

Air Force Health Study

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

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SUMMARY

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NOTICE

This report is an abstract from the complete and comprehensive report describing the results of the 1987 followup examination of the Air Force Health Study, the third in a series of epidemiological studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of the previous studies, the 1982 baseline study and the 1985 followup study, were presented in the Baseline Morbidity Study Results (24 February 1984) and the Air Force Health Study First Followup Examination Results (15 July 1987).

The complete report is available from the NATIONAL TECHNICAL INFORMATION SERVICE, 5285 Port Royal Road, Springfield, Virginia 22161, phone number AC(703)487-4650 (sales) or AC(703)487-4690 (information).

EXECUTIVE SUMMARY

1987 FOLLOWUP MORBIDITY REPORT

The Air Force Health Study is an epidemiologic investigation 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, based on a matched cohort design in a nonconcurrent prospective setting with followup studies. The Baseline study was conducted in 1982, and the first two followup morbidity studies were performed in 1985 and 1987. The purpose of this report is to present the results of the 1987 followup.

In the Baseline morbidity study, each living Ranch Hand was matched to the first living and compliant member of a randomly selected Comparison set based on age, race, and military occupation, producing an approximate 1:1 contrast. The Comparisons had served in numerous flying organizations that transported cargo to, from, and within Vietnam but were not involved in the aerial spraying of Herbicide Orange. All previous participants and refusals, newly located study members, and replacements (matched on reported health status) were invited. Eighty-four percent (995/1,188) of the eligible Ranch Hands and 77 percent (939/1,224) of the eligible Original Comparisons participated in the 1987 followup examination and questionnaire process. Participation among those who were fully compliant at Baseline was very high. Ninety-two percent of the Ranch Hands and 93 percent of the Comparisons who were fully compliant at Baseline also participated in the 1987 followup. In total, 2,294 study subjects, 995 Ranch Hands and 1,299 Comparisons, participated in the 1987 followup.

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 and 1985 data bases. As a contract requirement, all data collection personnel were unaware of each participant's 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, logistic regression, proportional odds models, t-tests, and log-linear models, all of which were specified in an analytical plan written prior to data analysis.

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 1987 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.

In the analyses in this report, Ranch Hand exposure to dioxin was quantified by use of a calculated index based on the quantity of herbicides containing dioxin sprayed each month and the number of Ranch Hands assigned to each occupational category in those months. The statistical relationships between the evaluated conditions and the calculated index were assessed for significance and patterns suggestive of dose-response. However, early results of serum dioxin studies in Ranch Hand personnel conducted at the Centers for Disease Control indicate the calculated index is not a good measure of actual dioxin exposure. Therefore, the results of analyses using the calculated exposure index should be interpreted with caution. A full report relating the serum assay results to the medical data contained in this report is expected in 1991.

The fixed size of the Ranch Hand cohort limits the ability of the study to detect group differences, particularly for the rare occurrences of soft tissue sarcoma and non-Hodgkin's lymphoma. The study has virtually no statistical power to detect low to moderate group differences for these malignancies. The study has good power to detect relative risks of 2.0 or more with respect to disease occurring at prevalences of at least 5 percent in the Comparison group, such as basal cell carcinoma.

Self-perception of health, appearance of illness or distress, relative age, and percent body fat were similar in the two groups. There has been a decline in the percentage of individuals reporting their health as fair or poor in both groups since the Baseline examination. A significantly greater percentage of Ranch Hands than Comparisons, however, had abnormal erythrocyte sedimentation rates. Only three participants (two Ranch Hands and one Comparison) had rates in excess of 100 mm/hr. The Comparison had lung cancer and died in early 1989. In neither of the Ranch Hands was a diagnosis established during the course of the 1987 followup. A significant difference was also detected at the 1985 followup examination, and it will be important to monitor the sedimentation rates in subsequent examinations.

For all verified neoplasms combined, Ranch Hands had a significantly greater frequency than the Comparisons. Ranch Hands also had a marginally significant greater frequency than the Comparisons when suspected neoplasms were included in the analysis. Because cancers fall into systemic or skin categories, group contrasts were performed within each category. Analyses restricted to systemic neoplasms revealed no significant differences between the Ranch Hands and Comparison groups. Focusing only on skin neoplasms, Ranch Hands had significantly or marginally significant higher frequencies for the following categories: all verified skin neoplasms, all verified and suspected skin neoplasms, all verified malignant skin neoplasms, and sun exposure-related malignant skin neoplasms. Significant group differences for the sun exposure-related malignant skin neoplasms are not surprising because approximately 90 percent of the participants with those neoplasms had verified basal cell carcinomas, and Ranch Hands had significant or marginally significant higher frequencies of verified basal cell carcinoma than the Comparisons.

The neurological assessment did not disclose significant findings detrimental to the health of the Ranch Hands, although several differences were noted. Of the six reported and verified neurological diseases and disorders,

the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological diseases. Unadjusted analyses for the 30 physical examination variables showed marginally more balance/Romberg sign and coordination abnormalities in the Ranch Hand group than in the Comparison group. In the adjusted analyses, a significant difference in the relative risk for the cranial nerve index (without range of motion) occurred with insecticide exposure. Stratified results showed that among those who had never been exposed to insecticides, significantly more Ranch Hands than Comparisons were abnormal on this index. Of those who had been exposed to insecticides, the percentage of abnormalities on this index was marginally higher in the Comparisons. The adjusted analysis for coordination detected two significant group-by-covariate interactions (group-by-occupation and group-by-insecticide exposure). Stratified analyses found a significant group difference for enlisted groundcrew after excluding the group-by-insecticide exposure interaction, and a significant adjusted group difference overall after excluding both group-by-covariate interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The trend of increasing abnormality in the enlisted groundcrew for coordination will be more fully evaluated in the analyses of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels.

The psychological assessment was based on the analysis of 52 variables, which included reported illnesses verified by medical record review, reported sleep disorders, and scores from two clinical psychological tests. The results showed that significant or marginally significant differences between the Ranch Hands and the Comparisons were found for some verified psychological disorders, reported sleep disorders, and the self-administered Symptom Checklist-90-Revised and Millon Clinical Multiaxial Inventory psychological examinations. For these differences, the Ranch Hands generally manifested higher percentages of abnormalities or higher mean scores than the Comparisons. However, this is not surprising since individuals who perceive themselves as having been harmed might be more likely to report the symptoms found to be significant in this analysis. These results will be reexamined for positive correlations between the complaints and dioxin levels when the serum assay data become available. Additionally, significant group-by-covariate interactions were frequently observed in the adjusted analysis, which often made direct contrast of the two groups with adjustment for significant covariates difficult. The covariates of age, alcohol history, and presence of post-traumatic stress disorder showed strong effects on many of the psychological measurements. There was generally a lack of consistency in the findings of similar variables in the psychological tests.

The gastrointestinal assessment found no significant group difference for historical liver disease, historical and current ulcer, and current hepatomegaly. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, but group differences for the other laboratory examination variables (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, lactic dehydrogenase, cholesterol, high density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, creatine kinase, and fasting glucose) were not significant.

In the dermatologic assessment, no cases of chloracne were diagnosed. For participants with no history of acne before the start of the first Southeast Asia (SEA) tour, a greater percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour. However, the anatomic pattern of these lesions was not suggestive of chloracne. No other significant group differences were detected in the remainder of the analyses. The exposure index and longitudinal analyses were also essentially negative; the few positive findings were inconsistent with dose-response effects and the available knowledge of current serum TCDD levels in the Ranch Hand group.

The cardiovascular evaluation showed that the health of the two groups was similar for reported and verified heart disease and central cardiac function. With regard to peripheral vascular function, the Ranch Hands manifested a marginally higher mean diastolic blood pressure than the Comparisons, but the percentage of individuals with a diastolic blood pressure above 90 mm Hg was not significantly different in the two groups. The Ranch Hands had a marginally higher percentage of individuals with carotid bruits, and there were also significant, or marginally significant, differences with respect to femoral pulses, dorsalis pedis pulses, and three aggregates pulse indices (leg, peripheral, and all pulses), as assessed by manual palpation. Significantly more pulse abnormalities in the Ranch Hands were also found at Baseline, when pulses were measured by manual palpation, but not in the 1985 followup, when both manual and Doppler measurements were utilized.

In the hematologic evaluation, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not significantly different in the two groups. The mean white blood cell and platelet counts were significantly greater in the Ranch Hands than in the Comparisons, but the magnitude of the difference was small in each case. The difference in platelet counts was significant despite that in the longitudinal analysis of the changes from Baseline to the 1987 followup examination, platelet counts in the Ranch Hands decreased to a significantly greater degree than in the Comparisons. The percentage of individuals with abnormally high platelet counts was also significantly greater in the Ranch Hand group, but the relative risk was less than 2. In addition, no platelet count was elevated into a pathologic range. Exposure index analyses did not generally support dose-response relationships.

The groups did not differ significantly in reported history of kidney disease/stones or for urinary protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, or urine specific gravity based on unadjusted analyses. In the adjusted analyses, there was no pattern of results that suggested a detriment to either group.

For the endocrinologic assessment, the Ranch Hand thyroid stimulating hormone (TSH) mean was marginally significantly higher than the Comparison TSH mean, but results of the TSH discrete analyses did not show statistically significant group differences. Mean levels for triiodothyronine percent (T_3 %) uptake, testosterone, and 2-hour postprandial glucose were similar between groups. The percentage of abnormal levels for each of these variables, and the composite diabetes indicator, was higher for the Ranch Hand group than for the Comparison group, but none of these differences was statis

tically significant. Self-reported data on current thyroid function and past history of thyroid disease were similar between groups. Also, the percentages of participants with thyroid or testicular abnormalities diagnosed at the physical examination were not statistically different between groups. Overall, the endocrinologic health status of the Ranch Hand group does not appear substantially different from the Comparison group.

For the immunologic assessment of the 1987 followup, Ranch Hands and Comparisons did not differ on the cell surface markers, functional stimulation tests, total lymphocyte counts, or quantitative immunoglobulins. Statistical analyses of the natural killer cell assay variables adjusting for covariate information were conducted within the Black and nonblack strata. These analyses showed that Black Ranch Hands had higher adjusted mean counts and average percent releases than the Black Comparisons for the natural killer assay measures. The meaning of this observation is unknown. Without adjusting for covariate information, significantly more Ranch Hands had a possibly abnormal reading on the composite skin reaction test than the Comparisons. Adjusting for covariate information resulted in performing group contrasts on the composite skin reaction variable within strata of the lifetime cigarette smoking history variable. For the heavier smoking participants, significantly more Ranch Hands had a possibly abnormal reading on the composite skin reaction test than the Comparisons. Within the other strata, there were no significant differences.

The pulmonary health of the two groups was reasonably similar based on the analyses without adjustment for covariates, although the Ranch Hands had significantly more thorax and lung abnormalities and marginally higher prevalence rates for hyperresonance. When significant interactions involving group were ignored, no significant differences were found in the adjusted analyses. Exploration of the interactions did not identify a consistent pattern. The adverse effects of smoking were evident in all analyses.

The process of inferring causality is complex and must be based on careful consideration of many factors. Any interpretations of the data must consider the biological plausibility, clinical significance, specificity and consistency of the findings, and a host of statistical factors, such as strength of the association, lack of independence of the measurements, and multiple testing. Based on direct and indirect evidence, it is concluded that this study is free of overt bias and the measurement systems used to obtain the data were accurate and valid.

In summary, there is not sufficient evidence at this time to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group. No cases of chloracne or porphyria cutanea tarda, the two most commonly accepted effects of dioxin exposure, were detected in this study. There was a single case of soft tissue sarcoma in each group and one case of non-Hodgkin's lymphoma in a Ranch Hand. The differences noted indicate that reanalysis using dioxin body burden levels and continued medical surveillance are warranted.

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AIR FORCE HEALTH STUDY
1987 FOLLOWUP MORBIDITY SUMMARY REPORT

BACKGROUND

INTRODUCTION

In January 1962, President John F. Kennedy approved a program of aerial herbicide dissemination, for the purpose of defoliation and crop destruction, in support of tactical military operations in the Republic of Vietnam (RVN). Under this program, code-named Operation Ranch Hand, approximately 19 million gallons of herbicides were dispersed on an estimated 10 to 20 percent of South Vietnam. From 1962 to 1971, approximately 11 million gallons of Herbicide Orange, the primary defoliant of the six herbicides utilized in the program, were disseminated.

Operation Ranch Hand was the subject of intense scrutiny from the start due to the controversial nature of the program and political sensitivity to chemical warfare charges contained in enemy propaganda. The concerns, which were initially based on military, political, and ecological issues, shifted during 1977 to health issues. Numerous claims of exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, and subsequent adverse health effects among U.S. military service personnel have resulted in class action litigation and substantial controversy. Social concern for the Herbicide Orange issue continues to be manifest by continuing scientific research, media presentations, congressional hearings, and legal action.

The U.S. Air Force Medical Service's concern for the health of Air Force personnel exposed to herbicides was demonstrated in October 1978 when the Air Force Deputy Surgeon General made a commitment to Congress and to the White House to conduct a health study on the Ranch Hand personnel, the men who disseminated the majority of the defoliants in the RVN. The prevailing reasons for the Air Force Health Study (AFHS) commitment included the availability of a definitive occupational exposure to herbicides, a sufficient sample size for survey and clinical research, the ability to ascertain the population at risk, and an opportunity for the Air Force Medical Corps to fulfill its adage "we care" to the Air Force community.

The Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas, was tasked by the Surgeon General to develop the Study Protocol. In 1982, after extensive peer review, the epidemiologic study began, and the Protocol was published.

Since 1978, numerous animal and human studies of dioxin effects have been planned or initiated by governmental agencies, universities, and industrial firms. The key scientific issue in these studies was the extent of exposure, e.g., who was exposed and how much each individual was exposed. Unfortunately, population identification and exposure estimation, which are critical for a valid study of ground troops, have been scientifically elusive.

It is believed that of all the military personnel who served in the RVN, the Ranch Hand population was the most highly exposed to herbicides. In 1987, the Air Force initiated a collaborative study with the Centers for Disease Control (CDC) to measure the serum dioxin levels in the AFHS morbidity population. The results of that study clearly demonstrate that substantially elevated levels of dioxin can still be found in the serum of some Ranch Hands, as opposed to the absence of elevated levels found in ground troops by CDC. Based on the principle of dose-response, the Ranch Hands should manifest more and/or earlier evidence of adverse health. Thus, the results of the AFHS should serve as an indicator of herbicide effects in ground personnel.

STUDY DESIGN

The purpose of the study is to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study, consisting of mortality and morbidity components, is based on a matched cohort design in a nonconcurrent prospective setting with followup studies. 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 attributable adverse health effects. Complete details on the design are provided in the Study Protocol.

For the Baseline study, the population ascertainment process identified 1,264 Ranch Hand personnel who served in the RVN between 1962 and 1971. By the time the first followup began in 1985, an additional 9 Ranch Hands had been identified. Two years later for the second followup, four additional Ranch Hands were identified. A Comparison group was formed, consisting of individuals assigned to Air Force units operating C-130 cargo aircraft in Southeast Asia. Using a computerized nearest neighbor selection procedure, a maximum of 10 Comparisons was selected for each Ranch Hand, matching on age, race, and military occupation. After personnel record reviews, each Ranch Hand who was determined to be eligible and fully suitable for study had an average of 8.2 Comparison subjects.

The mortality component addresses mortality from the time of the RVN assignment. A Baseline mortality study was conducted in 1982, and the mortality followup consists of annual mortality updates for 20 years. For the Baseline study and the first four updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design. Subsequent to 1987, the design was expanded to include all of the individuals in the Comparison population.

The Baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of mental and physical health, was based on comprehensive questionnaires and physical examinations given to the participants. For this component of the study, each living Ranch Hand and the first living member of his Comparison set were selected to participate in the examination. Sequential questionnaires, medical record reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002 comprise the morbidity study followup.

MORBIDITY COMPONENT

The Baseline morbidity assessment, conducted in 1982, disclosed some differences between the Ranch Hands and Comparisons, but those differences were generally not traditional indicators of dioxin-related disease. The sustained commitment of Congress and the Air Force to pursue the Agent Orange question to its scientific conclusion was demonstrated by the conduct of the first two morbidity followups in 1985 and 1987. The first (1985) followup provided the first opportunity to confirm or refute some of the Baseline findings and to explore longitudinal changes. For the 1985 followup, the mental and physical health status of the participants during the 3-year interval since the Baseline study was assessed. The results of the 1985 followup approximated those of the Baseline examination; however, the Ranch Hands continued to manifest slightly more adverse health conditions than the Comparisons.

In 1987, the second followup was initiated. During a 2-1/2 year period, the data were collected, automated, and analyzed. The 1987 followup was conducted by Science Applications International Corporation (SAIC) in conjunction with Scripps Clinic and Research Foundation and National Opinion Research Center, working as a team with the Air Force.

PURPOSE

The 1987 morbidity followup is the subject of this report. The objective of the morbidity followup is to continue the investigation of the possible long-term health effects following exposure to herbicides containing 2,3,7,8-tetrachlorodibenzo-p-dioxin (or TCDD). This summary describes the procedures and results of the second morbidity followup of the AFHS. Although the blood samples for the measurement of serum dioxin levels were collected during the 1987 followup, the results of this testing are not yet available.

