderline significant ( $0.05 < p \leq 0.10$ ).

\*\*\*\*Group-by-covariate interaction.

TABLE 12.

Unadjusted Analysis of History of  
Kidney Disease/Kidney Stones by Group

Group	<u>History of Kidney Disease/Stones</u>				Total	Est. Relative Risk (95% C.I.)	p-Value
	<u>Yes</u>		<u>No</u>				
	Number	Percent	Number	Percent			
Ranch Hand	94	9.3	920	90.7	1,014	0.93 (0.70, 1.23)	0.619
Comparison	128	9.9	1,163	90.1	1,291		

Baseline findings, which showed a marginally significant proteinuria in the Comparison group ( $p=0.055$ ), and overall, lower prevalence rates of proteinuria.

The unadjusted prevalence rates for hematuria were similar for both groups (Est. RR: 1.14, 95% C.I.: [0.91,1.42],  $p=0.239$ ). Three significant interactions involving group membership and covariates precluded a direct adjusted comparison of the estimated prevalence rates. Covariate analyses indicated increased hematuria in Blacks and among enlisted personnel. Ultimately via a series of stratified analyses, statistical equivalence was determined for the Black enlisted strata of both groups. Of particular note was the approximate tenfold increase in hematuria in both groups over that observed at Baseline, a finding most likely due to different laboratory techniques (reagent-strip testing versus microscopic observation).

Similar results were found for leukocyturia, i.e., a nonsignificant unadjusted analysis (Est. RR: 1.24, 95% C.I.: [0.93,1.64],  $p=0.145$ ), and a significant three-way interaction (group, age, race) in the adjusted analysis. Significant covariate effects were noted for diabetic class and occupation for nonblack participants, whereas age was a significant adjusting variable for Blacks. A significant group difference was found only for the younger, nonblack Ranch Hands. The overall results were consistent with the Baseline findings.

BUN levels did not vary significantly by group ( $p=0.554$ , unadjusted). Adjusted analyses showed significant covariate effects for age and occupation and interactions for group and race and for race and diabetic class. An analysis stratified by race revealed no significant group differences for nonblacks, but a significantly higher adjusted mean BUN level in Black Comparisons than in Black Ranch Hands. Overall, the BUN results were similar to those observed at the Baseline examination.

Urine specific gravity levels manifested marginally significant group differences ( $p=0.082$ , unadjusted). The adjusted analysis disclosed significant covariate effects of diabetic class and the interactions of group and race and group and occupation. Analyses by race showed no strata with significantly lower mean levels for Ranch hands. In contrast to the Baseline values, the followup urine specific gravities were lower, a finding most likely attributable to differences in laboratory methodology (falling drop method versus multistick procedure).

Exposure index analyses showed very little evidence of a dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates or mean levels among the exposure index levels were seen within occupational strata.

The longitudinal analysis was based solely upon a contrast of BUN levels between the two examinations. The unadjusted mean BUN value increased slightly from the Baseline to the followup examination, but the increases were symmetrical in the two groups and nonsignificant ( $p=0.48$ ).

In conclusion, none of the six renal assessment variables showed a significant difference between the Ranch Hand and Comparison groups by unadjusted tests. However, in the adjusted analyses, all renal measurements except

reported kidney disease revealed group-by-covariate interactions. These interactions were often complex, making it impossible to reach a firm conclusion as to the presence of an herbicide effect.

#### ENDOCRINOLOGY

Questionnaire and review-of-systems data for past thyroid disease were essentially equivalent in both the Ranch Hand and Comparison groups. These historical data were confirmed by medical record reviews. Physical examination findings were necessarily limited to data from palpation of thyroid glands and testicles; the unadjusted results showed no significant group differences.

TABLE 13.

Medical Record Verification Results  
of Reported Thyroid Disease by Group

Verification Status	Group	
	Ranch Hand	Comparison
Number with Reported Thyroid Conditions	7	21
Medical Records Reviewed	7	21
Medical Records Pending	0	0
Percent Thyroid Conditions Verified	100	100

The physical examination and laboratory testing results of all endocrinological variables are summarized in Table 14.

Evaluation of the endocrine system was conducted primarily by laboratory testing of hormone levels. The thyroid test battery consisted of  $T_3$  % Uptake and TSH assays. The  $T_3$  % Uptake data showed no group differences for either mean values or frequency of abnormally low or high values. Occupation was a significant covariate. TSH results revealed a significantly higher mean level in the Ranch Hand group, but this difference was not found by categorical testing of proportions of abnormally high TSH results.

Mean levels of testosterone were significantly elevated among Ranch Hands as contrasted with Comparisons in the 10 to 25 percent body fat category, but this was not reflected by the categorical tests. For the few participants

TABLE 14.

**Overall Summary Results of  
Unadjusted and Adjusted Continuous  
and Categorical Analyses of Endocrinological Variables**

Test	Unadjusted		Adjusted	
	Mean	Categorical	Mean	Categorical
<b>Questionnaire and Physical Examination</b>				
Past Thyroid Disease (Self-Administered)	-- <sup>a</sup>	NS	-- <sup>a</sup>	-- <sup>b</sup>
Past Thyroid Disease (Interviewer Administered)	-- <sup>a</sup>	NS*	-- <sup>a</sup>	-- <sup>b</sup>
Thyroid Abnormalities	-- <sup>a</sup>	NS	-- <sup>a</sup>	-- <sup>b</sup>
Testicular Abnormalities	-- <sup>a</sup>	NS	-- <sup>a</sup>	-- <sup>b</sup>
<b>Laboratory Testing</b>				
T <sub>3</sub> X Uptake	NS	Overall: NS Low vs. Normal: NS High vs. Normal: NS	-- <sup>b</sup>	Overall: NS Low vs. Normal: NS High vs. Normal: NS
TSH	0.019	NS	0.025	NS
Testosterone	0.035	Overall: NS Low vs. Normal: NS High vs. Normal: NS	****	Overall: NS Low vs. Normal: NS High vs. Normal: NS
Initial Cortisol	NS	Overall: NS Low vs. Normal: NS High vs. Normal: NS	NS	-- <sup>b</sup>
2-Hour Cortisol	NS	NS	-- <sup>b</sup>	-- <sup>b</sup>
Differential Cortisol	NS	-- <sup>a</sup>	****	-- <sup>a</sup>
2-Hour Postprandial Glucose	NS	Overall: 0.038 Impaired vs. Normal: 0.024 Diabetic vs. Normal: NS	NS	Overall: 0.034 Impaired vs. Normal: 0.022 Diabetic vs. Normal: NS
Diabetes (Composite Indicator)	-- <sup>a</sup>	NS	-- <sup>a</sup>	NS

--<sup>a</sup>Analysis not feasible.

NS: Not significant ( $p > 0.10$ ).

--<sup>b</sup>Analysis not performed.

NS\*: Borderline significant ( $0.05 < p \leq 0.10$ ).

\*\*\*\*Group-by-covariate interaction.

with less than 10 percent body fat (six Ranch Hands, four Comparisons), mean testosterone levels were lower for Ranch hands than for Comparisons. Age, occupation, and percent body fat were significant adjusting variables.

Two timed cortisol specimens showed no significant group differences in mean values and percent abnormalities. The difference between the timed cortisol results, termed the differential cortisol, showed no significant group differences for nonblacks or Blacks born before 1942, but Black Ranch Hands born in or after 1942 had a lower mean differential cortisol level than Comparisons. Age, percent body fat, and personality type were significant covariates in these analyses.

Group means of 2-hour postprandial glucose levels were not statistically different, but categorical testing revealed that there was a significantly higher frequency of glucose-impaired (at least 140 but less than 200 mg/dl) Comparisons than Ranch Hands. A constructed variable comprised of known diabetics and individuals classified as diabetic by the glucose tolerance test, showed no difference between the Ranch Hand and Comparison groups. As expected, past and current diabetes were highly influenced by the covariates age, race, and percent body fat.

Exposure index analyses did not reveal any pattern consistent with a dose-response relationship. Enlisted flyers in the medium exposure level were significantly different from those in the low exposure level for 2-hour cortisol, differential cortisol, and 2-hour postprandial glucose. However, the corresponding high versus low contrasts were not statistically significant.

Longitudinal analyses of  $T_3$  % Uptake, TSH, and testosterone levels on all individuals attending both the Baseline and followup examinations revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups in the interval between examinations.

In conclusion, both limited historical and physical examination data, seven endocrinological laboratory variables, and a composite indicator of diabetes did not demonstrate consistent patterns indicating an herbicide effect. However, there was a significant interaction between group and percent body fat for testosterone that could be interpreted as an herbicide effect. TSH and testosterone means tests were statistically significant, and in the expected direction of an herbicide effect, but these results were not confirmed by categorical testing. Also significant was the impaired category of the glucose tolerance test, which showed an excess in the Comparison group. The consistent demonstration of the classical effects of the covariates age, race, occupation, and percent body fat on appropriate endocrine variables provided support for these conclusions. Overall, the endocrine health status of both groups was reasonably comparable.