SUMMARY

The study population for the 1987 followup of the AFHS consisted of 2,294 participants: 995 Ranch Hands and 1,299 Comparisons. The personal characteristics and habits of the Ranch Hands and Comparisons were contrasted. The variables selected to characterize the two groups included all of the candidate covariates in the adjusted analyses of clinical endpoints.

The two groups were contrasted on the matching variables (age, race, and occupation), drinking habits, smoking habits, sun exposure characteristics, exposure to carcinogens, selected personal and family health variables, risk-taking behavior, and other characteristics (education, blood type, personality type, post-traumatic stress disorder (PTSD), current military status, and 1986 individual income).

No difference between the two groups were found for the matching variables, personal and family health variables, and other characteristics. The Ranch Hands and Comparisons reported similar current and lifetime alcohol use; however, the average current alcohol use was higher for the Comparisons and

the Ranch Hands had a higher average lifetime alcohol history. These differences were not significant. Significantly more Comparisons than Ranch Hands drank wine at the time of the 1987 followup; however, the mean numbers of wine drinks per day were not significantly different. For lifetime wine history, the distribution of wine drinkers (nonwine drinkers, moderate wine drinkers, and heavy wine drinkers) was significantly different for the two groups. The Comparisons had a higher percentage of moderate wine drinkers than the Ranch Hands. However, the mean number of wine drink-years for the two groups was similar.

At the time of the 1987 followup, the Ranch Hands smoked significantly more cigarettes than the Comparisons. The Ranch Hands had a higher average lifetime cigarette smoking history than the Comparisons, but this difference was not significant. The two groups had similar current cigar, current pipe, and past and recent marijuana smoking habits.

The two groups reported similar sun exposure characteristics. However, significantly more Comparisons than Ranch Hands had an average lifetime residential latitude of less than 37 degrees North.

Differences in reported exposure to carcinogens were assessed for 21 carcinogens or groups of carcinogens and one composite exposure variable constructed from reported exposure to 15 of 21 carcinogens. As anticipated, significantly more Ranch Hands than Comparisons reported being exposed to herbicides and insecticides. Reported ionizing radiation exposure was significantly higher in the Comparisons. Marginally significant differences were detected in reported exposure to arsenic (Comparisons>Ranch Hands), chromates (Ranch Hands>Comparisons), and naphthylamine (Ranch Hands>Comparisons). More Ranch Hands than Comparisons reported being exposed to at least one of the carcinogens used to construct the composite exposure variable; the difference was marginally significant. No differences were detected for the other 15 carcinogen variables.

The risk-taking behavior of the two groups was characterized by participation in nine potentially dangerous recreational activities. Significantly more Ranch Hands than Comparisons reported that they had ever ridden surfboards. No differences in participation in the other eight activities were identified.

In summary, the 995 Ranch Hands and 1,299 Comparisons who participated in the 1987 AFHS followup were found to have similar personal characteristics and habits.

EXPOSURE INDEX

INTRODUCTION

An increased incidence of adverse health effects at higher levels of exposure represents a classic increasing dose-response relationship. The potential relationship of clinical endpoints with herbicide exposure can be tested using an estimate of exposure, hereinafter called an exposure index, for each member of the Air Force Health Study Ranch Hand cohort.

An index of potential exposure to any of four 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-containing herbicides from fixed-wing spray missions was constructed for each Ranch Hand from the available historical data. The index serves as an estimate only, since the actual concentration of TCDD in the herbicides varied from lot to lot and individual assessments of actual body burden during or just after exposure in Vietnam were not feasible. The four TCDD-containing herbicides used in the development of the index are Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green. The exposure index was designed to correlate as closely as possible with exposure and is not an exact measure of actual individual exposures. Although the index contains errors when used to assess the exposure of a specific individual, it was thought to provide some degree of useful inference for groups of similarly exposed individuals. The exposure index for each subject is defined as the product of the TCDD weighting factor, the gallons of TCDD-containing herbicide sprayed in the Republic of Vietnam (RVN) theater during the tour of the subject, and the inverse of the number of men sharing the subject's duties during the tour of the subject. Each of these factors is described below.

The TCDD weighting factor reflects the estimated relative concentration of TCDD in the herbicides sprayed. The estimated mean concentrations of TCDD in Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green are 2 parts per million (ppm), 33 ppm, 66 ppm, and 66 ppm, respectively. Archived samples of Herbicide Purple indicate a mean concentration of approximately 33 ppm, and samples of Herbicide Orange had a mean concentration of about 2 ppm. Since Herbicide Pink and Herbicide Green contained twice as much 2,4,5-T as Herbicide Purple, the estimated mean concentration of TCDD in these two herbicides was approximately 66 ppm. Based on procurement records and dissemination information, a combination of Herbicide Green, Herbicide Pink, and Herbicide Purple was sprayed between January 1962 and 1965. Using available data on the number of gallons procured and sprayed, the estimated mean concentration of TCDD for this time period was 48.0 ppm.

The Herbs Tape and other data sources indicate that only Herbicide Orange was disseminated after 1 July 1965. Normalizing to Herbicide Orange, the weighting factor becomes 24.0 before 1 July 1965 and 1.0 after 1 July 1965.

Using the Herbs Tape, Contemporary Historical Evaluation and Combat Operations Reports, and quarterly operations reports, a table of gallons of TCDD-containing herbicide sprayed for each month of the operation was constructed. Gallons of Herbicides Purple, Pink, and Green were converted to Herbicide Orange equivalent gallons based on the TCDD weighting factor of 24.0. This information is provided in Table E-1 in the main report.

The dates and occupational category of each Ranch Hand's tour(s) in the RVN were obtained by a manual review of military records. The study design specified five occupational categories: (1) officer-pilot, (2) officer-navigator, (3) officer-nonflying, (4) enlisted flyer, and (5) enlisted groundcrew. Based on the review of the records, the Ranch Hand manning for each occupational category by month was compiled.

A numeric exposure index reflecting the effective number of gallons of Herbicide Orange to which each individual was potentially exposed was computed. For analysis purposes, the values were categorized as high, medium, or

low for each occupational category. Only three occupational categories were used. The three officer categories were combined into one since pilots and navigators were exposed in the same manner and the officer-nonflying category, which included a relatively small number of participants, consisted of administrators whose exposure was considered to be essentially zero. The overall group of "nonexposed" Ranch Hands, estimated at approximately 2 percent of the Ranch Hand group, was analyzed in the low exposure category (see Table 1), conceivably leading to dilution of the exposure analyses and group contrasts.

TABLE 1.
Exposure Index Categorization of
995 Compliant Ranch Hands

Occupational Group	Exposure Category	Effective Herbicide Orange Gallons Corresponding to Exposure Category	Number of Ranch Hand Participants in Exposure Category
Officer	Low	<35,000	130
	Medium	35,000-70,000	124
	High	>70,000	125
Enlisted Flyer	Low	<50,000	55
	Medium	50,000-85,000	63
	High	>85,000	53
Enlisted Groundcrew	Low	<20,000	147
	Medium	20,000-27,000	158
	High	>27,000	140
Total			995

The exposure index categorizations developed for the Baseline study and used in this report are provided in Table 1, along with the frequencies of Ranch Hand participants by occupation and exposure level. The cutpoints for the categories of the exposure index were the 33rd and 66th percentiles of the exposure index distributions within each of the three occupational strata (officer, enlisted flyer, and enlisted groundcrew). Ranch Hands with administrative duties were assigned an index of zero.

DISCUSSION

The calculated exposure index is not specific to each individual and, therefore, may underestimate exposure for those individuals whose jobs required routine handling of herbicide. For example, maintenance schedules for the aircraft herbicide spray tank required that an emergency dump valve be periodically greased, requiring entry into the tank. The current exposure

index cannot distinguish between men who received such exposure and men who did not. The extent to which individuals are misclassified by the current exposure index is not known, precluding bias calculations at this time.

Every laboratory and physical examination endpoint in this study was assessed for dose-response effects versus the calculated exposure index. Current TCDD assay results did not correlate with the exposure index, with or without adjustment for time since exposure. These exposure index analyses are presented because some members of the Advisory Committee of the Science Panel of the Agent Orange Working Group advised that they be included in this report.

Because of the acknowledged imprecision of the exposure index, Air Force efforts are under way to measure TCDD levels in serum collected from participants in the 1987 followup. Serum was obtained for 1,999 of the 2,294 participants and is currently being analyzed by the Centers for Disease Control. As of September 1989, results of 1,366 serum specimens (888 Ranch Hands and 468 Comparisons) have been reported. These results are summarized in Table 2.

These results indicate that (1) Comparisons have background levels; (2) Ranch Hands have higher current TCDD levels than Comparisons; and (3) among Ranch Hands, nonflying enlisted personnel have the highest and officers have the lowest TCDD levels.

The relationship between current TCDD body burden and the constructed exposure index will be described in a future report. This report is expected in early 1991.

TABLE 2.
Serum TCDD Results

Stratum	Ranch Hand			Comparison		
	Sample Size	Median*	Range*	Sample Size	Median*	Range*
Officer--Pilot	247	7.3	0.0-42.6	118	4.7	0.0-13.1
Officer--Navigator	63	9.3	1.1-36.0	27	4.9	2.4-7.9
Officer--Nonflying	19	6.7	3.0-24.9	4	4.0	0.0-4.6
Enlisted Flyer	152	17.2	0.0-195.5	76	4.3	0.0-12.8
Enlisted Groundcrew	407	23.6	0.0-617.8	243	4.2	0.0-54.8
All Personnel	888	12.4	0.0-617.8	468	4.4	0.0-54.8

*In parts per trillion.

GENERAL HEALTH

INTRODUCTION

The effects of heavy, acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin) have been demonstrated in a number of different organ systems. It is plausible, therefore, that chronic low-dose exposure to TCDD might induce subtle, interrelated effects that are not organ-system specific, but are manifest only in general terms, or affect the state of "well-being." Numerous animal studies and studies of exposed populations have shown that many enzyme induction systems throughout the body are affected by TCDD, which may have wide-ranging results. However, it is difficult to measure overall health objectively. For this reason, general health outcomes, as defined by this study, should be judged in context with other more specific clinical endpoints.

DISCUSSION

In clinical practice, the assessment of general health must be based on subjective and objective indices. In ambulatory medicine, particularly, the presence of occult disease cannot be excluded by negative laboratory tests directed at specific organ systems. Further, in the present study, it is reasonable to assume that the self-perception of health might be influenced by a participant's perception or concern of prior herbicide exposure.

The five variables considered in this section are frequently employed by clinicians in outpatient practice. On physical examination, the facial appearance of distress or of premature aging can often alert the physician to the presence of occult disease despite the absence of abnormalities in laboratory testing.

The erythrocyte sedimentation rate can be a sensitive, if nonspecific, index of general health. Pertinent to the longitudinal design of the current study is the effect of age: a rate as high as 40 mm per hour is considered within the range of normal for age 65. Extreme elevations in the erythrocyte sedimentation rate are consistently associated with serious underlying disease, usually malignancy.

Like the erythrocyte sedimentation rate, the percent body fat is an easily measurable, objective parameter of good health. Whereas obesity is a risk factor for cardiovascular disease and can contribute to hypertension and diabetes mellitus, it is often the patient with unexplained weight loss who is clinically of concern. Among the disorders considered in the current study that can induce unintentional weight loss were metabolic diseases (such as diabetes mellitus and hyperthyroidism); occult malignancy (most often lung or colon); drug abuse (for example, alcoholism and cocaine addiction); and emotional illness (such as anxiety or depression). To the extent that it can reflect significant weight gain or loss, the percent body fat can serve as a clinical clue to the presence of occult disease.

With regard to the self-perception of health, both Ranch Hand and Comparison group distributions were similar, with 6.7 percent of the members

in each group reporting fair or poor health. Also, a trend of fewer individuals reporting fair or poor health in 1987 than at the Baseline or 1985 followup studies was observed. As expected, analysis of the age covariate reveals slightly poorer self-perception of health with advancing age.

In the present study, only 16 participants were reported as appearing ill; 9 from the Ranch Hand group and 7 from the Comparisons. The total number is small and the difference was not statistically significant. In addition, the chronically ill suffered from a diverse group of illnesses, including severe anemia, diabetes, renal failure, and malignancy. No single diagnosis or group of similar diagnoses contributed to the appearance of illness or distress. As would be anticipated, there was an increased incidence of chronic illness over time.

With regard to relative age, there was no difference found between the two groups. In 1985, the mean percent body fat was lower in the Ranch Hand group than in the Comparisons, but by 1987, the difference was not statistically significant.

Though (geometric) mean sedimentation rates were very similar in the two groups, there was a statistically significant difference in the percentage of individuals with a sedimentation rate above 20 mm/hr (7.0% of the Ranch Hands vs. 4.2% of the Comparisons). However, only three participants (two Ranch Hands and one Comparison) were found to have rates in excess of 100 mm/hr. One participant, a Comparison, proved to have lung cancer and died in early 1989. In neither of the other participants was a diagnosis established during the course of the 1987 followup.

Based on the current examination variables, no clinically significant group differences were found in the general health of the Ranch Hands versus the Comparisons. Some concern is raised in the overall and longitudinal analyses of the erythrocyte sedimentation rate data. In contrast to the 1982 Baseline, a higher percentage of Ranch Hands was found to have abnormally elevated (>20 mm/hr) levels in both the 1985 and 1987 followup examinations ($p=0.013$ and $p=0.003$, respectively). Though of uncertain cause, this finding raises the possibility that some clinically occult disease process may be present in the Ranch Hand cohort and highlights the need to follow the sedimentation rate in subsequent examination cycles.

SUMMARY

General health was assessed by five measures (self-perception of health, appearance of illness or distress, relative age, percent body fat, and erythrocyte sedimentation rate). Table 3 presents a summary of all of the unadjusted and adjusted analyses performed for these five variables.

There were no significant differences, unadjusted or adjusted for covariates, nor any significant group-by-covariate interactions, for self-perception of health, appearance of illness or distress, relative age, or percent body fat. The percentage of participants reporting their health as fair or poor was equal in the Ranch Hand and Comparison groups, namely, 6.7 percent. This percentage was slightly less than that observed at the 1985 followup examination and less than half of that noted at the Baseline examination.

Sixteen individuals were reported by their examining physicians as appearing acutely ill or distressed at the 1987 Followup, nine (0.9%) from the Ranch Hand group and seven (0.5%) from the Comparisons. Relative age was likewise distributed similarly in the two groups, with 5.5 percent of the Ranch Hands and 5.8 percent of the Comparisons appearing older than their stated ages, and approximately 1 percent in each group appearing younger than their stated ages.

Only nine individuals (four Ranch Hands and five Comparisons) were lean (<10% body fat); 19.3 percent of the Ranch Hands and 22.0 percent of the Comparisons were obese (>25% body fat). The mean percent body fat was 21.6 in the Ranch Hands and 21.8 in the Comparisons. These means were not significantly different.

Continuous analyses of sedimentation rate did not reveal a significant group difference. Geometric mean values were 5.3 mm/hr in the Ranch Hands and 5.1 mm/hr in the Comparisons. However, there was a highly significant group difference in the percentage of individuals with an abnormal sedimentation rate (>20 mm/hr): 7.0 percent of the Ranch Hands compared to 4.2 percent of the Comparisons (Est. RR: 1.74, 95% C.I.: [1.21, 2.51], p=0.003)*. The relative risk was essentially unchanged after adjustment for age, race, occupation, and personality type (Adj. RR: 1.70). A significant group difference in the percentage of individuals with an abnormal sedimentation rate was also found at the 1985 followup examination, but not at the Baseline examination.

Unadjusted exposure index analyses did not detect any significant dose-response relationships in any of the occupational cohorts (officers, enlisted flyers, enlisted groundcrew). Adjusted exposure index analyses did reveal a significant exposure index-by-age interaction for percent body fat within the enlisted flyers and significant exposure index-by-age and exposure index-by-race interactions for sedimentation rate, also within the enlisted flyers. Further examination of these interactions, however, did not reveal significant dose-response relationships except for percent body fat among individuals born in or after 1942 (p=0.048, based upon small numbers). None of the 11 individuals in the low exposure category was obese, compared to 2 of 18 in the medium exposure category and 4 of 11 in the high exposure category.

Longitudinal analyses of self-perception of health and sedimentation rate found no significant difference for health perception, with a similar decline in both groups over time in the percentage of individuals reporting their health as fair or poor. For sedimentation rate, there was a significant group difference in the change from the Baseline to the 1987 followup examination: four times as many Ranch Hands went from normal at Baseline to abnormal at the 1987 followup than vice versa, whereas roughly equal numbers shifted in each direction among the Comparisons. The clinical implication of the statistical difference in this nonspecific medical parameter is unclear, and its relevance to the health of the Ranch Hand group must be evaluated in the light of the results in the other clinical areas.

*Est. RR - estimated relative risk

C.I. - confidence interval

p = p-value

See Chapter 7 (Statistical Methods) in the main report for a complete definition of terms.

TABLE 3.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of General Health Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
<u>Questionnaire</u>					
Self-Perception of Health	NS	--	NS	--	
<u>Physical Examination</u>					
Appearance of Illness/Distress	NS	--	NS	--	
Relative Age	NS	--	NS	--	
Percent Body Fat	NS	NS	NS	NS	
<u>Laboratory</u>					
Sedimentation Rate	0.003	NS	0.005	NS	RH>C

--Analysis not performed.

NS: Not significant ($p > 0.05$).

RH>C: Ranch Hand percent abnormal greater than Comparison percent abnormal.