## IMMUNOLOGY

Immunologic competence was measured by cell surface marker (phenotypic) studies and cell stimulation studies on 47 percent of the study population, and by a four antigen series of skin tests in 76 percent of participants to assess the delayed hypersensitivity response. Table 15 summarizes the results of all unadjusted and adjusted analyses on 11 primary variables spanning the first two of these three functional areas.

TABLE 15.

**Overall Summary Results  
of Unadjusted and Adjusted  
Analyses of Immunological Variables**

<u>Variable</u>	<u>Unadjusted</u>	<u>Adjusted</u>
Total T Cells ( $T_{11}$ )	NS	****
Helper T Cells ( $T_H$ )	NS	NS
Suppressor T Cells ( $T_S$ )	NS	NS
B Cells	NS	****
Monocytes	NS	****
HLA-DR Cells	NS	****
$T_H/T_S$ Ratio	NS	NS
Unstimulated Response (PHA)	NS	NS
PHA Net Response	NS	NS
Pokeweed Net Response	NS	NS
MLC Net Response	NS	****

NS: Not significant ( $p > 0.10$ ).

\*\*\*\* Significant group-by-covariate interaction.

Cell surface marker studies were conducted for total T cells ( $T_{11}$ ), helper T cells ( $T_H$ ), suppressor T cells ( $T_S$ ), B cells, monocytes, and HLA-DR cells; the ratio of  $T_H/T_S$  cells was included in the analysis. Because of inherent significant day-to-day and batch-to-batch variation, all results (including functional stimulation studies) were adjusted for blood-draw day variation. Statistical testing of the seven phenotypic cell markers did not reveal any significant group differences (interactions excepted), either unadjusted or adjusted for the covariates of age, race, occupation, current smoking, lifetime smoking history (pack-years), current alcohol use, or lifetime alcohol use (drink-years). Similarly, none of the unadjusted or adjusted analyses of the functional stimulation studies (for phytohemagglutinin, pokeweed mitogen, or mixed lymphocyte culture) showed any statistically significant group differences. However, the adjusted analyses for total T cells, B cells, monocytes, HLA-DR cells, pokeweed mitogen, and net mixed lymphocyte culture stimulation showed some significant group-by-covariate interactions, precluding direct adjusted group contrasts. Overall, no discernible pattern was identified to suggest a detriment in any subgroup of either the Ranch Hands or Comparisons. Results were similar between the analyses of the total Comparison group and the analyses of the Original Comparisons.

The covariate effects of age, race, smoking, and alcohol use were generally profound on most variables in the phenotypic and stimulation studies. Consistently decreasing values of all cell markers and stimulated cells were associated with increasing age, whereas increased levels of smoking were usually associated with increases in the values of those variables. Blacks

had consistently higher stimulated cell counts than nonblacks, but this effect was not observed for counts of T cells, B cells, or HLA-DR cells. Enlisted personnel generally had higher cell surface marker counts than officers.

Exposure index analyses of cell surface markers revealed no pattern consistent with a dose-response relationship. For enlisted groundcrew, the mean total T cell and suppressor T cell counts for the medium exposure level were significantly lower than those of the low exposure level, but were slightly lower than those of the high exposure level. The exposure index analyses of the functional stimulation tests revealed no consistent significant dose-response patterns for net PHA counts or net MLC counts. For net pokeweed counts, enlisted flyers in the high exposure level had a significantly lower adjusted count than enlisted flyers in the low exposure level, and a decreasing trend was apparent.

The delayed hypersensitivity response was assessed by the skin test antigens of mumps, Candida albicans, Trichophyton, and staph-phage-lysate. The 48-hour measurements of skin induration and erythema for the four tests showed marked inter-reader variation. Analyses showed that one of the three skin test readers too often measured induration larger than erythema (a clinically unacceptable finding), in an average of 30 percent of the readings, and did not yield measurements that detected a case of possible or overt allergy, whereas the other two readers found this condition in 5.6 percent of the participants. Remaining data from Readers 1 and 3, however, were found to vary significantly in clinical interpretation over duration of the examination. Consequently, all skin test data were declared invalid, and were not used in the assessment of group differences. The skin test reading problems led to the use of additional clinical quality control procedures for the AFHS followup examination begun in May 1987.

In conclusion, no significant group differences were judged present for the comprehensive cell surface marker or functional stimulation studies. The profound effects of age, smoking, and alcohol use were observed in these immunologic tests. The assessment of delayed hypersensitivity skin responses was precluded by poor data quality and excluded from further analysis. Overall, there was no indication of impaired immunologic competence in either group.

## RESPIRATORY SYSTEM

A summary of the results on the analyses of reported history of respiratory illness and of radiological and clinical findings is given in Table 16.

Based on the 31 December 1986 mortality data, there were seven deaths from respiratory conditions in the Comparison group and none in the Ranch Hand group.