MALIGNANCY

INTRODUCTION

Cancer is a major suspect disease following exposure to chlorophenols, phenoxy herbicides, and dioxin. Both systemic cancer and skin cancer are key focal points of this study.

The issue of military service-related cancer in Vietnam veterans first arose in 1978-1979. Media presentations emphasized early cancer deaths in several Army veterans, which were allegedly caused by exposure to Agent Orange. The media reinforced this perception of increased cancer risk by citing animal studies, which demonstrated a carcinogenic effect, and a few human studies, which showed excessive cancer in specific occupational groups.

Traditional difficulties in extrapolating animal data to humans and inter-species variability have limited the direct applicability of much of the experimental work. Other major challenges have included difficulties in the ability to control or characterize bias; selection of suitable controls or reference groups; quality and quantity of exposure; misclassification of exposure; confounding exposure to known injurious chemicals; sample size and statistical power; number and selection of relevant risk factors; and the lack of clearly defined clinical endpoints for study.

For these reasons, there is no scientific consensus on the dioxin-cancer question. There is, however, concern over soft tissue sarcomas (STS) and non-Hodgkin's lymphoma (NHL).

Numerous animal studies have been conducted to delineate the role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on tumor initiation, tumor promotion, mutagenesis, cocarcinogenesis, and deoxyribonucleic acid (DNA) reactivity. The consensus of most research is that TCDD is only weakly mutagenic, does not covalently bind to DNA or cause it to initiate repair synthesis, and behaves as a strong tumor promoter in already initiated cells. Recent animal studies have supported the theory that TCDD-induced response is mediated by a nongenotoxic mechanism. TCDD, binding to the Ah receptor, appears to alter cellular regulatory mechanisms that are reflected by enhanced cellular proliferation.

DISCUSSION

In ambulatory medicine, the recommendation that asymptomatic individuals undergo periodic physical examinations is based largely on the assumption that such screening will reveal occult malignancy. Although the guidelines for the frequency and content of such examinations are subject to debate, there is no doubt that early detection affords the best and, in most forms of cancer, the only chance for cure. In this regard, while no one screening test is absolutely reliable, the scope and depth of the protocol employed in this longitudinal study far exceed what would be considered routine in clinical practice.

As the anatomic point of contact with industrial toxins and as the only organ system with a clearly defined clinical endpoint (chloracne) for TCDD exposure, the skin deserves the special emphasis it has received in this and in previous examination cycles. Though to date there is no epidemiologic evidence that TCDD exposure causes or that chloracne is associated with the development of basal cell carcinoma, an increased incidence of these skin cancers in the Ranch Hand cohort was found in the Baseline, and in the 1985 followup and 1987 followup examinations. Subsequent to the Baseline, heightened efforts were made to clarify the contribution of such well-known risk factors as hair and eye color, complexion, ethnic background, and lifetime sun exposure.

While most of the systemic neoplasms subjected to analysis can be detected based on the history, physical examination, and laboratory data collected, several would require diagnostic studies beyond the scope of the current study. Reliably found on physical exam are tumors of the face, head and neck, oral cavity and pharynx (but not the hypopharynx or larynx), thyroid, prostate, and genitalia. The chest x ray can be relied upon to screen for tumors

of the thymus, mediastinum, and lung, while the routine urinalysis, in disclosing hematuria, can signal the presence of kidney and bladder cancer. Recognizing the silent nature of digestive tract cancers, particularly those of colorectal origin, participants were encouraged to complete Hemoccult panels and, in positive cases, were offered sigmoidoscopy during their examinations.

Most of the significant dependent variable-covariate associations defined in these analyses would be expected based on patterns established in clinical practice. For basal cell skin cancers, positive associations were found with the classical risk factors of age, fair complexion, and average residential latitude.

Given the current knowledge of exposure levels in the Ranch Hand cohort, the higher frequency of basal cell carcinomas in the officers relative to the enlisted groundcrew (8.7% vs. 5.3%) does not provide evidence for the role of herbicides in the etiology of these cutaneous cancers. Of interest was the reduced frequency of basal cell cancer in those participants with the greatest skin sensitivity to sunlight, a finding that is consistent with behavior modification and exposure precaution in those most at risk.

In practice, dermatologists will vary in what they consider to be indications for the biopsy of suspicious lesions as called for in the study protocol. Acting independently and strictly blinded to the participants' exposure status, three dermatologists performed a total of 39 biopsies. As noted in Chapter 14 of the main report, the close to equal number of biopsies in the Ranch Hands (19) and Comparisons (20) provides reassurance against the possibility of any significant selection bias in those lesions verified histologically.

With reference to the analysis of systemic neoplasms, the expected age-related increase in the incidence of cancer was documented in the total study population. The well-established clinical correlation of alcohol consumption with the development of systemic cancer was also observed ($p=0.041$). The Ranch Hand and the Comparison groups did not differ with respect to the frequency of systemic neoplasms. As in the Baseline and 1985 followup examinations, the relative frequency of verified cases of malignant systemic neoplasms did not differ significantly by group (2.1% in Ranch Hands, 1.6% in Comparisons). The number of cancers in specific categories was small and therefore statistical power to detect relative risks for specific cancers was low.

For the 1985 followup, one Ranch Hand and one Comparison had verified STS (fibrous histiocytoma and fibrosarcoma, respectively). The Ranch Hand was not part of the 1987 followup because he died; the Comparison with the fibrosarcoma was part of the 1987 followup. At the 1985 followup, one Ranch Hand was classified as a suspected leukemia, Hodgkin's Disease, or NHL. He was diagnosed as a verified leukemia by the time of the 1987 followup. At the 1987 followup, there was one verified case of NHL in a Ranch Hand.

The incidence of systemic cancer in all participants enrolled in this longitudinal study remains similar to the general population. As in the 1985 examination cycle, basal cell skin cancer appears to occur more frequently in the Ranch Hand cohort. With respect to systemic cancers, the Ranch Hand and

Comparison group frequencies did not differ significantly. As in the past, no significant difference in cancer-related mortality was found between the study groups. To date, there has been one death in the Ranch Hand group related to soft tissue malignancy. One individual in the Comparison group has this diagnosis, but is still alive.

SUMMARY

For the 1987 followup analyses of skin neoplasms, a number of unadjusted analyses were performed to compare the Ranch Hand and Comparison groups on specified sets of verified skin malignancies and specified sets of verified and suspected skin malignancies. Selected adjusted analyses, which accounted for effects of specified covariates, were also undertaken. Table 4 summarizes the outcomes of the various unadjusted and adjusted analyses that were performed for the skin neoplasm assessment.

The unadjusted analyses of verified malignant skin neoplasms indicated a significant difference between the Ranch Hand and Comparison relative frequencies ($p=0.047$). For the verified and suspected malignant skin neoplasms, the relative frequencies for the Ranch Hands and Comparisons did not differ significantly ($p=0.101$). Unadjusted analyses of both the benign skin neoplasms and skin neoplasms of uncertain behavior or unspecified nature did not display significant group differences. Analyzing all skin neoplasms, (i.e., including the benign skin neoplasms and skin neoplasms of uncertain behavior or unspecified nature), unadjusted analyses indicated significant group differences at the 1987 followup ($p=0.012$ for the verified set; $p=0.029$ for the verified and suspected set).

For the 1987 followup, unadjusted analyses were performed comparing the Ranch Hands and Comparisons on their relative frequencies of basal cell carcinoma, squamous cell carcinoma, melanoma, and sun exposure-related malignant skin neoplasms. For basal cell carcinoma, there was a borderline significant unadjusted group difference for the verified set ($p=0.076$), and there was no significant difference for the verified and suspected set. Following adjustment by covariates, the group contrast for the verified set of basal cell carcinoma was significant ($p=0.030$). The adjusted group contrast for the verified and suspected set of basal cell carcinoma was borderline significant ($p=0.053$). At Baseline, a significantly higher rate of verified basal cell carcinoma was found for Ranch Hands in the unadjusted analysis. For the 1985 followup, the adjusted analysis of verified basal cell carcinoma displayed a significant group difference and the unadjusted analysis did not exhibit a significant group difference.

The group contrast for the unadjusted analyses of sun exposure-related malignant skin neoplasms was significant for the verified set ($p=0.042$) and borderline significant for the verified and suspected set ($p=0.081$). Covariate adjustment analyses produced significant group contrasts ($p=0.019$ and $p=0.044$, respectively).

The unadjusted group contrast analyses for squamous cell carcinoma and melanoma were not significant.

Unadjusted analyses comparing the Ranch Hand and Comparison groups on relative frequency of basal cell carcinoma, melanoma, and sun exposure-related malignant skin neoplasms by anatomical location/site were also performed. For sun exposure-related malignant skin neoplasms, Ranch Hands and Comparisons differed for malignancies of the upper extremities ($p=0.044$ for the verified set; there were no suspected malignant neoplasms at this site). No other significant differences were found at the sites of interest for the sun exposure-related malignant skin neoplasms, or for any of these sites for basal cell carcinoma or melanoma.

Unadjusted group comparisons were performed comparing the frequencies of basal cell carcinoma and sun exposure-related malignant skin neoplasms occurring on the ear, face, head, and neck by occupation. For basal cell carcinoma (both the verified set and the verified and suspected set), there were no significant group differences for any occupation. For sun exposure-related malignant skin neoplasms, the officers exhibited a borderline significant group difference ($p=0.078$) for the verified set. For these unadjusted analyses, there were no other significant differences for sun exposure-related malignant skin neoplasms.

The following conditional unadjusted analyses of relative frequencies were performed for the Ranch Hand and Comparison groups: skin neoplasm conditioned on the presence of any neoplasm; malignant skin neoplasm conditioned on the presence of any skin neoplasm; basal cell carcinoma conditioned on the presence of a malignant skin neoplasm; basal cell carcinomas of the ear, face, head, neck, or upper extremities conditioned on the presence of basal cell carcinoma; and sun exposure-related malignant skin neoplasms of the ear, face, head, neck, or upper extremities conditioned on the presence of sun exposure-related malignant skin neoplasms. Conditioned on the presence of a neoplasm, the Ranch Hand and Comparison percentages of skin neoplasms were marginally significantly different ($p=0.095$ for the verified set of neoplasms; $p=0.100$ for the verified and suspected set of neoplasms). None of the other conditional analyses exhibited significant group differences.

The Ranch Hand and Comparison groups were also compared on the distributions of participants with zero, one, or multiple basal cell carcinomas. For the verified set, there was a significant group difference ($p=0.050$). For the verified and suspected set of basal cell carcinoma, the Ranch Hand and Comparison groups did not differ significantly on the frequency of participants with zero, one, or multiple basal cell carcinoma. Contrasting 1987 followup participants with zero basal cell carcinomas versus multiple basal cell carcinomas, the groups differed on their relative frequencies ($p=0.032$) for the verified set. For the verified and suspected set, the groups were borderline significantly different ($p=0.069$). For the 1985 followup, the group contrasts for none versus multiple basal cell carcinomas were not significant.

Table 4 also summarizes the results of the unadjusted and adjusted analyses performed for the systemic neoplasm assessment. Unadjusted analyses comparing the Ranch Hands and Comparisons on their relative frequencies of systemic neoplasms by behavior (malignant, benign, and uncertain behavior or unspecified nature) and all systemic neoplasms were not significant. Analyses of malignant systemic neoplasms adjusting for covariate information also indicated no significant differences between the Ranch Hands and Comparisons.

TABLE 4.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Malignancy Variables**

Variable	Verification Status	Unadjusted	Adjusted	Direction of Results
Skin Neoplasms				
<u>Behavior</u>				
Malignant	V	0.047	--	RH>C ^d
	VS	NS	--	
Benign	V ^a	NS	--	
Uncertain Behavior or Unspecified Nature	V	NS	--	
	VS	NS	--	
All	V	0.012	--	RH>C ^d
	VS	0.029	--	RH>C ^d
<u>Cell Type</u>				
Basal Cell Carcinoma	V	NS*	0.030	RH>C ^d
	VS	NS	NS*	RH>C ^d
Squamous Cell Carcinoma	V ^a	NS	--	
Melanoma	V ^a	NS	--	
Sun Exposure-Related Malignant Skin Neoplasm	V	0.042	0.019	RH>C ^d
	VS	NS*	0.044	RH>C ^d
<u>Basal Cell Carcinoma by Location/Site</u>				
Ear, Face, Head, and Neck	V	NS	--	
	VS	NS	--	
Trunk	V	NS	--	
	VS	NS	--	
Upper Extremities	V ^a	NS	--	
Lower Extremities	V ^a	-- ^b	--	
Other Sites and Sites NOS	V	NS	--	
	VS	NS	--	

TABLE 4. (continued)

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Malignancy Variables**

Variable	Verification Status	Unadjusted	Adjusted	Direction of Results
<u>Melanoma by Location/Site</u>				
Ear, Face, Head, and Neck	V ^a	NS	--	
Trunk	V ^a	NS	--	
Upper Extremities	V ^a	-- ^b	--	
Lower Extremities	V ^a	-- ^b	--	
Other Sites and Sites NOS	V ^a	-- ^b	--	
<u>Sun Exposure-Related Malignant Skin Neoplasms by Location/Site</u>				
Ear, Face, Head, and Neck	V	NS	--	
	VS	NS	--	
Trunk	V	NS	--	
	VS	NS	--	
Upper Extremities	V ^a	0.044	--	RH>C ^d
Lower Extremities	V	-- ^b	--	
Other Sites and Sites NOS	V	NS	--	
	VS	NS	--	
<u>Basal Cell Carcinoma of the Ear, Face, Head and Neck by Occupation</u>				
Officer	V	NS	--	
	VS	NS	--	
Enlisted Flyer	V	NS	--	
	VS	NS	--	
Enlisted Groundcrew	V	NS	--	
	VS	NS	--	

TABLE 4. (continued)

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Malignancy Variables

Variable	Verification Status	Unadjusted	Adjusted	Direction of Results
<u>Sun Exposure-Related Malignant Skin Neoplasms of the Ear, Face, Head, and Neck by Occupation</u>				
Officer	V	NS*	--	RH>C ^d
	VS	NS	--	
Enlisted Flyer	V	NS	--	
	VS	NS	--	
Enlisted Groundcrew	V	NS	--	
	VS	NS	--	
<u>Conditional Analyses</u>				
Skin Neoplasm Conditioned on Neoplasm	V	NS*	--	RH>C ^d
	VS	NS*	--	
Malignant Skin Conditioned on Skin Neoplasm	V	NS	--	
	VS	NS	--	
Basal Cell Carcinoma Conditioned on Malignant Skin Neoplasm	V	NS	--	
	VS	NS	--	
Basal Cell Carcinoma of Ear, Face, Head, and Neck Conditioned on Basal Cell Carcinoma	V	NS	--	
	VS	NS	--	
Sun Exposure-Related Malignant Skin Neoplasm of Ear, Face, Head, and Neck Conditioned on Sun Exposure-Related Malignant Skin Neoplasm	V	NS	--	
	VS	NS	--	
<u>Multiple Basal Cell Carcinoma</u>				
Zero, One, or Multiple	V	0.050	--	RH>C ^d
	VS	NS	--	
One vs. Zero	V	NS	--	
	VS	NS	--	
Multiple vs. Zero	V	0.032	--	RH>C ^d
	VS	NS*	--	

TABLE 4. (continued)

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Malignancy Variables

Variable	Verification Status	Unadjusted	Adjusted	Direction of Results
Systemic Neoplasms				
<u>Behavior</u>				
Malignant	V	NS	NS	
	VS	NS	NS	
Benign	V	NS	--	
	VS	NS	--	
Uncertain Behavior or Unspecified Nature	V	NS	--	
	VS	NS	--	
All	V	NS	--	
	VS	NS	--	
<u>Malignant Systemic Neoplasms by Location/Site</u>				
Oral Cavity, Pharynx, and Larynx	V ^a	NS	--	
Thyroid	V ^a	NS	--	
Bronchus and Lung	V	NS	--	
	VS	NS	--	
Colon and Rectum	V ^a	NS	--	
Kidney and Bladder	V ^a	NS	--	
Prostate	V ^a	NS	--	
Testicles	V ^a	NS	--	
Hodgkin's Disease	V ^a	NS	--	
Ill-Defined Sites	VS ^c	NS	--	
Thymus and Mediastinum	V ^a	NS	--	
Head, Face, and Neck	V ^a	NS	--	

TABLE 4. (continued)

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Malignancy Variables

Variable	Verification Status	Unadjusted	Adjusted	Direction of Results
<u>Malignant Systemic Neoplasms by Location/Site (continued)</u>				
Brain	V ^a	NS	--	
Other Malignant Neoplasms of Lymphoid and Histiocytic Tissue	V ^a	NS	--	
Leukemia	V ^a	NS	--	
Carcinoma In Situ of Penis	V ^a	NS	--	
Carcinoma In Situ of Other Specified Sites	V ^a	NS	--	
<u>Conditional Analyses</u>				
Malignant Systemic Neoplasm Conditioned on All Systemic	V VS	NS NS	-- --	
Skin and Systemic				
All Skin and Systemic Neoplasms Combined	V VS	0.032 NS*	-- --	RH>C ^d RH>C ^d
Nonverifiable Neoplasm	--	NS	--	

V: Verified neoplasms.

--Analysis not performed or not applicable.

RH>C: Larger incidence in Ranch Hands.

VS: Verified and suspected neoplasms.

NS: Not significant ($p > 0.10$).^aNo suspected neoplasms.NS*: Borderline significant ($0.05 < p \leq 0.10$).^bNo neoplasms for either Ranch Hands or Comparisons.^cNo verified neoplasms.^dThese group contrasts are related. For example, basal cell carcinoma is part of the sun exposure-related malignant skin neoplasms, and the sun exposure-related malignant skin neoplasms are part of the malignant skin neoplasms, which are part of all skin neoplasms.

For specified locations/sites, Ranch Hands and Comparisons did not differ with respect to their relative frequencies of malignant systemic neoplasms. Ranch Hands and Comparisons also did not differ on their relative frequencies of malignant systemic neoplasms conditioned on the occurrence of a systemic neoplasm.

Table 4 also presents the results of unadjusted analyses for the combined set of all skin and systemic neoplasms. For the combined set of verified skin and verified systemic neoplasms, the Ranch Hand and Comparison 1987 followup groups differed significantly ($p=0.032$). For the verified and suspected combined set of skin and systemic neoplasms, the Ranch Hand and Comparison 1987 followup groups were borderline significant ($p=0.079$). This difference is due to the previously described group difference in skin malignancy. Table 4 also presents the results of unadjusted analyses comparing Ranch Hands and Comparisons on the frequency of nonverifiable skin and systemic neoplasms. No significant group difference was found.

The statistical power for detecting group differences on the frequency of systemic neoplasms at specified sites is low. The statistical power of the systemic neoplasm analyses improved somewhat when malignancies were aggregated across sites. Statistical power was strongest for the aggregated skin neoplasm analyses.

The frequency of basal cell carcinomas and sun exposure-related malignant skin neoplasms in the Ranch Hand group was compared across exposure index categories within each occupation strata. For the unadjusted analyses of basal cell carcinomas, there was a borderline significant difference among enlisted flyers for the verified set ($p=0.067$) and a significant difference among enlisted flyers for the verified and suspected ($p=0.031$) basal cell carcinomas. For adjusted analyses, significant exposure index-by-age interactions were present among the enlisted flyers for both sets of basal cell carcinomas. Analysis of the exposure index data within age strata did not support a dose-response relationship. For the unadjusted analyses of sun exposure-related malignant skin neoplasms, there was a borderline significant difference among enlisted flyers for the verified set ($p=0.059$) and a significant difference among enlisted flyers for the verified and suspected set ($p=0.028$). Again adjusting for covariate information resulted in significant exposure index-by-age interactions for both sets of sun exposure-related malignant skin neoplasms for the enlisted flyers. Results of stratified analyses did not support a dose-response relationship. No other significant differences were found for the exposure index analyses of these skin neoplasms.

The frequency of verified systemic malignant neoplasms in the Ranch Hand group was compared across exposure index categories within each occupation strata. For the unadjusted exposure index analyses, there were no significant differences by occupation. For the officers and enlisted flyers, the adjusted analyses were nonsignificant. However, there was a significant exposure index-by-race interaction for the enlisted groundcrew. Comparing the relative frequencies of systemic neoplasms across exposure levels within each race category for the enlisted groundcrew produced a significant difference for the nonblack Ranch Hands ($p=0.046$). However, the results from analyses stratified by race did not support a dose-response relationship (the midrange exposure group had more malignancies than either the low or high strata).

Table 5 displays the unadjusted relative risks for verified basal cell carcinoma at the Baseline, 1985 followup, and 1987 followup examinations. Ranch Hands showed a higher frequency of basal cell carcinoma than the Comparisons, a finding also noted at Baseline and the 1985 followup.

TABLE 5.
Unadjusted Analyses of Verified Basal Cell Carcinoma at Baseline, 1985 Followup, and 1987 Followup Examinations

Number of Participants ^d With Neoplasms/Percent	Baseline ^a	1985 Followup ^b	1987 Followup ^c
Ranch Hand	31 3.0%	53 5.5%	78 8.3%
Comparison	21 1.7%	50 4.1%	76 6.2%
Est. Relative Risk	1.71	1.36	1.36
p-Value	0.047 ^e	0.128 ^{e, f}	0.076 ^{e, f}

^aBaseline participants: 1,045 Ranch Hands, 1,224 Comparisons.

^b1985 followup participants: 1,016 Ranch Hands, 1,293 Comparisons.

^c1987 followup participants: 995 Ranch Hands, 1,299 Comparisons.

^dNonblacks only for the 1985 followup (956 Ranch Hands, 1,210 Comparisons); nonblacks only for the 1987 followup (938 Ranch Hands, 1,219 Comparisons); both nonblacks and Blacks for the Baseline.

^eBaseline p-value based on chi-square test; 1985 and 1987 followup p-values based on Fisher's exact test.

^fAdjusted analyses performed for the 1985 and 1987 followups produced the following estimated relative risks and associated p-values: 1.56 (p=0.035) and 1.46 (p=0.030), respectively.

In addition to the higher frequency of basal cell carcinoma, Ranch Hands had a greater relative frequency of multiple basal cell carcinomas than the Comparisons at the 1987 followup. Sun exposure-related malignant skin neoplasms also exhibited an increased frequency for the Ranch Hands relative to the Comparisons. The increase was not surprising because the majority of the sun exposure-related malignancies were basal cell carcinomas. Ranch Hands and Comparisons did not differ significantly for systemic neoplasms. There has been one case of soft tissue sarcoma in both the Ranch Hand and the Comparison groups (both described in the report of the 1985 physical examination) and one case of Hodgkin's lymphoma in a Ranch Hand. The results of the exposure index analyses were not supportive of a dose-response relationship.

NEUROLOGICAL ASSESSMENT

INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Thus, the neurological system comprises a major examination focal point in all dioxin morbidity studies. This report separates central and peripheral neurological status from "neurobehavioral" parameters, which are discussed in Chapter 12 of the main report.

DISCUSSION

Although definitive diagnosis usually requires laboratory testing beyond the scope of the current study, the data analyzed in the present section can be relied upon to detect the presence, if not the cause, of neurological disease. Of the clinical disciplines included in these examinations, the neurological assessment is by far the most complex and places a particular premium on meticulous detail in the performance of the physical examination. Pertinent to the current study, the neurological examination is highly sensitive in detecting the presence of peripheral neuropathy.

In practice, it is convenient to subdivide the neurological assessment into examinations of the peripheral and the cranial nerves. The 5 motor and 3 sensory peripheral nerve variables and the 12 cranial nerve variables can provide highly specific clues in the anatomic site of neurological lesions and clarify which additional diagnostic studies would be most helpful in establishing a diagnosis.

As indices of central nervous system (CNS) function, tremor and coordination are far less specific and are more subject to individual variation in the absence of underlying neurological disease. Tremor, for example, may occur as a benign familial trait, may be reflective of alcohol withdrawal, or may be a marker of extrapyramidal motor system disease as in Parkinson's syndrome. The Romberg sign may signal a lesion in the cerebellum but is more often indicative of impaired position sense in the lower extremities or of inner ear disease. Finally, the mental status examination is of obvious importance in the CNS assessment and, as in previous examination cycles, extensive psychometric studies were conducted.

Most of the dependent variable-covariate associations documented in this chapter confirmed relationships that are well established in clinical practice. A decline in CNS function would be expected with advancing years, though individual variation is the rule and it is often impossible to sort out the effects of age from environmental and psychosocial factors. The gradual attrition of central and peripheral neurons over time is associated with diminished vibratory sensation in the lower extremities and reduction in the Achilles reflex, findings confirmed in the current study.

Diabetes mellitus was found to be associated with multiple manifestations of neurological disease, including deficits in pin prick, light touch, and vibratory sensation. Depending on the criteria applied, peripheral neuropathy will occur in up to 60 percent of diabetics and will increase in frequency with age and duration of disease. Though a single etiology of the sensory deficits in diabetes is unlikely, accelerated peripheral vascular disease with microangiopathy, common to all diabetics, is no doubt a contributing factor.

Alcohol abuse is classically associated with a wide range of central and peripheral neurological disorders, as confirmed in the current study. While acute inebriation is related to direct toxic effects on the central nervous system, a peripheral polyneuropathy solely attributable to the chronic effects of ethanol has not been demonstrated with certainty. Rather, the neurological complications of chronic alcohol abuse (e.g., Wernicke's disease, Korsokoff's psychosis, cerebellar ataxia, and polyneuropathy) appear to be different manifestations of a secondary nutritional deficiency.

Several of the neck range of motion covariate associations are difficult to explain clinically. The decrease in neck range of motion with age is associated with degenerative arthritis of the cervical spine and is usually painless. A minority of cases will be secondary to cervical disc disease and nerve root compression. In future examination cycles, the classification of neck range of motion as a neurological dependent variable will take into account the presence or absence of pain. The associations with race (non-blacks have more abnormalities than Blacks) and with diabetes were of uncertain cause and of doubtful clinical significance.

Of all the neurological variables examined, no clinically significant group differences were found. A small number of Ranch Hand participants (four) and no Comparisons were found to have an abnormal Romberg sign, an incidence of marginal statistical significance given the small numbers involved. Finally, the exposure index analyses failed to reveal any consistent trends suggestive of a dose-response relationship.

SUMMARY

The 1987 neurological assessment focused on extensive physical examination data for cranial nerve function, peripheral nerve status, and central nervous system coordination processes. Verified histories of neurological diseases were also examined. The statistical results for the Ranch Hand and Comparison group contrasts are summarized in Table 6.

Information from the questionnaire was verified and grouped into six categories of neurological diseases: inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, disorders of the eye, disorders of the ear, and other neurological disorders. Unadjusted analyses found that Ranch Hands had a higher incidence of hereditary and degenerative diseases than Comparisons, but group differences for the other categories were not significant. Examples of hereditary and degenerative disease include Parkinson's disease and benign essential tremor, among others.

TABLE 6

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results
<u>Questionnaire</u>			
Inflammatory Disease	NS	--	
Hereditary and Degenerative Disease	0.030	--	
Peripheral Disorders	NS	--	
Disorders of the Eye	NS	--	
Disorders of the Ear	NS	--	
Other Neurological Disorders	NS	--	
<u>Physical Examination: Cranial Nerve Function</u>			
Smell	NS	--	
Visual Fields	NS	--	
Light Reaction	NS	--	
Ocular Movement	NS	--	
Facial Sensation	NS	--	
Jaw Clench	NS	--	
Smile	NS	--	
Palpebral Fissure	NS	** (NS)	
Balance	NS*	--	RH>C ^a
Gag Reflex	NS	--	
Speech	NS	--	
Tongue Position Relative to Midline	NS	--	
Palate and Uvula Movement	NS	--	
Neck Range of Motion	NS	NS	
Cranial Nerve Index	NS	NS	
Cranial Nerve Index Without Range of Motion	NS	****	
<u>Physical Examination: Peripheral Nerve Status</u>			
Pin Prick	NS	NS	
Light Touch	NS	NS	
Muscle Status	NS	NS	
Vibration	NS	** (NS)	
Patellar Reflex	NS	NS	
Achilles Reflex	NS	NS	
Biceps Reflex	0.012	--	C>RH
Babinski Reflex	NS	--	

TABLE 6. (continued)

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results
Physical Examination: Central Nervous System Coordination Processes			
Tremor	NS	NS	
Coordination	NS*	** (0.036)	RH>C
Romberg Sign	NS*	--	RH>C ^a
Gait	NS	NS	
CNS Index	NS	NS	

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

--Analysis not done.

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table H-2 in the main report for a detailed description of this interaction.

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

RH>C: More abnormalities in Ranch Hands.

****: Group-by-covariate interaction ($p \leq 0.01$).

C>RH: More abnormalities in Comparisons.

** (0.036): Group-by-covariate interaction ($0.01 < p \leq 0.05$); significant when interaction is deleted; refer to Table H-2 in the main report for a detailed description of this interaction.

^aBalance (Romberg sign).

Seventeen variables were examined to assess group differences in cranial nerve function (smell, visual fields, light reaction, ocular movement, facial sensation, corneal reflex, jaw clench, smile, palpebral fissure, balance, gag reflex, speech, tongue position relative to midline, palate and uvula movement, neck range of motion, the cranial nerve index, and the index without neck range of motion). No group difference was statistically significant, although the prevalence of balance abnormalities based on four cases was marginally higher for the Ranch Hand group than for the Comparison group. The adjusted analyses revealed a significant group-by-lifetime alcohol history interaction for palpebral fissure and a significant group-by-insecticide

exposure interaction for the cranial nerve index without neck range of motion. Stratified results for the cranial nerve index without neck range of motion showed a relative risk significantly greater than 1 for participants who had never been exposed to insecticides and a relative risk marginally less than 1 for participants who had been exposed to insecticides. Stratified analyses for palpebral fissure failed to detect a significant group difference.

The variables analyzed to assess peripheral nerve status were pin prick, light touch, muscle status, vibration, patellar reflex, Achilles reflex, biceps reflex, and Babinski reflex. The prevalence of biceps reflex abnormalities was significantly less for Ranch Hands than for Comparisons. The unadjusted group contrasts for the other variables were not significant. Results of the adjusted analyses were also not significant, except for a group-by-diabetic class interaction that was found for vibration. Exploration of this interaction showed that the adjusted relative risk was marginally greater than 1 for participants categorized as having normal glucose metabolism.

Tremor, coordination, Romberg sign (balance), gait, and the CNS summary index were analyzed to assess the central nervous system coordination processes. Unadjusted group contrasts revealed that Ranch Hands had marginally significantly more abnormalities than Comparisons for the Romberg sign and for coordination. The adjusted analysis for coordination detected two significant group-by-covariate interactions (group-by-occupation and group-by-insecticide exposure). Stratified analyses showed a significant group difference for enlisted groundcrew who had never been exposed to insecticides. Further investigation found a significant group difference for enlisted groundcrew after excluding the group-by-insecticide exposure interaction, and a significant adjusted group difference overall after excluding both group-by-covariate interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis.

Results for the exposure index analyses were generally not significant for each occupational cohort. Isolated significant findings did not indicate an effect due to herbicide exposure.

In conclusion, the 1987 neurological assessment did not find the health of the Ranch Hand group to be substantially different from the Comparison group, but several differences were noted. Of the questionnaire variables, Ranch Hands had a higher incidence of hereditary and degenerative diseases than Comparisons. Unadjusted analyses for the physical examination variables showed that Ranch Hands had marginally more abnormalities than Comparisons for balance/Romberg sign and coordination, but significantly fewer biceps reflex abnormalities. No significant group differences were detected for the other 26 physical examination variables.

PSYCHOLOGICAL ASSESSMENT

INTRODUCTION

Emotional illnesses or psychological abnormalities are not generally recognized as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. "Neurobehavioral effects" occasionally ascribed to such exposures have been, in fact, predominantly neurological symptoms for which causation is not disputed. Higher central nervous system (CNS) functioning, in terms of cognitive skills, personality, and reactivity, may be temporarily or permanently impaired depending on the exposure and the ability to measure accurately the psychological changes.

DISCUSSION

Prior to the Air Force Health Study (AFHS) 1982 Baseline study, little scientifically validated information existed regarding the relationship between dioxin exposure and disturbances of cognition and emotions in man. The Baseline and 1985 followup studies attempted to explore these possible relationships using well-established questionnaires, personality inventories, and neuropsychological assessment techniques. These instruments included the Cornell Medical Index (CMI), the Minnesota Multiphasic Personality Inventory (MMPI), and the Halstead-Reitan Battery (HRB).

Analysis of extensive data generated by the CMI, MMPI, and HRB revealed few statistically significant differences between those Air Force veterans who sustained some level of exposure to dioxin (Ranch Hands) and their unexposed Comparison group. More specifically, the two groups did not differ significantly on several tests of cognitive (brain) function. The exposed (Ranch Hand) group reported a moderately greater number of diffuse medical (somatic) complaints on the CMI. They also registered moderately higher (but not statistically significant) scores on the MMPI scales that are influenced most heavily by physical complaints such as generalized feelings of lassitude and malaise, energy loss, mental and physical slowing, etc. The herbicide-exposed groundcrew group only demonstrated significantly higher scores on the MMPI depression scale.

Factors contributing to the modest differences between groups were not clearly indicated by estimated dioxin exposure data. It is possible that observed differences in psychological dependent variables might be related to some combination of negative expectations, anxiety, and amplified somatic sensitivity on the part of the exposed personnel. As the 1985 followup concluded, the possibility existed that subjectively experienced and reported symptoms were more accurate than available exposure data.

A limited number of previous dioxin exposure studies reported similar findings to those described above. Investigations of both military and civilian groups failed to reveal evidence for organic brain dysfunction. However, evidence of significantly elevated levels of tension/anxiety and anger/hostility were reported for at least one civilian group. Psychological tests employed by some of these previous studies were limited when viewed in relation to the range of psychological assessment included in the prior Air

Force studies. Nevertheless, the existence of independent corroborating data combined with previous AFHS findings indicated the importance of continuing some form of appropriate psychological assessment for the 1987 followup.

At the conclusion of the 1985 followup, a significant number of participants registered complaints regarding the lengthy and repetitious nature of the psychometric evaluation. Subsequent concern regarding potential loss of subjects for the 1987 followup led to specific changes in the psychometric component of the study. Previously unrevealing tests of cognition (HRB) were suspended, thereby reducing testing time by several hours. The issue of test-retest boredom was addressed by selecting two new psychometric instruments that would provide ongoing assessment of important psychological variables, while requiring one-half the administration time of the MMPI.