TABLE 16.

**Overall Summary Results of Unadjusted and  
Adjusted Analyses of Pulmonary Disease**

<b>Pulmonary Disease</b>	<b>Unadjusted</b>	<b>Adjusted</b>
<b><u>Reported History of Respiratory Illness</u></b>		
Asthma	NS	NS
Bronchitis	NS	NS
Pleurisy	NS	****
Pneumonia	NS	NS
Tuberculosis	NS	****
<b><u>Radiological and Clinical Findings</u></b>		
Thorax and Lungs	NS	NS
Asymmetrical Expiration	NS	NS
Hyperresonance	NS	NS
Dullness	NS	NS
Wheezes	NS	NS
Rales	NS	****
X Ray	NS	NS

NS: Not significant ( $p > 0.10$ )

\*\*\*\*Group-by-covariate interaction.

There were no group differences found for reported history of asthma, bronchitis, pleurisy, or tuberculosis based on the unadjusted analyses. Adjustments for age and lifetime smoking did not alter the findings of group similarity, although there was a significant group-by-pack-year interaction for pleurisy and for tuberculosis.

Similarly, there were no significant group differences in the unadjusted analyses for the radiological and clinical respiratory findings of thorax and lungs, asymmetrical expiration, hyperresonance, dullness, wheezes, rales and x-ray interpretations. These findings were supported by the adjusted analyses, although there was a group-by-age interaction for rales.

The exposure index analyses revealed no consistent dose-response pattern.

Analyses of past history of respiratory illness and the clinical and radiological examination of the chest and lungs did not reveal any statistically significant differences between the Ranch Hand and Comparison groups suggestive of herbicide related disease. Several group-by-covariate interactions did exhibit statistical significance, but these findings did not indicate any consistent patterns suggesting different disease experience in the two groups.

## CONCLUSIONS

This chapter summarizes the conclusions drawn from the statistical analyses that have been conducted on the Air Force Health Study data base. The followup study, which began in 1985, was the logical extension of the 1982 Baseline, building upon the strengths of the Baseline study and utilizing the data collected at both the Baseline and the followup. The high level of Government support and outstanding participation of the study subjects that characterized the Baseline study were maintained through this first followup.

### STUDY PERFORMANCE ASPECTS

Of the living Baseline study participants, 99.2 percent were located and asked to participate in the followup. Participation in the followup physical examination and questionnaire was very high. Of the fully compliant Baseline participants, 971 of the 1,045 Ranch Hands (92.9%) and 1,139 of the 1,224 Comparisons (93.1%) participated in the followup. Thus, there was no group difference in compliance of the Baseline participants at the followup. Overall, the 2,309 participants in the followup (1,016 Ranch Hands and 1,293 Comparisons) represented a loss of 159 individuals and a gain of 199 since Baseline. One percent of the fully compliant Baseline population died between 1982 and the 1985 followup examination.

The bias/compliance analyses suggested that there had been no change between Baseline and the followup in the way replacements volunteered for entry into the study, and that no additional bias had been introduced at the followup due to scheduling differences. Although replacements were not health-matched at Baseline as they were at the followup, they were similar to refusals with respect to reported health, medication use, and income level. This result supported the conclusion that there has been little, if any, selection bias due to differential participation in the Comparison group and supported the use of the total Comparison group in the main analyses presented in this report.

### POPULATION CHARACTERISTICS

Overall, the Ranch Hands and Comparisons reported similar social and behavioral characteristics. No significant differences were found in age, educational background, religious preference, current military status, and income level. Significantly more Ranch Hands smoked cigarettes at the time of the followup examination than did Comparisons, but there was no significant difference between groups on past cigarette, cigar, and pipe use and on recent and past use of marijuana. A much higher percentage of participants reported past marijuana use at the followup than at Baseline. This difference was most likely due to a greater level of confidentiality afforded by the questionnaire technique. Risk taking behavior, assessed by questions on potentially dangerous recreational activities, revealed borderline significance. Slightly more Comparisons were scuba divers and more Ranch Hands raced motor vehicles. The difference in scuba diving was also significant at Baseline.