The SCL-90-R is a 90-item checklist of physical and mental symptoms that provides a reasonable measure of health-related concerns and associated anxiety, depression, and general emotional discomfort. The second test selected for the 1987 reevaluation was the MCMI. The MCMI provided backup measures of depression, anxiety, somatization, and hypochondriasis for the SCL-90-R, while also screening for personality disorders and major psychiatric syndromes including psychosis. Both the SCL-90-R and the MCMI have been extensively used in clinical and research settings requiring economical assessment of psychiatric disorder, physical disability status and response to specific therapies. Some methodological difficulties occurred when comparing data generated by these two tests to scores previously obtained using the MMPI. However, factor analysis and correlational studies indicated that specific scales and factors included in the new tests correlated reasonably well with comparable elements of the MMPI. Therefore, acceptable continuity of psychological dependent variables was assured.

Addition of data concerning sleep disorders, as well as the 29 scales and 3 indices comprising the SCL-90-R and the MCMI, produced a relatively substantial increase in the number of psychological dependent variables requiring analysis for the 1987 followup. Similarly, the number of dependent variable-covariate associations requiring examination increased, as did the probability of observing a proliferation of statistically significant interactions.

Examination of the psychological dependent variable-by-covariate associations reported to date indicates a host of statistically significant relationships. For example, previously well-known relationships between advancing age and disturbed sleep were noted, as was the well-known phenomenon of sleep disturbance following excessive consumption of alcohol. An additional predictable outcome involved a strong relationship between the presence of PTSD and a disturbance of virtually all sleep and psychological variables. Although the number of participants with PTSD was relatively small (approximately 1% of each group), the effects of this condition were quite striking and make this an important finding. A more definitive method for the diagnosis of PTSD is the structured psychiatric interview, a technique considered to be too logistically difficult in the context of this study. Therefore, the assessment of PTSD using a subscale of the MMPI was used. While the MMPI subscale may be less precise than the psychiatric interview, it was significantly associated with expected psychological endpoints in the covariate adjusted analyses, and it appears to be a useful technique in the assessment of PTSD in population-based studies.

On the other hand, some significant but puzzling and questionably valid or useful relationships were also demonstrated. For example, white subjects reported sleep disturbances more frequently than their Black counterparts. In addition, the study revealed a powerful relationship between education level and the number of sleep disorders registered. While 38.3 percent of high school-educated subjects reported sleep disturbances, only 30.4 percent of those with college-level education complained of disordered sleep. The 30.4 percent figure compares reasonably well with the 33.0 percent figure cited by sleep researchers as the number of adult Americans likely to report some sleep disturbances in any given year. The apparent fact that study subjects with 12 or fewer years of education experience more sleep disturbance might be caused by greater levels of dissatisfaction with employment, financial pressures, participation in higher rates of shift work, and less regular exercise.

Further inspection of the 1987 data revealed a general persistence of several psychological results that were described as noteworthy in the Baseline and 1985 followup studies. On the SCL-90-R, the Ranch Hand group demonstrated statistically greater levels of depression than Comparison group members. They also manifested more physical complaints (somatization) and health-related anxieties than their Comparison group counterparts. The Ranch Hands also recorded higher scores on those MCMI scales thought to reflect antisocial and passive-aggressive traits and psychotic delusional tendencies. These latter psychological variables might be described as "new" in that they were not reported in the earlier studies. However, the appearance of these maladaptive traits and symptoms probably represents the emergence of artifacts related more to differences in the psychometric properties of the tests used than in the appearance of some new symptom complex.

Continuing manifestations of depression, somatic complaints, and health-related anxiety by members of the Ranch Hand cohort are not surprising. A similar persistence of entrenched symptom complexes has been demonstrated by other populations who have received exposure to known or suspected toxins. Such individuals frequently demonstrate a pattern of self-perpetuating psychological and somatic symptoms that individual group members tend to experience in varying degrees. Air Force groundcrew members who report high levels of herbicide exposure may be particularly vulnerable to repeated suggestions that they have suffered negative psychological and physical consequences secondary to their exposure. Individuals with psychological makeups predisposing them to higher levels of anxiety, psychophysiological disturbances, and somatic concern tend to react rather dramatically to their situation. This type of response can operate to perpetuate a static and/or escalating number of physical and psychological symptoms.

Research has been conducted on the psycho-maintenance* of chronic physical illness that clearly indicated that a significant percentage (5-10%) of any medical population possess a psychological makeup that predisposes them to the development of symptom-reactive anxiety and psychophysiological disturbances that tend to develop in an escalating manner. As a result, individuals of this type included in the current study may have obtained relatively high scores on those SCL-90-R and MCMI measures that are sensitive to the presence of anxiety, depression, and psychophysiological disturbances. Further,

*Psycho-maintenance refers to psychological and behavioral perpetuation and/or exacerbation of physical illness.

individuals who perceive themselves as injured may tend to harbor significant feelings of resentment and hostility that may contribute significantly to the previously noted high scores on antisocial, passive-aggressive, and psychotic delusion scales. In addition, a significantly higher level of alcohol consumption that may represent a form of self-medication may have also contributed to the significantly higher scale scores of the herbicide-exposed group members.

While factors other than dioxin exposure may have contributed to Ranch Hand test score abnormalities, previous studies in clinical medicine also suggest that caution may be appropriate. Studies have followed medical patients who were originally diagnosed as suffering from hysteria, hypochondriasis, or other psychiatric disorders. In some of these studies, more than 60 percent of the patients given psychiatric diagnoses eventually demonstrated neurological diseases, endocrine dysfunction, and other medical disorders. It is therefore important to monitor the health of the study participants over the ensuing years.

SUMMARY

The 1987 psychological assessment was based on verified psychological disorders; reported sleep disorders; and two psychological instruments, the SCL-90-R and the MCMI. The results of the psychological assessment are summarized in Table 7.

Five psychological disorders, which were self-reported and verified by medical record review, were analyzed in the psychological assessment: psychoses, alcohol dependence, drug dependence, anxiety, and other neuroses. No significant differences between the Ranch Hands and the Comparisons were detected based on the unadjusted analyses of psychoses, drug dependence, and anxiety. A marginally significant difference between the two groups was found for alcohol dependence and other neuroses ($p=0.068$ and $p=0.056$, respectively), with a greater percentage of Ranch Hands than Comparisons having these conditions.

The sleep disorder segment of the psychological assessment consisted of self-reported responses on 12 individual sleep disorders, 2 composite sleep disorder variables (based on the individual sleep disorders), and average hours of sleep each night. The results of the analyses without adjustments for covariates indicated that significantly more Ranch Hands than Comparisons reported that they experience great or disabling fatigue during the day and that they talk in their sleep ($p=0.026$ and $p=0.041$, respectively). The adjusted analysis of great or disabling fatigue during the day was marginally significant ($p=0.065$). In the adjusted analysis of talking in sleep, there was a significant group-by-PTSD interaction. Further analysis identified that of the participants without PTSD, marginally more Ranch Hands than Comparisons reported that they talk in their sleep ($p=0.089$).

The unadjusted analyses of the other 13 sleep disorder variables did not reveal any significant differences: trouble falling asleep, waking up during the night, waking up too early and can't go back to sleep, waking up unrefreshed, involuntarily falling asleep during the day, frightening dreams, sleepwalking, abnormal movement or activity during the night, sleep problems

TABLE 7.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Psychology Variables**

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<u>Psychological Disorders</u>				
Psychoses	D	NS	--	
Alcohol Dependence	D	NS*	--	RH>C
Drug Dependence	D	NS	--	
Anxiety	D	NS	--	
Other Neuroses	D	NS*	--	RH>C
<u>Sleep Disorders</u>				
Trouble Falling Asleep	D	NS	NS	
Waking up During the Night	D	NS	****	
Waking up Too Early and Can't Go Back to Sleep	D	NS	** (NS)	
Waking Up Unrefreshed	D	NS	NS	
Involuntarily Falling Asleep During the Day	D	NS	NS	
Great or Disabling Fatigue During the Day	D	0.026	NS*	RH>C
Frightening Dreams	D	NS	NS	
Talking in Sleep	D	0.041	****	RH>C
Sleepwalking	D	NS	NS	
Abnormal Movement/Activity During the Night	D	NS	** (NS)	
Sleep Problems Requiring Medication	D	NS	NS	
Snore Loudly in All Sleeping Positions	D	NS	NS	
Insomnia	D	NS	** (NS)	
Overall Sleep Disorder Index	D	NS	** (NS)	
Average Sleep Each Night	C	NS	NS	
<u>SCL-90-R</u>				
Anxiety	D	NS	NS	
Depression	D	NS*	NS	RH>C
Hostility	D	NS	****	
Interpersonal Sensitivity	D	NS	NS	
Obsessive-Compulsive Behavior	D	NS	NS	
Paranoid Ideation	D	NS	NS	
Phobic Anxiety	D	NS	NS	

TABLE 7. (continued)

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Psychology Variables

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<u>SCL-90-R (continued)</u>				
Psychoticism	D	NS	NS	
Somatization	D	NS*	** (NS)	RH>C
GSI	D	NS*	NS	RH>C
PSDI	D	NS	** (NS)	
PST	D	NS	NS	
<u>MCMJ</u>				
Schizoid Score	C	NS	NS	
Avoidant Score	C	NS	****	
Dependent Score	C	0.048	** (0.020)	C>RH
Histrionic Score	C	NS	** (NS)	
Narcissistic Score	C	NS*	0.015	RH>C
Antisocial Score	C	<0.001	0.001	RH>C
Compulsive Score	C	NS	** (NS)	
Passive-Aggressive Score	C	NS	** (NS)	
Schizotypal Score	C	NS	** (NS)	
Borderline Score	C	NS	** (0.050)	C>RH
Paranoid Score	C	0.011	0.014	RH>C
Anxiety Score	C	NS	****	
Somatoform Score	C	NS	NS	
Hypomania Score	C	NS	NS	
Dysthymia Score	C	NS	NS	
Alcohol Abuse Score	C	NS	** (NS)	
Drug Abuse Score	C	NS	NS	
Psychotic Thinking Score	C	NS	NS	
Psychotic Depression Score	C	NS	****	
Psychotic Delusion Score	C	NS*	NS*	RH>C

D: Discrete analysis performed.

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

--: Analysis not done.

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

RH>C: Higher prevalence rate or mean in Ranch Hands than in Comparisons.

****: Group-by-covariate interaction ($p \leq 0.01$); refer to Table I-2 in the main report for a detailed description of this interaction.** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table I-2 in the main report for a detailed description of this interaction.

C: Continuous analysis performed.

** (0.020) and ** (0.050): Group-by-covariate interaction ($0.01 < p \leq 0.05$); significant when interaction is deleted (p -value given).

C>RH: Higher mean in Comparisons than in Ranch Hands.

requiring medication, snoring loudly in all positions, insomnia, overall sleep disorder index, and average sleep each night. In general, this finding was supported by the results of the adjusted analyses, although significant group-by-covariate interactions were present in 5 of the 13 analyses. Further exploration of the interactions revealed no significant group differences in any stratum for three of the five variables. Of participants born in or before 1922, significantly more Comparisons than Ranch Hands were classified as having insomnia ($p=0.012$). Marginally more Comparisons than Ranch Hands who were born in or before 1922 reported that they wake up during the night ($p=0.078$).

The SCL-90-R, a multidimensional self-reported symptom inventory designed to measure symptomatic psychological distress, yields nine primary symptom dimensions and three global indices of distress. No differences between the two groups were found for 7 of the 12 SCL-90-R scores: anxiety, interpersonal sensitivity, obsessive-compulsive behavior, paranoid ideation, phobic anxiety, psychoticism, and positive symptom total. Marginally significant differences between the two groups were detected for depression ($p=0.090$), somatization ($p=0.073$), and GSI (an index of symptom severity) ($p=0.081$), with a higher percentage of abnormalities in the Ranch Hands than in the Comparisons, based on the unadjusted analyses. For depression and the GSI, no differences were revealed after adjustment for covariates. In the adjusted analysis of somatization, there was a significant group-by-education interaction present in the model. Further investigation of the interaction showed that the high school-educated Ranch Hands had a significantly higher percentage of abnormalities on somatization than the Comparisons with a high school education ($p=0.025$).

Although no difference between the two groups was revealed in the unadjusted analysis of the SCL-90-R PSDI (an index of symptom intensity), there was a significant group-by-race interaction in the adjusted analysis. Exploration of the interaction revealed that the Black Comparisons had a marginally higher percentage of abnormalities than the Black Ranch Hands on this index ($p=0.079$). The unadjusted analysis of hostility from the SCL-90-R did not identify a significant difference between the two groups, and there was a significant group-by-PTSD interaction in the adjusted analysis. Stratifying by the presence or absence of PTSD did not reveal any significant differences between the Ranch Hands and the Comparisons in either stratum.

The MCMI, a self-administered test that measures eight basic personality patterns, three pathological personality disorders, and nine clinical symptom syndromes. The results of the unadjusted analyses of the MCMI scores showed no significant group differences for 15 of the 20 scores: schizoid, avoidant, histrionic, compulsive, passive-aggressive, schizotypal, borderline, anxiety, somatoform, hypomania, dysthymia, alcohol abuse, drug abuse, psychotic thinking, and psychotic depression. In the adjusted analyses of these variables, there were significant group-by-covariate interactions for 9 of the 15 analyses, which made the direct contrast of the two groups more difficult. Stratifying by the covariates in order to contrast the two groups within each stratum did not reveal a consistent pattern of significant detriment to either group. Significant differences were noted in 10 strata, and there were marginally significant differences detected in 6 strata. The mean score of the Ranch Hands exceeded that of the Comparisons for five of the significant strata and four of the marginally significant strata. However, many of these were strata where few participants were present (e.g., Blacks, participants with PTSD). Consequently, corresponding unadjusted results and models without

the significant group-by-covariate interaction are primarily nonsignificant. For all except one variable where the analysis was repeated without the group-by-covariate interaction(s), no significant differences were revealed. In the analysis of the borderline score without the significant interaction involving group, the results showed that the Comparisons had a significantly higher mean score than the Ranch Hands ($p=0.050$).

The Ranch Hands were found to have significantly higher mean antisocial and paranoid scores than the Comparisons (antisocial: $p<0.001$ for unadjusted and $p=0.001$ for adjusted; paranoid: $p=0.011$ for unadjusted and $p=0.014$ for adjusted). On the psychotic delusion score, the mean score for the Ranch Hands was marginally higher than the Comparison mean score ($p=0.061$ for unadjusted and $p=0.062$ for adjusted). The results of the unadjusted analysis of the narcissistic score showed that the mean score for the Ranch Hands was marginally significantly higher than the mean score for the Comparisons ($p=0.090$); after adjusting for covariates, a significant difference was detected ($p=0.015$). Based on the unadjusted analysis, the Comparisons had a significantly higher mean dependent score than the Ranch Hands ($p=0.048$). In the adjusted analysis, there was a significant group-by-race interaction. Stratifying by race revealed that the nonblack Comparisons had a significantly higher mean score than the nonblack Ranch Hands ($p=0.005$) and the Black Ranch Hands had a marginally higher mean score than the Black Comparisons ($p=0.086$). Without the group-by-race interaction in the model, the Comparisons had a significantly higher mean score than the Ranch Hands ($p=0.020$).

The results of the exposure index analyses did not reveal a consistent pattern of an increasing dose-response relationship for any occupational cohort across the variables. The majority of the unadjusted analyses did not detect any significant differences among the exposure categories for the different occupational cohorts. Interactions involving the exposure index were frequently found in the adjusted analyses; however, exploration of the interactions did not identify a subgroup within the Ranch Hands that consistently demonstrated an increasing dose-response relationship. The occasional observation of significant and borderline findings in the officer cohort is difficult to interpret in view of the evolving understanding of the relatively low level of dioxin exposure experienced by officers.

Significant or marginally significant differences between the Ranch Hands and the Comparisons were found for some variables within each of the four psychological assessment instruments of verified psychological disorders, reported sleep disorders, and the self-administered SCL-90-R and MCMI psychological examinations. However, there was a lack of consistency across similar variables included on the SCL-90-R, MCMI, and reported information. For these differences the Ranch Hands generally manifested a higher percentage of abnormalities or a higher mean score than the Comparisons. However, this is not surprising in light of the fact that individuals who perceive themselves as having been harmed might be more likely to report the symptoms observed as significant in this analysis. Profound effects of PTSD were noted for most all psychological variables. These results should be reexamined carefully for positive correlations between the complaints and increased levels of dioxin exposure when data from the serum dioxin assay become available. Additionally, significant group-by-covariate interactions were observed frequently in the adjusted analysis, which often made direct contrast of the two groups with adjustment for significant covariates difficult.

GASTROINTESTINAL ASSESSMENT

INTRODUCTION

This system assessment centers on reported peptic ulcer and liver disease, and current hepatic function and porphyria as determined by comprehensive laboratory testing and the physical examination. The liver is a major target organ for single high-dose and continued low-dose exposure to chlorophenols and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Peptic and stomach ulcer disease and porphyria cutanea tarda (PCT) are suspected clinical endpoints following moderate- to high-level exposures.

DISCUSSION

Signs and symptoms referable to the gastrointestinal system are those most frequently encountered in ambulatory medicine. As screening tools in the outpatient investigation of digestive disorders, the historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice. More definitive diagnostic studies, such as barium and endoscopic surveys of the bowel, were not included in the current study and, except in emergent circumstances, are rarely indicated in the initial evaluation of gastrointestinal disease.