## Patterns of Results

Both the chapter conclusions and the final conclusions of this report have been predicated upon concepts of consistency, specificity, coherence, strength, and plausibility as they apply to the interpretation of group differences. In particular, careful consideration has been given to a variety of data and patterns of results that have emerged from the clinical evaluations. Specifically, there were few differences in the proportions of abnormalities between groups; the positive associations have not aggregated in the clinical areas of prime dioxin concern, nor have they been of serious clinical importance; the unadjusted results have been remarkably concordant with the adjusted results, both in terms of relative risk and p value; the analyses using the Original Comparison set have largely mirrored the results found with the total Comparison group; many of the group differences noted at Baseline have disappeared at the followup examination, and only a few new associations have emerged; almost all of the covariates have acted as expected in the adjusted analyses; and the exposure index analyses and the group-by-covariate interactions have not demonstrated biological patterns of concern and appeared to be more likely due to chance than not. Due to the acknowledged limitations of the exposure index used in this report (and considering the potential use of dioxin body burden levels at the next followup), dose-response relationships have not been emphasized in reaching final conclusions.

The overall pattern of these findings indicates that this followup study cannot be viewed as alarming from the traditional perspectives of clinical medicine or epidemiology. This study, in fact, demonstrates similarity in current health status between the Ranch Hand and Comparison groups.

## CLINICAL ASPECTS

### General Health

The nonspecific assessment of general health showed relatively close similarity between the two groups. Ranch Hands rated their health as fair or poor more frequently, but this difference was found only in the enlisted groundcrew and not in the officers nor enlisted flyers. The perception of health in both groups had improved since Baseline. Physician-rated appearance of relative age was not found to be significantly different at the followup in contrast to the Baseline finding that a higher percent of Ranch Hands than Comparisons looked younger than their stated age. The categorical analysis of sedimentation rate showed that the Ranch Hands had more abnormalities than the Comparisons. These results were not supported by the continuous analysis of mean sedimentation rates and were opposite to the Baseline results, which showed that younger Comparisons had elevated sedimentation rates. The categorical analysis of percent body fat showed no significant differences between the two groups, which was consistent with Baseline. However, the continuous analysis found that the Ranch Hands had a significantly lower mean percent body fat using age, race, and occupation as covariates. The detailed exposure analyses revealed no consistent exposure effects, and this result was consistent with the Baseline analysis. No longitudinal difference was found on perception of health. A significant group difference was found over time for the longitudinal analysis of sedimentation rate due to the change in the findings between the two examinations, possibly related to a change in laboratory methodology.

## Malignancy

Skin and systemic cancers, both suspected and verified by medical records, showed no significant group differences for the Baseline-followup interval (1982-1985). However, for all neoplasms combined (malignant, benign, and uncertain), a borderline significant excess in the Ranch Hand group was noted in an unadjusted analysis. The analyses of interval cancers revealed group interactions for verified and verified plus suspected basal cell carcinoma and verified plus suspected systemic cancers. Nonsignificant findings were observed for verified and verified plus suspected sun exposure-related cancers. Verified systemic cancers did not differ significantly between groups.

The analyses of lifetime cancer found significant results for verified basal cell carcinoma and verified sun exposure-related skin cancers. Group interactions were noted for systemic cancer categories and for verified plus suspected basal cell carcinoma. The higher rate of basal cell carcinoma in the Ranch Hands versus the Comparisons found at Baseline was nonsignificant for the followup interval, but due to the effect of the larger number of Baseline cases and the significant confounding of average residential latitude, the adjusted analysis of lifetime basal cell carcinoma emerged as statistically significant.

There were several disparities in the distribution of testicular, colon, and smoking-related tumors in the groups. Further, one case of soft tissue sarcoma and one possible lymphoma (both in Ranch Hands) were diagnosed in the interval, balancing the two similar cases found in the Comparison group at Baseline. Considering that the systemic cancer curves are in their early stages for both groups, with perhaps insufficient latency, the cancer results of the followup examination should not be viewed as disturbing, but as cause for continued monitoring.

## Neurological Assessment

None of the 27 neurological variables demonstrated a significant group difference, although several variables had relative risks which were greater than one. There was no group difference in reported neurological illnesses for the interval or for a lifetime history. Of the cranial nerve variables, speech and tongue position were marginally significant, with the Ranch Hands at a slight detriment. The analyses of peripheral nerve function showed no significant differences between the Ranch Hands and the Comparisons. In the analysis of central nervous system function, hand tremor was found to be of borderline significance, with the Ranch Hands faring slightly worse than the Comparisons. A borderline significant group interaction (Ranch Hand hand tremor by insecticide exposure) may have had biological and operational significance. Overall, substantially fewer neurological abnormalities were detected at the followup examination than at the Baseline examination. The exposure analyses showed only occasional statistically significant results, although no consistent pattern with increasing exposure was evident. In the longitudinal analysis of the Babinski reflex, a significant change over time was observed. This was due to a nonsignificant finding in the Ranch Hands at the followup, which differed from the significant adverse finding at Baseline. The covariates of age, alcohol history, and diabetes showed classical effects with many of the neurological measurements. Overall, the followup examination results were quite similar to the Baseline findings.

## Psychological Assessment

The reported and verified data on lifetime psychological illnesses showed no significant differences between groups. Distributional tests of the 14 Minnesota Multiphasic Personality Inventory (MMPI) scales, stratified by occupation, revealed that only 2 of the 42 results approached significance. For the total Cornell Medical Index (CMI), separate distributional tests were conducted with stratification by age, race, occupation, education, and current drinking status; a significant difference was found for one status of each of the covariates. In all cases, the mean of the Ranch Hand distribution was greater than the mean of the Comparisons. The analysis of the 14 MMPI scales showed that there was a significant difference between the two groups for denial and masculinity/femininity, with more abnormalities in the Comparisons than the Ranch Hands. The results of the analyses for hysteria were of borderline significance, with more abnormalities in the Ranch Hands. There were more abnormalities in the Ranch Hands than the Comparisons for social introversion, which was of borderline significance. Differences in the total CMI and A-H area subscore were found to be significant, with more abnormalities in the Ranch Hands. There was no significant difference between the two groups on the Halstead-Reitan Battery impairment index, a measure of the functional integrity of the CNS. The exposure index analyses did not reveal any pattern consistent with a dose-response relationship. As expected, the effects of age, educational level, and alcoholic history showed profound effects on many of the psychological measurements.

## Gastrointestinal Assessment

Although the followup gastrointestinal assessment disclosed more statistically significant findings than the Baseline examination, the abnormalities were distributed equally between the two groups, and there was no clinical, statistical, or exposure pattern consistent with an herbicide-related effect on health. No historical or biochemical evidence was found to suggest an increased likelihood of porphyria cutanea tarda (PCT) in the Ranch Hand group. Only sparse and nonsignificant liver disorders were reported for the interval between Baseline and followup. Also, for the lifetime history of liver disorders, there were no significant differences between groups. Further, there were no significant group differences in reported lifetime peptic ulcer disease. A review of digestive system mortality showed a relative excess in the Ranch Hands but a relative lack of malignant neoplasms. The results of the physical examination showed a borderline increase of hepatomegaly in the Ranch Hand group. There was a significantly lower mean serum glutamic-pyruvic transaminase (SGPT) level, a greater mean alkaline phosphatase level, and a lower mean uroporphyrin level in the Ranch Hand group. The analysis of coproporphyrin was of borderline significance, with the mean of the Ranch Hands in excess of the mean of the Comparisons. No group differences were found for serum glutamic-oxaloacetic transaminase (SGOT), gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, or triglycerides. The numerous group-by-covariate interactions did not disclose any consistent subgroup patterns detrimental to the Ranch Hands. These findings were generally consistent with the results of the 1982 assessment. The longitudinal analyses for SGOT, SGPT, and GGTP showed no significant differences between results by group over time.

## Dermatological Evaluation

No significant group differences were identified in the dermatological evaluation. None of the questionnaire data showed an increased likelihood of past chloracne, as determined by anatomic patterns of acne, and no cases were diagnosed in the physical examination. Analyses were conducted on six dermatologic disorders (comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation) and on a composite variable of 16 other minor conditions (the latter not generally associated with chloracne). Exposure index analyses did not reveal consistent patterns suggestive of a dose-response relationship. The longitudinal analysis, based on a composite dermatology index, showed no significant differences between the results over time. Substantially more dermatologic abnormalities were detected at the followup examination than at the Baseline examination. In general, however, the followup results were consistent with the findings at Baseline.

## Cardiovascular Evaluation

Overall there was remarkable similarity in the cardiovascular health of the Ranch Hands and the Comparisons. Of the 27 cardiovascular variables, there was a significant difference for only one, verified heart disease, with an excess in the Ranch Hand group. This finding was largely unsupported by other cardiac measurements. The cardiovascular assessment was based on reported and verified heart disease; the measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and ECG findings; and the evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Doppler recordings of five peripheral pulses were similar in both groups, a finding which was in marked contrast to the Baseline examination that found significant pulse deficits in the Ranch Hand group. This change was most likely due to a required 4-hour abstinence from tobacco prior to the pulse measurements. Overall, the exposure analyses were unresponsive of any meaningful dose-response relationship. The longitudinal analyses confirmed the change in pulse abnormalities in the Ranch Hand group over time, but showed no significant group change in overall ECG findings between the examinations.