In the diagnosis of digestive disorders it is important to recognize certain limitations in the extent to which data from the history and physical examination can be relied upon. Rather than pointing to a particular diagnosis, digestive symptoms are frequently nonspecific and intermittent. In this setting, even the best designed medical history questionnaire can be subject to error. "Ulcer" and "colitis" are diagnoses that are commonly reported but often not accurately established. In contrast, most cases of hepatitis are anicteric and escape detection. As a common target organ for situational stress, the bowel frequently gives rise to symptoms that can be severe but that are functional in nature and resolve in time. These caveats highlight the importance of the type of medical record verification conducted in the current study and, in the case of hepatitis, the need for serologic confirmation.

In contrast to some organ systems, the physical examination in gastrointestinal disease is often of limited value and can be misleading in the differential diagnosis. The ability of the examiner to detect hepatomegaly will be unreliable in the obese patient. In obstructive airway disease, with hyperinflation of the lungs and flattening of the diaphragms, the liver edge may descend abnormally below the right costal margin in the absence of hepatomegaly. In the best of circumstances, the span of the liver by palpation or percussion is often an unreliable index of liver size. Recognizing that in the most advanced stages of cirrhosis hepatomegaly is often not present, other stigmata of chronic liver disease were sought during the physical examination. Palmar erythema, ascites, telangiectasias, and gynecomastia were examined as part of this physical examination.

In contrast to the limitations of the history and physical examination outlined above, data collected in the laboratory can provide early insight into the presence of occult liver disease. The four hepatic enzymes analyzed

as dependent variables [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and lactic dehydrogenase (LDH)] are common to most chemistry panels ordered in the outpatient setting. Present in high intracellular concentration, these enzymes are released in virtually all toxic, inflammatory, and neoplastic diseases with hepatic involvement. As reliable laboratory markers of liver disease, the GGT is considered the most sensitive, while the LDH, with iso-enzymes derived from multiple organ systems, is the least specific.

As the hepatic enzymes are used in the detection and followup of parenchymal disease, so are the serum alkaline phosphatase and bilirubin reflective of hepatobiliary function in "cholestatic" or "obstructive" disease. Though present in virtually all organ systems, the serum alkaline phosphatase in the adult population under study is of dual origin and close to a 50-50 mixture of liver- and bone-derived fractions. An elevated alkaline phosphatase is by no means diagnostic of liver disease and can occur in a broad range of unrelated clinical conditions including drug-induced cholestasis, Paget's disease (3% of males over age 40), neoplasia with metastases to bone, and congestive heart failure.

Similarly, and pertinent to the current study, the bilirubin indices are subject to numerous hereditary and acquired disorders unrelated to intrinsic hepatic disease. The benign hyperbilirubinemia of Gilbert's syndrome will occur in 5 percent of the population under study. A long list of medications, including many over-the-counter preparations, have been implicated in the overproduction of bilirubin in the hemolytic reactions associated with glucose-6-phosphate dehydrogenase deficiency, which may occur in up to 15 percent of Black American males.

Most of the dependent variable-covariate associations analyzed in the present section are consistent with established clinical observations. Alcohol consumption was associated with hepatomegaly and elevated liver enzymes with the most sensitive GGT showing the greatest deviation from the normal. The difficulty in estimating alcohol consumption by history may account for the unexpectedly higher percentage of two enzyme abnormalities (ALT and GGT) in non- versus moderate alcohol consumption. Alcohol use per se should not affect consumption were not significant.

Documented in the adjusted analyses were a number of covariate associations that would be expected with age including gradual elevations in serum cholesterol, triglycerides, and fasting blood sugar. The decrease in ALT over time is not readily explained and probably not significant as an isolated finding. The decline in serum creatine kinase would be consistent with decreasing muscle mass over time.

Significant ($p < 0.001$) race-related differences in two serum enzymes (GGT and creatine kinase) were documented and, in the case of the creatine kinase, the mean for Blacks was almost twice that for nonblacks. These data are consistent with observations confirmed in a small number of studies over the past decade. The elevation, not yet explained, appears to be race- and gender-specific and is limited to Black males.

With reference to prior herbicide exposure, most group differences were not statistically significant, though, as in the 1985 followup examination, Ranch Hands had a significantly higher mean alkaline phosphatase (93.7 U/L) than did the Comparisons (90.3 U/L). As an index subject to multiple organ variables, however, this difference should not be considered clinically significant. Longitudinal analysis of three enzyme variables confirmed no significant group differences over time. The decline in serum AST in both groups cannot be explained on the basis of any difference in methodology as the laboratory assay techniques in the 1985 and 1987 examination cycles were identical.

The gastrointestinal assessment data confirmed observations that are well established in clinical practice and reflect no apparent increase in organ-specific mortality or morbidity in the Ranch Hand group versus the Comparison group over time.

SUMMARY

Table 8 summarizes the statistical results of the Ranch Hand and Comparison group contrasts that were analyzed for the 1987 gastrointestinal assessment.

Information collected at the health interview was verified and grouped into eight categories of liver disorders. There were no significant group differences for any of these conditions. Self-reported data on history of ulcers and on occurrences of skin patches, bruises, and sensitivity also did not differ significantly between groups. In contrast, Ranch Hands reported significantly more skin patches, bruises, and sensitivity than Comparisons at both the Baseline and 1985 followup examinations.

Hepatomegaly was diagnosed at the physical exam. No significant group difference was found for the unadjusted analysis. The adjusted analysis detected a significant group-by-degreasing chemical exposure interaction; the group relative risk for participants never exposed to degreasing chemicals was marginally significant and less than 1. After excluding the interaction, the adjusted group difference was not significant.

Ranch Hand and Comparison group contrasts were assessed for 13 laboratory variables. Each variable was examined in both continuous and discrete forms. Statistical analysis of these variables revealed only one significant group difference. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, a finding also noted at the 1985 followup study. In contrast, the percentage of abnormal alkaline phosphatase values was very similar between groups. Aside from significant group-by-covariate interactions, results of the adjusted analyses always supported the unadjusted analyses results. Results based on stratified analyses to explore group-by-covariate interactions were generally not significant. The following stratum specific significant results were noted: for participants with more than 40 drink-years, the Ranch Hand ALT mean was marginally higher than the Comparison mean; the direct bilirubin mean for Black Ranch Hands was significantly higher than the mean for Black Comparisons; and Ranch Hands exposed to degreasing chemicals had significantly fewer direct bilirubin abnormal levels than Comparisons who had been exposed to degreasing chemicals.

TABLE 8.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Gastrointestinal Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
<u>Questionnaire</u>					
Viral Hepatitis Acute and Subacute Necrosis of the Liver	NS	--	--	--	
Chronic Liver Disease and Cirrhosis (Alcohol Related)	NS	--	--	--	
Chronic Liver Disease and Cirrhosis (Nonalcohol Related)	NS	--	--	--	
Liver Abscess and Sequelae of Chronic Liver Disease	NS	--	--	--	
Other Disorders of the Liver	NS	--	--	--	
Jaundice (Unspecified)	NS	--	--	--	
Hepatomegaly	NS	--	--	--	
Reported Ulcer	NS	--	NS	--	
Skin Patches, Bruises, or Sensitivity	NS	--	--	--	
Verified Ulcer	NS	--	NS	--	
<u>Physical Examination</u>					
Diagnosed Hepatomegaly	NS	--	** (NS)	--	
<u>Laboratory</u>					
AST	NS	NS	NS	NS	
ALT	NS	NS	NS	** (NS)	
GGT	NS	NS	NS	NS	
Alkaline Phosphatase	NS	<0.001	NS	<0.001	RH>C
Total Bilirubin	NS	NS	** (NS)	NS	
Direct Bilirubin	NS	NS	****	** (NS)	
LDH	NS	NS	NS	NS	
Cholesterol	NS	NS	NS	NS	
HDL	NS	NS	NS	** (NS)	
Cholesterol-HDL Ratio	NS	NS	NS	NS	

TABLE 8. (continued)

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Gastrointestinal Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
Triglycerides	NS	NS	NS	NS	
Creatine Kinase	NS	NS	NS	NS	
Fasting Glucose	NS	NS	NS	NS	

--: Analysis not done.

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

****: Group-by-covariate interaction ($p \leq 0.01$).

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted.

RH>C: Higher mean value Ranch Hands than in Comparisons.

The adjusted exposure index analyses detected one statistically significant result supportive of a herbicide effect (GGT discretized for the officer cohort), and one marginally significant result that suggested a herbicide effect (direct bilirubin treated as a continuous variable for the enlisted groundcrew cohort). Other significant or marginally significant results did not indicate an effect due to dioxin exposure. Although few exposure index results were statistically significant, trends in the data showed positive dose-response relationships for many variables, particularly for the officer and enlisted groundcrew cohorts.

Longitudinal analyses for AST, ALT, and GGT disclosed no statistically significant differences over time between groups.

In conclusion, results of the 1987 gastrointestinal assessment did not indicate an overall detriment to the health of the Ranch Hand group. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, but for all other variables, differences between groups were not statistically significant. In many instances, patterns in the data for the exposure index analyses supported a herbicide effect, but the results were generally not significant.

DERMATOLOGIC EVALUATION

INTRODUCTION

The skin is a major target organ following heavy exposure to chlorophenols and dioxin and, therefore, is a primary focus of the Air Force Health Study (AFHS) clinical examination.

DISCUSSION

In any study of the biological effects of herbicides and their contaminants in humans, particular emphasis must be placed on the dermatologic examination. Of the organ systems subjected to analysis, only the skin has a clinical endpoint--chloracne--which has been conclusively related to dioxin exposure. Further, while the intact skin is a most effective protective barrier to even high concentrations of a wide range of industrial chemicals, it also serves, by cutaneous absorption, as a significant portal of entry through which internal organ systems are placed at risk of toxicity.

In dermatologic practice, as in all clinical disciplines, the history can be more important to accurate diagnosis than objective physical findings. This is particularly true in the case of chloracne which, apart from the characteristic cutaneous distribution, has no hallmark features that distinguish it from other more common acneiform eruptions. In the current study, examiners were strictly forbidden from taking any occupational history. Though at obvious variance with traditional practice, such restrictions were essential to the elimination of observer bias. During the examinations, dermatologists were instructed to biopsy lesions that were felt to be suspicious of skin cancer. Though blinded to the participants' herbicide exposure status, examiners performed a similar number of biopsies in the Ranch Hand (19) and Comparison (20) groups.

The rarity of chloracne is such that few dermatologists will encounter even a single case in a lifetime of practice. Experimental dose-response studies in animals and in humans have confirmed that the topical concentrations of TCDD required to produce overt lesions are far greater than that to which participants in the current study were likely to have been exposed in SEA. It is therefore not surprising that, in the three examination cycles completed to date, no active cases of chloracne have been detected. Recognizing the remote possibility that acute cases of chloracne may have occurred and resolved, several long-term complications of all forms of acne (scarring and hyperpigmentation) were included as dependent variables in comparative and longitudinal analyses. Neither of these complications of acne diseases were different in the two groups.

Most of the dependent variable-covariate associations documented in the current section would be expected in clinical practice. Though subject to considerable individual variation, age-related changes in the epidermis, stratum corneum, and corium are associated with thinning of the skin, an increase in capillary fragility, abnormalities in keratinization, dyshydrosis with wrinkling and scaling, and loss of elasticity. Hyperplasia of the epidermis is typically associated with keratoses (seborrheic and senile) and basal cell carcinomas.

Among the dermal appendages, the sebaceous glands typically become less active with age, though an increase in comedones in selected areas (often infraorbital and nasal) may occur. Also noted and present in various forms were pigmentation disorders. In association with atrophy of the skin, depigmentation is common whereas with epidermal hyperplasia, hyperpigmentation can occur. With the exception of typical acne, which is more common at an early age, an increase in most other forms of skin disease would be expected over time and was documented in the current study.

Consistent with established clinical patterns, a number of skin diseases were found to occur more commonly in Black participants. As nonspecific sequelae to trauma or inflammation, hypo- and, more commonly, hyperpigmentation occur more frequently in dark skinned races. Acneiform lesions and, in fact, all follicular diseases occur more commonly in Blacks and may relate to race-specific variations in the shape and orientation of the hair follicles. Finally, as a genetically determined trait, exaggerated mesenchymal responses to trauma and inflammation are common in Blacks, with keloid formation being the most familiar example.

With one exception, group comparison of the variables analyzed revealed no significant differences between the Ranch Hands and Comparisons. As noted previously, close to an equal number of biopsies was performed in each group. The Ranch Hands were found to have a statistically significant increase in the incidence of post-SEA basal cell carcinoma, a finding that is discussed in Chapter 10 of the main report. Though Ranch Hands were found to have a slightly greater incidence of reported acne developing after SEA service, the distribution of locations of acne was similar to that of the Comparisons and not in a pattern consistent with chloracne. This difference in reported acne was not corroborated on physical examination of the participants. Finally, longitudinal analysis of all cutaneous disorders over three examination cycles failed to reveal any health detriment related to group.

SUMMARY

The 1987 dermatologic assessment was based on reported occurrence, duration, and location of acne; six dermatologic disorders: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, and hyperpigmentation; other abnormalities; and a dermatology index based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts. Results of the Ranch Hand and Comparison contrasts are summarized in Table 9.

A significantly higher percentage of Ranch Hands than Comparisons reported that they had experienced at least one occurrence of acne during their lifetime ($p=0.026$); the occurrence of acne in this analysis included episodes before the start of the first SEA tour. Subsequent analysis indicated that, for participants with no history of acne before the start of the first SEA tour, a higher percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour ($p=0.007$). No difference in the occurrence of acne after the start of the first Southeast Asia (SEA) tour was present for participants with an occurrence of acne before the start

Table 9

Overall Summary Results of Unadjusted and
Adjusted Group Contrast Analyses of Dermatology Variables

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
Occurrence of Acne				
Lifetime	D	0.026	--	RH>C
Relative to SEA Tour ^a				
Post-SEA vs. Pre-SEA/None		0.010	--	
Post-SEA/Pre- and Post-SEA vs. Pre-SEA/None		0.019	--	
Post-SEA vs. None		0.007	--	
Pre- and Post-SEA vs. Pre-SEA		NS	--	
Duration of Acne	C	NS	--	
Location of Acne	D	NS	--	
Comedones	D	NS	** (NS)	
Acneiform Lesions	D	NS	NS	
Acneiform Scars	D	NS	NS	
Depigmentation	D	NS	NS	
Inclusion Cysts	D	NS	NS	
Hyperpigmentation	D	NS	NS	
Other Abnormalities	D	NS	NS	
Dermatology Index	D	NS	NS	

D: Discrete analysis performed.

--Analysis not performed.

RH>C: Higher prevalence rate in Ranch Hands than in Comparisons.

^aThe analyses of occurrence of acne relative to SEA tour are contrasts resulting from the further classification of lifetime occurrence of acne.

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

C: Continuous analysis performed.

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table K-2 in the main report for a detailed description of this interaction.

of the first SEA tour. There was also no difference between the Ranch Hands and Comparisons based on the analysis of duration or location of acne, which was limited to participants with acne after the start of the first SEA tour. These observations suggest that the increased reports of acne after service in SEA were not due to chloracne.

The results revealed no significant differences between the two groups based on the unadjusted and adjusted analyses of acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and the dermatology index determined at the physical examination. In the unadjusted analysis of comedones, no significant difference between the Ranch Hands and Comparisons was found; however, there was a significant group-by-race interaction in the adjusted analysis ($p=0.049$). Exploration of the interaction revealed that the Black Ranch Hands had a marginally higher prevalence rate of comedones than the Black Comparisons ($p=0.083$). No difference was found for the non-Blacks. Without the group-by-race interaction in the model, no significant difference between the two groups was found based on the prevalence of comedones. The fact that there were no differences in duration or location of reported acne subsequent to service in SEA and the lack of group differences in the physical examination strongly suggest that the increase in reported acne was not due to chloracne. This increase in reported skin disease could be due to differential reporting or wartime living conditions among study participants.

In the exposure index analyses, most of the results did not suggest an increasing dose-response relationship that was consistent across the three exposure levels. However, in the unadjusted analysis of depigmentation for the enlisted groundcrew cohort, borderline significant differences were identified that were consistent with an increasing dose-response relationship. In the adjusted analysis of depigmentation for this cohort, there was an exposure index-by-race interaction. Exploration of the interaction resulted in significant and marginally significant differences; however, the percentages were no longer consistently increasing with exposure level. In the officer cohort, the overall tests and medium versus low exposure contrasts were significant based on the analyses of other abnormalities; however, the high versus low contrasts were not significant. In the adjusted analysis of the dermatology index, a significant exposure index-by-presence of pre-SEA acne interaction was found in the enlisted groundcrew. The high versus low contrast was significant for participants with pre-SEA acne, and the percentage of participants classified as abnormal increased as exposure levels increased. Clarification of these exposure analyses must await the completion of the serum dioxin assays.

Based on the longitudinal analysis of the dermatology index, the difference between groups did not change significantly between the 1982 Baseline and the 1987 followup examinations.

In conclusion, no current cases of chloracne were diagnosed at the 1987 physical examination. Although more Ranch Hands reported having experienced at least one occurrence of acne in their lifetime, the remainder of the dermatologic evaluation showed that the two groups were similar.

CARDIOVASCULAR EVALUATION

INTRODUCTION

Cardiac disease and peripheral vascular disease are not recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both bradycardia and tachycardia have been suggested following acute heavy exposure to the 2,4-D and 2,4,5-T components, but the cardiovascular effects after chronic low-dose exposure are essentially unknown.

DISCUSSION

Of the diseases encountered by the primary care physician, circulatory disorders are among the most common. The sources of the noninvasive data analyzed in the current chapter occupy a time-honored place in cardiovascular practice. Specifically, the history, physical examination, chest x ray, and resting electrocardiogram remain highly reliable indices that can alert the clinician to the presence of underlying cardiovascular disease and point to the need for additional, more specific, noninvasive, or invasive studies. Though arbitrary, dividing data collection into central and peripheral cardiovascular functions is convenient and forms a reasonable basis for comparison of the cohorts under study.

The limitations of the history in cardiovascular diagnosis deserve emphasis. In peripheral vascular disease, for example, signs and symptoms will vary depending on the degree of development of collateral circulatory channels. While hemodynamically significant arterial disease of lower extremities is almost always associated with claudication, severe carotid occlusive disease can be present in the absence of symptoms of transient cerebral ischemia. Further, conclusive evidence shows that advanced coronary artery disease can occur in the absence of angina and present as "silent" myocardial ischemia. Lastly, it is well recognized that the cardiovascular history, as related by patients, is often subject to error. The generic term "heart attack," for example, can be used to describe any type of cardiac event from an isolated episode of unstable angina or arrhythmia, to an actual myocardial infarction. These imperfections highlight the importance of the type of medical record verification conducted in the current study.

In the cardiovascular assessment, particularly, the physical examination can provide valuable clues to the presence of asymptomatic but significant underlying disease. Because the examinations were conducted by internists rather than cardiologists, steps were taken to simplify data collection and to reduce interobserver differences among the examining physicians. All blood pressure readings, for example, were taken by automated sphygmomanometric instruments. Auscultory endpoints--murmurs and bruits--were recorded as present or absent by anatomic location, thus eliminating speculation as to specific valvular or vessel origin and hemodynamic significance. As markers of occult arterial occlusive disease, vascular bruits are relatively easy to detect and were carefully sought.

Pertinent to the longitudinal design of the AFHS, several of the physical findings recorded must be viewed in the context of the aging population under

study. A gradual increase in systolic blood pressure will occur with advancing years. Related to the normal progression of arteriosclerosis and, more specifically, to arterial tortuosity, vascular bruits may occur in vessels free of occlusive disease, particularly in the carotid arteries. Again, all bruits were recorded by location without attempting to comment on the hemodynamic significance or specific vessel of origin (i.e., internal vs. external carotid). The occurrence of abnormal heart sounds, particularly S_4 , would also be expected to increase with age.

The data collected in the current chapter were limited to the resting 12-lead electrocardiogram and the standard two-view chest x ray. This x ray is used to detect the presence of cardiac enlargement or abnormalities in pulmonary vasculature, as reported in Chapter 20 of the main report, Pulmonary Disease. In current practice, these techniques are supplemented, but not replaced, by such noninvasive studies as the treadmill exercise test, nuclear isotope studies, and the echocardiogram. With few exceptions, these technically sophisticated and costly procedures do little more than confirm diagnoses that can be made based on data available in the current assessment. For example, when correlated with the history and physical examination, the chest x ray and electrocardiogram enable the clinician to draw highly accurate conclusions regarding the presence and hemodynamic significance of valvular heart disease of any etiology. As defined by the chest x ray, the pulmonary vascularity can provide reliable clues to the presence of global left ventricular dysfunction with pulmonary venous congestion and of pulmonary hypertension of any cause.

The dependent variable-covariate associations analyzed in the current chapter confirm findings that have been well documented in numerous long-term epidemiologic studies. The lack of clearly defined cardiovascular endpoints to dioxin exposure places a premium on the careful analysis of risk factors as potentially confounding variables. More than any other, the cardiovascular system is subject to the effects of lifestyle and heredity.

As a degenerative disease with multiple manifestations, arteriosclerosis develops in all organ systems over time. With few exceptions, an age-related increase in the incidence of abnormal physical findings was documented in both the Ranch Hand and Comparison groups. As expected, reported and verified heart disease and, particularly, previous myocardial infarction, were highly correlated with the classical risk factors of age, positive family history, and cigarette use. Although an apparent exception was the negative correlation between the systolic blood pressure and current cigarette use, this may reflect the contributions of former smokers, who have stopped smoking in response to a diagnosed disease. This is the group that had the highest percentage of abnormal systolic blood pressures (above 140 mm Hg). Lifetime cigarette use, on the other hand, was consistently positively associated with abnormalities in all variables analyzed.

The effects of current and lifetime alcohol consumption were less consistent. Clinically, it is clear that in cases of severe, chronic abuse, alcohol is directly cardiotoxic and can lead to an irreversible congestive cardiomyopathy. On the other hand, when consumed in moderation, alcohol may favorably influence the ratio of high density lipoprotein (HDL) to low density lipoprotein (LDL) cholesterol and may actually be protective with respect to the future development of cardiovascular disease.

Group comparisons generally revealed no significant differences between the Ranch Hand and Comparison cohorts. As in the Baseline examination (but not in the 1985 followup), Ranch Hands had a greater incidence of peripheral pulse abnormalities of the lower extremities than the Comparisons (15.3% vs. 12.2%). As noted above, the 1985 followup included Doppler ultrasound studies, which have proven to be more sensitive than traditional manual palpation. Further analysis of specific pulse sites suggests that the current group difference relates mainly to an increased incidence of femoral, rather than more peripheral, sites, a finding that should be relatively easy to confirm on subsequent examination cycles. Arterial occlusive disease is often unilateral rather than bilateral and can affect large vessels proximally or smaller vessels distally in segmental fashion. Distal circulation may be maintained by good collateral vessels even in the presence of proximal, partial pulse deficits. The Doppler should be more reliable than palpation in such cases, but neither method is perfect. This observed pulse difference does not appear to be related to exposure since abnormalities were not increased in the enlisted groundcrew, the group with the highest serum TCDD levels.

Recently, there has been renewed interest in the role of personality type as a risk factor for cardiovascular disease. In the current study, Type B personality was found to be associated with an increased incidence of elevated systolic blood pressure and with deficits in four of the five peripheral pulses assessed by palpation. Though at variance with classical teaching, these results are consistent with recent evidence that Type B personality may be at equal or greater risk than Type A for the development of coronary artery disease.

The historical, physical examination, and laboratory data provide a reasonable basis for comparison of the cohorts under study and indicate that neither the Ranch Hand nor the Comparison group is at significant health detriment relative to the other. The slightly greater incidence of heart disease documented in the Ranch Hand cohort in the 1985 followup examination was not evident after continuing review of medical records. The incidence is now similar in the two groups. Finally, as in the Baseline examination (but not in the 1985 followup), a slightly greater incidence of pulse deficits has been found in the Ranch Hand group and will bear continued surveillance in future examination cycles as more accurate methods to measure the body burden of dioxin become available.

SUMMARY

The cardiovascular evaluation of the Ranch Hand and Comparison groups was based upon reported and verified heart disease events (essential hypertension, cardiac disease, and myocardial infarction); assessment of central cardiac function [systolic blood pressure, heart sounds, and electrocardiograph (ECG) findings]; and assessment of peripheral vascular function (diastolic blood pressure, funduscopic abnormalities, carotid bruits, and peripheral pulse abnormalities). Table 10 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

TABLE 10.

Overall Summary Results of Unadjusted and Adjusted Group
Contrast Analyses of Cardiovascular Variables

Variable	Unadjusted	Adjusted	Direction of Results
<u>Questionnaire Variables</u>			
Reported/Verified Essential Hypertension*	NS	NS	
Reported Heart Disease (Excluding Hypertension)	NS	NS	
Verified Heart Disease (Excluding Hypertension)	NS	NS	
Reported/Verified Myocardial Infarction*	NS	** (NS)	
<u>Central Cardiac Function</u>			
Systolic Blood Pressure (continuous)	NS	NS	
Systolic Blood Pressure (discrete)	NS	** (NS)	
Heart Sounds	NS	NS	
ECG-Overall	NS	NS	
RBBB	NS	NS	
LBBB	NS	--	
Nonspecific T-Waves	NS	****	
Bradycardia	0.049	NS*	C>RH
Tachycardia	NS	--	
Arrhythmia	NS	NS*	RH>C
ECG-Other Diagnoses	NS	NS	

TABLE 10. (continued)

Overall Summary Results of Unadjusted and Adjusted Group
Contrast Analyses of Cardiovascular Variables

Variable	Unadjusted	Adjusted	Direction of Results
<u>Peripheral Vascular Function</u>			
Diastolic Blood Pressure (continuous)	NS*	** (NS*)	RH>C
Diastolic Blood Pressure (discrete)	NS	** (NS)	
Funduscopy Examination	NS	--	
Carotid Bruits	NS*	--	RH>C
Radial Pulses	NS*	--	C>RH
Femoral Pulses	0.016	0.018	RH>C
Popliteal Pulses	NS	NS	
Dorsalis Pedis Pulses	NS*	NS*	RH>C
Posterior Tibial Pulses	NS	****	
Leg Pulses	0.049	NS*	RH>C
Peripheral Pulses	NS*	NS	RH>C
All Pulses	NS*	NS	RH>C

*All conditions reported were verified; therefore, reported and verified analyses are the same.

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

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table L-2 in the main report for a detailed description of this interaction.

--Adjusted analyses not performed (sparse data).

****: Group-by-covariate interaction ($p \leq 0.01$); refer to Table L-2 in the main report for a detailed description of this interaction.

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

C>RH: Higher mean in Comparisons than in Ranch Hands.

RH>C: Higher prevalence rate or mean in Ranch Hands than in Comparisons.

** (NS*): Group-by-covariate interaction ($0.01 < p \leq 0.05$); borderline significant when interaction is deleted; refer to Table L-2 in the main report for a detailed description of this interaction.

In the evaluation of heart disease from questionnaire data, there were no statistically significant differences, unadjusted or adjusted, in the frequency of reported/verified essential hypertension, reported heart disease, or verified heart disease. For reported/verified myocardial infarction, there was no statistically significant difference between the two groups in the unadjusted analysis, but in the adjusted analyses, there was a statistically significant group-by-family history of heart disease interaction ($p=0.042$). The relative risk was less than 1 in those with no family history of heart disease and greater than 1 in those with a family history of heart disease; neither within-stratum estimate of risk was statistically significant. An adjusted model fit after deletion of the interaction term was not statistically significant.

For the parameters of central cardiac function there were no statistically significant differences, unadjusted or adjusted, in the mean systolic blood pressure, nor in the percentage of individuals with abnormal heart sounds, overall ECG abnormalities, right bundle branch block (RBBB), left bundle branch block (LBBB), tachycardia, or other ECG diagnoses. In the discrete analysis of systolic blood pressure, there was no significant difference between the Ranch Hands and Comparisons in the unadjusted analysis, but a significant group-by-cholesterol-HDL ratio interaction was detected in the adjusted analysis ($p=0.020$). The adjusted relative risk was less than 1 in those with cholesterol-HDL ratios less than or equal to 4.2 and less than 1 in those with ratios between 4.2 and 5.5, but greater than 1 in those with cholesterol-HDL ratios greater than 5.5. However, none of these within-stratum relative risks was statistically significant, nor was the group comparison after deletion of the interaction term from the model. For nonspecific T-waves, the unadjusted difference was not statistically significant. However, there was a highly significant ($p=0.004$) group-by-lifetime cigarette smoking history interaction in the adjusted analysis. The relative risk was less than 1 in nonsmokers and moderate lifetime smokers and greater than 1 in heavy smokers. None of these within-stratum risks reached statistical significance. Significantly fewer Ranch Hands than Comparisons had bradycardia (Est. RR: 0.67, 95% C.I.: [0.44,1.00], $p=0.049$). The adjusted relative risk for bradycardia was borderline significant (Adj. RR: 0.69, 95% C.I.: [0.46,1.04], $p=0.068$). For arrhythmia there was no significant difference in the unadjusted analysis, but there was a borderline significant difference in the adjusted analysis (Adj. RR: 1.56, 95% C.I.: [0.98,2.49], $p=0.062$).

In the analysis of peripheral vascular function, no unadjusted or adjusted statistically significant differences were detected in funduscopic abnormalities or in popliteal pulses. The mean diastolic blood pressure was borderline significantly different in the two groups (unadjusted $p=0.099$); in the adjusted analysis, a significant group-by-age interaction was detected ($p=0.028$). In individuals born in or after 1942, the Ranch Hand adjusted mean was significantly greater than the Comparison adjusted mean (74.91 vs. 73.56 mm Hg, $p=0.026$). In those born between 1923 and 1941 and in those born in or before 1922, the adjusted group means were not significantly different. (The difference in the overall adjusted group means was borderline significant [$p=0.100$] after deleting the interaction term from the model.) The percent with abnormal diastolic blood pressure was not significantly different in the two groups in the unadjusted analysis, but in the adjusted discrete analysis there was a significant group-by-family history of heart disease before age 50 interaction ($p=0.043$). The relative risk was greater than 1 in those with a family

history before age 50 and nearly equal to 1 in those without such a history. The former was of borderline significance ($p=0.057$) but was based on small numbers (5 of 26 Ranch Hands, 1 of 30 Comparisons). After deletion of the interaction term from the model, the adjusted relative risk was not statistically significant.

There was a borderline significant difference in the percentage of individuals with carotid bruits (Est. RR: 2.97, 95% C.I.: [0.91,9.67], $p=0.058$). For radial pulse abnormalities, there was also a borderline significant difference; in this case, the estimated relative risk was less than 1 (Est. RR: 0.29, 95% C.I.: [0.06,1.34], $p=0.076$). Adjusted analyses could not be performed because these abnormalities were so rare.

Both the unadjusted and the adjusted analyses of femoral pulses revealed a significantly greater percentage with abnormalities in the Ranch Hand group than in the Comparison group ($p=0.016$, unadjusted and $p=0.018$, adjusted). The estimated relative risk was 2.52 (95% C.I.: [1.16,5.44]) and the adjusted relative risk was 2.52 (95% C.I.: [1.15,5.56]). Both unadjusted and adjusted differences in dorsalis pedis pulses were borderline significant, with a higher percent abnormal in the Ranch Hands than in the Comparisons (Est. RR: 1.30, 95% C.I.: [0.98,1.72], $p=0.071$ and Adj. RR: 1.29, 95% C.I.: [0.97,1.72], $p=0.078$). In the case of posterior tibial pulses, there was no significant difference in the unadjusted analyses, but a highly significant group-by-differential cortisol interaction emerged in the adjusted analysis ($p=0.004$). There was little group difference in those with differential cortisol response less than or equal to 0.6, but the risk was significantly greater than 1 in those with differential cortisol levels between 0.6 and 4.0 (Adj. RR: 3.04, 95% C.I.: [1.06,8.68], $p=0.030$). The relative risk was less than 1 and not statistically significant in those with differential cortisol response greater than 4.0. In the variable combining all leg pulses, the Ranch Hands exhibited significantly more abnormalities than the Comparisons (Est. RR: 1.30, 95% C.I.: [1.00,1.67], $p=0.049$). The adjusted relative risk for leg pulses was of borderline significance ($p=0.079$). For peripheral pulses, the estimated relative risk was borderline significant (Est. RR: 1.26, 95% C.I.: [0.97,1.62], $p=0.082$). This was also the case for all pulses (Est. RR: 1.26, 95% C.I.: [0.97,1.62], $p=0.081$).

There was agreement between the physical examination findings and the past medical history, with a number of positive and statistically significant associations detected between various physical parameters and the heart disease history.

Exposure index analyses conducted within the Ranch Hand group did not detect any significant effects in any of the three occupational cohorts for reported/verified essential hypertension, reported/verified myocardial infarction, heart sounds, overall ECG findings, RBBB, LBBB, tachycardia, funduscopic examination findings, and carotid bruits, nor in any of the pulse variables or pulse aggregates. For reported and verified heart disease, there were no significant differences in the enlisted flyers or enlisted groundcrew. In the officers, the group with the lowest current serum TCDD levels, the adjusted medium versus low exposure level contrast was significantly less than 1 ($p=0.019$), and the high versus low contrast was also less than 1 and of borderline significance ($p=0.082$).

No significant differences were detected in the analysis of systolic blood pressure in the officers and enlisted groundcrew, but in the enlisted flyers there was a significant difference in the means that was consistent with a dose-response relationship ($p=0.037$)--mean values were 124.14, 128.79, and 133.55 in the low, medium, and high exposure level categories, respectively. After covariate adjustment, however, the differences were no longer statistically significant ($p=0.181$). There were no statistically significant differences in nonspecific T-wave findings in the officers or enlisted groundcrew. Although not entirely consistent with a dose-response relationship, there was a borderline significant difference in the enlisted flyers ($p=0.075$, unadjusted and $p=0.091$, adjusted).

No statistically significant exposure level effects were detected in the unadjusted analyses of bradycardia, nor in the adjusted analyses within the enlisted flyers or enlisted groundcrew. In the officers, however, a significant exposure index-by-cholesterol-HDL ratio interaction was detected ($p=0.045$). Upon stratification, there were fewer abnormalities in the medium and high exposure level categories than in the low exposure level category for those with cholesterol-HDL ratios less than or equal to 4.2 and for those with levels between 4.2 and 5.5, but slightly more abnormalities in the medium and high exposure level categories as compared to the low category for those with ratios greater than 5.5. These were all based upon small numbers.