## Hematological Evaluation

The hematological evaluation found that neither group manifested an impairment of the hematopoietic system, consistent with similar findings at the Baseline. The evaluation was based on eight peripheral blood variables: red blood cells (RBC), white blood cells (WBC), hemoglobin (HGB), hematocrit concentration (HCT), corpuscular volume (MCV), corpuscular hemoglobin (MCH), corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). Both the discrete and categorical analyses revealed no significant group differences. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the variables. Two group-by-covariate interactions in the analyses of mean differences did not appear to have a meaningful interpretation. The exposure index analyses did not support any plausible dose-response relationship. The longitudinal

analyses of MCV, MCH, and PLT found significant differences only for PLT between the Baseline and the followup, with the Ranch Hands exhibiting a slight decline in mean level from Baseline and the Comparisons showing an opposite change.

### Renal Assessment

None of the six renal variables of reported kidney disease, urine protein, occult blood, urine white blood cell count, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups based on the unadjusted analyses. In the adjusted analyses of the laboratory variables, however, there were significant group-by-covariate interactions that did not yield a consistent pattern to suggest a renal detriment to either group. The finding of group equivalence for past kidney disease was in contrast to the Baseline examination, which found significantly more reported disease in the Ranch Hand group. The difference in findings is more likely due to a change in questionnaire wording than to a true change in renal health. Like the Baseline findings, the exposure index analyses showed very little evidence of a dose-response relationship. In the longitudinal analyses of blood urea nitrogen, there were no significant changes between the examinations by group.

### Endocrine Assessment

In general, the endocrine health status of the Ranch Hands and the Comparisons was reasonably comparable. The examination found no significant differences between the two groups for past thyroid disease, or thyroid and testicular abnormalities determined by palpation. In the analyses of the seven laboratory values ( $T_3$  % Uptake; thyroid stimulating hormone (TSH); testosterone; initial, second, and differential cortisol; and postprandial glucose), significant differences were found for TSH and testosterone, with higher mean levels in the Ranch Hands. These analyses were not supported by the categorical analyses. The thyroid test results were conflicting with respect to an assertion of hypothyroidism in the Ranch Hands (a possible dioxin effect). Mean levels of testosterone were significantly elevated in the Ranch Hand group as contrasted with the Comparisons in the 10-25 percent body fat category. The effects of personality score and percent body fat on the differential cortisol levels were not fully expected. Although tests of 2-hour postprandial mean values showed no significant group differences, comparable categorical tests revealed that significantly fewer Ranch Hands had impaired glucose levels, but conversely, had more (nonsignificant) diabetic levels of glucose. Analyses of the composite diabetes indicator (history plus 2-hour postprandial results) did not disclose significant group differences. The exposure index analyses suggested that the enlisted flyers in the medium exposure level were significantly different from those in the low exposure level for differential cortisol, postprandial glucose, and testosterone. The corresponding high to low contrasts were not significant. The longitudinal analyses were based on  $T_3$  % Uptake, TSH, and testosterone, and revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups over the time interval.

## Immunological Evaluation

Overall, there were no significant group differences or any indication of impaired immunological competence in either group based on comprehensive cell surface marker and functional stimulation studies. Six cell surface markers (total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and a constructed helper/suppressor ratio variable) and three functional stimulation studies (PHA, pokeweed, and mixed lymphocyte culture) were conducted on 47 percent of the study population. No significant differences were revealed for five of these variables. In the analyses of the other five variables, there were significant group-by-covariate interactions, but no discernible pattern was identified to suggest a detriment in any subgroup of either group. Skin test assessments of delayed hypersensitivity were characterized by inter-reader variation and shifting diagnostic criteria for energy. The skin test data were judged invalid and were not subjected to statistical testing for group differences. No consistent pattern of immunological deficits could be associated with increasing levels of herbicide exposure in the Ranch Hand group.

## Pulmonary Disease

The pulmonary assessment did not reveal any statistically significant differences between the Ranch Hand and Comparison groups that were suggestive of an herbicide-related disease. The analyses consisted of group assessments of respiratory disease incidence, physical examination abnormalities, and the current prevalence of x-ray abnormalities. There were no significant differences between the Ranch Hands and Comparisons for history of asthma, bronchitis, pneumonia, or for six of seven clinical variables (excluding rales) determined by x-ray or auscultation. Analyses of history of pleurisy, history of tuberculosis, and rales showed significant but inconsistent group-by-covariate interactions. These findings did not indicate any patterns suggesting a different disease experience in the two groups. The exposure index analyses did not reveal any consistent pattern suggestive of an increasing dose response.

## CONCLUSION

The results of the first followup study in 1985 have shown a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline Study in 1982. The 1985 examination results provide reassuring evidence that the current state of health of the Ranch Hand participants is unrelated to herbicide exposure in Vietnam. Continued close medical surveillance of these military populations is strongly indicated. This followup report concludes that there is not sufficient plausible or consistent scientific evidence at this time to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

## FUTURE DIRECTIONS

The scope and complexity of the AFHS has required gradual refinement and correction to meet the challenges of changing technology and scientific direction, and to ensure continued participation of all enrolled members.

This chapter outlines some of the changes incorporated in the fifth-year followup examination and identifies several areas of future work expected to significantly augment the study.

#### FIFTH-YEAR FOLLOWUP EXAMINATION

Since the fifth-year followup examination was initiated prior to the full analysis of the data from the third-year examination, most modifications were founded upon quality control issues and the desire to make the clinical content of the examination more responsive to the medical needs of the participants.

Clinical quality control enhancements were made to improve measurement techniques. The digit preference noted in systolic and diastolic blood pressure readings led to the use of automated blood pressure recording; all other parameters of the blood pressure readings (e.g., sitting position, three recordings, nondominant arm at heart level) were not changed.

The problem in skin test reading was met by a rigorous quality control plan that included the following elements: refresher training for readers; a required reading of the four skin tests of all participants by both readers, each blind to the results of the other; a required reread of 10 percent of all tests by each of the readers, each blind to the previous reading; and a required weekly report citing numbers and proportions of participants with possible anergy, reversal of induration-erythema measurements, and untoward skin reactions or other reading problems (e.g., participant refusal).

In addition, new skin test forms were developed to facilitate accurate recording and transcription; specific clinical criteria were formulated to require consultation by an allergist; and the skin test measurement criterion for possible anergy, consistent with current World Health Organization guidelines, was adopted for the clinical interpretation of all skin test readings. It is anticipated that this clinical quality control program will standardize both readings and interpretations, and will produce a uniformly superior data set.

#### EXPOSURE INDEX REFINEMENTS

Since the development of the Study Protocol and the analysis of the 1982 Baseline data, there has been concern among some scientists and the principal investigators over the accuracy and validity of the exposure estimates. It is unclear whether statistically significant differences in some variables between the Ranch Hand and Comparison groups, unsupported by dose-response estimates, have been due to chance, or whether true differences are obscured by an inadequate exposure index or group misclassification.

In mid-1986, strong correlations between dioxin levels in fat tissue and serum were demonstrated by the CDC and other institutions. Because of these results, the Air Force is currently engaged in a collaborative study with CDC to determine whether serum dioxin levels vary significantly in the Ranch Hand population. Approximately 200 AFHS volunteers have supplied a pint of blood to be analyzed for dioxin at the CDC laboratories. If clear and meaningful

exposure findings are evident from this study, several additional studies are feasible: testing can be expanded to the entire study population and a meaningful exposure index based on total current TCDD body burden may be developed; and by means of archived AFHS serum samples from the Baseline study, it may be possible to calculate a reasonably precise half-life of TCDD in humans. These expanded studies will allow the estimation of body burdens of TCDD at the time of departure from SEA (assuming the absence of intervening vocational and recreational exposures).

If, in fact, these potential studies become reality within the next 2 years, the fifth-year followup study data will be statistically analyzed using a more appropriate exposure index. In anticipation of this advance, the AFHS is currently collecting 280-350 ml of blood from all volunteers attending the fifth-year followup study.

#### ADDITIONAL ANALYSES AND STUDIES

As in the 1984 Baseline Report, not all of the measured dependent variables were subjected to statistical analysis (e.g., prothrombin, leutinizing hormone, follicle stimulating hormone), largely because they were not within the bounds of the Air Force-prescribed analyses. Exploration of many of the unanalyzed variables is contemplated as time and resources permit. Similarly, many analytic opportunities to define possible symptom-clinical sign clusters or syndromes by multivariate analysis of variance techniques were passed over due to time and charter. Particularly challenging as an area of future work may be the changing relationships of some immunological variables over time and the biological impact of these changes on the induction of diseases such as cancer. Likewise, future efforts to define shifting cardiovascular disease patterns are a logical extension of the rich longitudinal data base of the AFHS. Such efforts await future analysis and publication.

The assessment of possible selection and participation bias has been addressed in a comprehensive manner in this report (see Chapter 5). The analyses and discussion suggest that statistical use of the total Comparison group (versus the Original Comparison group) is justified in this report, and that the impact of selection and participation biases have been minimal. As the followup studies continue, it is anticipated that a wealth of data on compliance-participation factors will be available for continued comprehensive bias analyses. In particular, it is hoped that more complete data will exist to examine the true differences in current health status between refusals and their replacements. As the data set grows over time, the bias analyses will become more complex and will have to deal with changing motivations of the participants to continue in this study. Such bias analyses and assessments will always be of great importance to this study as they ultimately set the bounds for an inference on herbicide causality.