For arrhythmia, there were no significant differences in the officers or enlisted groundcrew, but in the enlisted flyers, there were six abnormalities in the high exposure level category as compared to none in the low category and none in the medium category ($p=0.025$ for the high vs. low contrast). Adjusted analyses could not be performed due to the small numbers. For other ECG diagnoses, no significant differences were found except for a significant exposure index-by-age interaction in the officer cohort ($p=0.018$). The differences within each of the age strata were not consistent with a dose-response relationship, however. Finally, there were no significant exposure level effects on diastolic blood pressure in the enlisted flyers. In the officers, there was a significantly greater percentage of abnormalities in the higher exposure level category as compared to the low exposure level category ($p=0.039$), but there was no excess risk in the medium exposure level group. Also, in the enlisted groundcrew there was a significant exposure index-by-personality type interaction ($p=0.012$), but the within-stratum differences were not consistent with a dose-response relationship.

Longitudinal analysis of the overall ECG findings did not detect any significant differences between the Ranch Hand and Comparison groups in the change in the overall ECG status from Baseline to the 1987 followup examination. Mortality-morbidity analyses did not indicate excess cardiovascular risk in the Ranch Hands.

In summary, the cardiovascular evaluation showed that the health of the Ranch Hand and Comparison groups was similar for reported and verified heart disease and central cardiac function. For peripheral vascular function, the Ranch Hands had a marginally higher percentage of individuals with carotid bruits. There were also significant, or marginally significant, differences (more abnormalities in the Ranch Hands than in the Comparisons) in femoral

pulses, dorsalis pedis pulses, and in the three pulse aggregates (leg, peripheral, and all pulses), as determined by manual palpation. These findings emphasize the importance of including further evaluations of peripheral pulses in subsequent examinations in this study.

HEMATOLOGIC EVALUATION

INTRODUCTION

Animal experiments have confirmed both direct and indirect hematopoietic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). Although direct impairment of the hematopoietic system may result from exposure to chlorophenols or dioxin, marked abnormalities in many of the circulating hematologic elements may also be due to the severe toxicity observed in other organs or organ systems.

DISCUSSION

The complete blood count is the most frequently ordered laboratory test in ambulatory medicine. As indices of the three peripheral blood cell lines (erythrocytes, leukocytes, and platelets) the eight variables examined in the current section are heavily relied upon to indicate disease of the hematopoietic system and, perhaps more often, to alert the clinician to the presence of disease in other organ systems as well.

In contrast to most organ systems, in which disease is usually apparent based on the history and physical examination, particular emphasis is placed on the laboratory in the detection of hematologic disorders. As quantitative indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) can provide helpful insight into the morphologic classification of anemias.

The total white cell count (WBC) is subject to variation in a broad range of disease states. Though lacking specificity, leukocytosis or leukopenia can serve as a sensitive clue to the presence of a host of infectious, inflammatory, and neoplastic disorders, and point to the need for further investigation.

As essential elements to normal coagulation, the platelets have a short half-life and are most subject to decreased survival in the presence of a wide range of diseases and numerous prescription and over-the-counter medications. The wide range of normal (130,000-400,000/cubic mm) is such that subtle changes in platelet survival could occur and not be identified as abnormal. Conversely, small differences in the total platelet count do not have a clinically significant effect on clotting mechanisms. Seven participants were found to have platelet counts greater than 500,000/cubic mm, with the highest count of 595,000/cubic mm. Detailed chart review failed to reveal any common diagnosis in this subgroup, and the similar distribution (four Ranch Hands, three Comparisons) weighs against the presence of a herbicide effect.

Analysis of the covariate-dependent variable data confirmed several expected clinical associations. In cigarette smokers, cellular hypoxia related to carboxyhemoglobin formation and systemic arterial desaturation in obstructive airway disease combine to raise the hemoglobin and hematocrit in comparison to nonsmokers. Less understood but recognized clinically is an elevation in the total white cell count, a finding that may relate to the increased incidence of chronic bronchitis in a nicotine dependent population.

While finding anemia should be considered abnormal at any age and should prompt appropriate medical evaluation, it is common to find a gradual decline in selected red cell (RBC) indices with aging, an observation confirmed in the current study. Older participants were found to have statistically significant reductions in total red cell count and hemoglobin, associations that may reflect the increased incidence of chronic disease of multiple etiologies with advancing age. Several mechanisms have been suggested for the "anemia of chronic disorders," including a decreased red cell life span, diminished erythropoietin production, and impaired gastrointestinal absorption of iron.

The race-related associations can be explained on the basis of established clinical observations. In relation to nonblacks, Black participants had statistically significant reductions (or a higher percentage of individuals with abnormally low levels) in all red cell indices and in the total white cell count. In other studies, the mean hemoglobin level of Blacks averages 0.5 to 1.0 g/dl below that of nonblacks, a finding that may relate to the increased incidence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and of hemoglobin variants (S and C) associated with heterozygous sickling disorders.

Blacks were found to have a greater incidence of abnormally low white cell counts than nonblacks (19% versus 6%). While the degree of leukopenia was slight and not likely of clinical significance, the cause of this finding is uncertain.

Of the eight laboratory variables examined, only two significant group differences were found. The Ranch Hands had a slightly higher (geometric) mean WBC count than the Comparisons. This small difference was not significant after covariate adjustment. Consistent with the Baseline and 1985 followup examinations, the Ranch Hands had a higher mean platelet count than the Comparisons and, in the present study, the difference has become statistically significant. The percentage of individuals with abnormally high platelet count values was also significantly greater in the Ranch Hands than in the Comparisons. Examination of the data from the three cycles shows that there has been a gradual reduction in platelet counts in both groups (although greater in the Ranch Hands) over time, suggesting an effect of age common to all participants. As a nonspecific reaction, the platelet count can be elevated in any occult disease process; this may be related to the slightly elevated erythrocyte sedimentation rate found in the Ranch Hands and reported in the General Health chapter. There is a highly significant association between sedimentation rate and platelet count, with 8.9 percent of those with abnormally high sedimentation rates exhibiting abnormally high platelet counts, compared to only 1.8 percent in those with normal sedimentation rates ($p < 0.001$); the correlation between the (log) sedimentation rate and platelet

count was also statistically significant ($r=0.156$, $p<0.001$). Whatever the cause, the difference in means of less than 10,000 per cubic mm is not clinically significant.

SUMMARY

The hematologic status of the Ranch Hand and Comparison groups was assessed by eight variables--RBC, WBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count. Table 11 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

TABLE 11.

Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Hematologic Variables

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
RBC	NS	NS	NS	NS	
WBC	NS	0.038	NS	NS	RH>C
Hemoglobin	NS	NS	NS	NS	
Hematocrit	NS	NS	NS	NS	
MCV	NS	NS	NS	NS	
MCH	NS	NS	NS	NS	
MCHC	NS	NS	--	NS	
Platelet Count	0.035	0.017	0.035	0.018	RH>C, RH ^H >C ^H

--Analysis not performed (no abnormalities present).

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

RH>C: Ranch Hand mean greater than Comparison mean.

RH^H>C^H: Ranch Hand percent abnormally high greater than Comparison percent abnormally high ($p=0.027$).

There were no unadjusted or adjusted statistically significant differences between groups for RBC. For WBC, there was a statistically significant difference between groups in the mean unadjusted (log) levels (geometric means in the Ranch Hand and Comparison groups were 6.875 and 6.703 thousand per cubic mm, respectively). The adjusted mean counts were not significantly different.

No statistically significant differences were detected in either the unadjusted or adjusted analyses of hemoglobin, hematocrit, MCV, MCH, and MCHC. For platelet count, the mean level was significantly greater in the Ranch Hands than in the Comparisons (265.47 vs. 259.62 thousand per cubic mm; $p=0.017$), and the percent of participants with elevated abnormally high values was also greater in the Ranch Hands than in the Comparisons (2.9% vs. 1.6%, Est. RR: 1.92, 95% C.I.: [1.08, 3.41], $p=0.027$ [overall p -value = 0.035]). These differences remained statistically significant after adjustment for covariates ($p=0.018$ and $p=0.035$ for the continuous and overall discrete analyses, respectively). The elevation of platelets is not what one would expect based on the results of animal studies.

Exposure index analyses in the Ranch Hand group did not detect any significant dose-response relationships or interactions in any of the occupational cohorts (officers, enlisted flyers, enlisted groundcrew) for WBC or MCH. There was a statistically significant ($p=0.029$) exposure index-by-age interaction in the continuous analysis of RBC in the enlisted flyers. There were highly significant exposure index-by-age interactions in the continuous analysis of hemoglobin and hematocrit in the enlisted flyers ($p=0.003$ and $p=0.002$, respectively), as well as significant exposure index-by-lifetime cigarette smoking history interactions for these variables in the enlisted groundcrew ($p=0.012$ and $p=0.010$, respectively). Within each of the stratum, however, these results did not suggest a dose-response relationship. In the case of hematocrit, there was also a significant ($p=0.025$) exposure level effect in the unadjusted discrete analysis for the officers, with five individuals having abnormally low values in the high exposure index group, compared to one and none in the low and medium exposure level categories, respectively. This effect was of borderline significance after adjustment for covariates ($p=0.086$). For MCV, in the enlisted groundcrew, there was a significant difference in the mean values for the three exposure level categories, both unadjusted ($p=0.015$) and adjusted ($p=0.028$). These were consistent with a dose-response relationship. A significant difference in the adjusted means for MCHC emerged in the enlisted flyers ($p=0.049$). A significant difference was also detected for platelet count in the discrete analysis of the enlisted flyers ($p=0.046$). Continuous adjusted analyses of platelet count in the enlisted flyers detected a highly significant exposure index-by-race interaction ($p=0.008$) and a significant exposure index-by-current cigarette smoking interaction ($p=0.014$). The MCHC and platelet count findings did not generally support dose-response relationships.

Longitudinal analyses found no significant difference between the Ranch Hand and Comparison groups in the change in MCV and MCH from Baseline to the 1987 followup examination. However, the mean change in platelet count (a decrease) was significantly greater ($p=0.015$) in the Ranch Hand group than in the Comparison group.

In summary, there is little consistent evidence in this study to implicate an adverse effect of herbicide exposure on hematologic status. The Ranch Hands exhibited a slight, but statistically significant, increase in platelets, but data from animal studies suggest that TCDD exposure should cause a lowering of the platelet count, rather than an elevation.

RENAL ASSESSMENT

INTRODUCTION

Renal dysfunction and overt renal disease are not generally considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, renal failure due to acute intoxication from another phenoxy herbicide (MCP) has been shown in two human cases, along with other severe toxic symptoms.

DISCUSSION

In clinical practice, the presence of renal or urinary tract disease can be determined with confidence based on the medical history, physical examination, and the five laboratory indices included in the present study.

Though subject to some day-to-day variation related to diet and state of hydration, the blood urea nitrogen is considered a reliable index of glomerular filtration, while the integrity and concentrating ability of the renal tubular system are reflected in the urinary specific gravity. In documenting the presence of red or white blood cells in significant numbers, the examination of the urinary sediment can provide valuable clues to the presence of a broad range of infectious, inflammatory, and neoplastic conditions intrinsic to the upper and lower urinary tracts.

The frequent finding in ambulatory medicine of isolated abnormalities in the routine urinalysis of healthy individuals who in fact have no disease of the genitourinary system is pertinent to interpretation of the renal assessment data. With normal fluid balance, the healthy kidneys can excrete up to 100-150 mg of total protein in 24 hours. The qualitative dipstick test used in the current study is sensitive to protein concentrations as low as 10-15 mg per deciliter and, particularly in specimens collected after overnight fasting, will often give a trace to 1+ positive reaction in the absence of parenchymal renal disease. Similarly, on microscopic examination of the urinary sediment, it is not uncommon to intermittently find a few red or white blood cells in the absence of definable neoplastic or inflammatory cause, trauma, or kidney stones. When documented as an isolated finding in the absence of symptoms or other signs, such intermittent microcyturia can usually be considered benign.

With reference to the current study, no significant group differences in the renal indices were found between the Ranch Hands and Comparisons in the unadjusted analyses. In the dependent variable-covariate analysis, several associations were defined that are consistent with established clinical observations.

In the adjusted analyses, significant covariate associations with age were documented. The twofold increased historical incidence of genitourinary disease would be expected with aging in this all male population with the development of benign prostatic hypertrophy and bladder outlet obstruction.

In association with benign nephrosclerosis of the normally aging kidney, there is a gradual reduction in renal mass (from an average of 260 grams in the young adult to 190 grams in the eighth decade) and a 50 percent reduction in renal plasma flow (from 600 cc/min to 300 cc/min). An age-related increase in blood urea nitrogen and proteinuria would be expected findings and were documented in the current study.

Several of the race-dependent variable associations can be explained on the basis of established clinical correlations. The increased incidence of hypertension with hypertensive nephropathy in Blacks is well recognized and might account for the increased incidence of proteinuria, hematuria, and elevated blood urea nitrogen in this population. Though the numbers are small, microinfarction of the renal medulla in sickle cell trait (8-10% incidence in Blacks) might have been a minor contributing factor in the incidence of hematuria. The cause of the twofold increased incidence of leukocyturia in Blacks is uncertain and the very slight difference in mean specific gravity (1.0209 vs. 1.0198) is not clinically significant.

In the diabetic class, the increased incidence of hypertensive and arteriosclerotic vascular disease and of urinary tract infections related to glycosuria provide reasonable explanation for the significant covariate association of proteinuria, leukocyturia, and elevated blood urea nitrogen in this population.

The renal assessment data revealed abnormalities in five laboratory indices at a prevalence that is common in ambulatory practice. There were no significant overall differences between the Ranch Hand and Comparison cohorts. Most of the covariate associations can be explained on the basis of established clinical correlations. Finally, when documented as isolated findings, the benign nature of these abnormalities should be emphasized.

SUMMARY

The 1987 renal assessment was based on six variables. The results of the Ranch Hand and Comparison contrasts are summarized in Table 12.

The historical assessment of kidney disease/stones based on self-reported data showed no significant differences between the Ranch Hand and Comparison groups. These results are consistent with the results of the 1985 followup but appear to be in marked contrast to the Baseline findings. The Comparison cohort is different between the Baseline report and the 1987 followup study (Original Comparisons vs. all Comparisons), and the definition of kidney disease has been expanded from the Baseline study to include kidney stones. However, when the analysis of the 1987 followup data was restricted to the Original Comparisons and kidney stones were not included in the definition of kidney disease, the prevalence rate of kidney disease was comparable between the two examinations, but the difference between groups was still nonsignificant ($p=0.952$).

TABLE 12.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Renal Variables**

Variable	Type of Analysis	Unadjusted	Adjusted
<u>Questionnaire</u>			
History of Kidney Disease/Stones	D	NS	NS
<u>Laboratory</u>			
Urinary Protein	D	NS	** (NS)
Urinary Occult Blood	D	NS	** (NS)
Urinary White Blood Cell Count	D	NS	NS
Blood Urea Nitrogen	C	NS	** (NS)
Urine Specific Gravity	C	NS	NS

D: Discrete analysis performed.

C: Continuous analysis performed.

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

** (NS): Group-by-covariate interaction ($0.01 \leq p \leq 0.05$); not significant when interaction is deleted; refer to Table N-2 in the main report for a detailed description of this interaction.

The current renal function was evaluated by five laboratory variables: urine protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, and urine specific gravity.

There was no significant difference detected between the two groups based on the unadjusted analysis of urinary protein. In the adjusted analysis, there was a significant interaction between group and occupation. Stratifying by occupation revealed that the Comparison enlisted flyers had a higher percentage of abnormalities than the Ranch Hand enlisted flyers ($p = 0.036$). After deleting the group-by-occupation interaction, no difference between the two groups was observed. This result differed from the twofold increase of proteinuria observed in Comparisons at Baseline.

No difference was identified between the Ranch Hands and the Comparisons based on the analysis of urinary occult blood without adjustments for covariates. However, after stratifying by race due to a significant group-by-race interaction, the estimated prevalence rate for the Black Ranch Hands was noted as being statistically higher than the corresponding rate for the Black Comparisons ($p=0.013$). The estimated prevalence rates were not detected as being different based on an adjusted model without the group-by-race interaction.

Based on the analyses of urinary white blood cell count, no differences were detected between the two groups in either the unadjusted or adjusted analyses.

The mean blood urea nitrogen levels of the Ranch Hands and Comparisons did not vary significantly when compared without adjustments. The adjusted analysis detected a significant group-by-race interaction. Stratifying by race revealed that the mean of the Black Comparisons was statistically higher than the mean of the Black Ranch Hands ($p=0.022$). The adjusted means were also not significantly different when estimated without the group-by-race interaction in the model.

There was no evidence that the mean urine specific gravity was different between the Ranch Hands and Comparisons in either the unadjusted or adjusted analysis.

The exposure index analyses showed very little evidence of a dose-response relationship at the 1987 followup examination. No pattern in the relationship of abnormality rates or mean levels was seen within occupational cohort.

The longitudinal analysis was based solely upon the contrast of blood urea nitrogen levels between the 1982 and 1987 examinations. The unadjusted mean levels increased slightly from 1982 to 1987, but the change between the Ranch Hands and Comparisons over time was not significantly different.

In conclusion, none of the six variables of the renal assessment showed a significant difference based on the unadjusted analyses. For three of the variables, the adjusted results supported the findings of the unadjusted analyses; there were significant group-by-covariate interactions for the other variables. Further examination by strata revealed that in one case the Ranch Hand prevalence rate was higher than the Comparison rate and that the opposite relationship existed for another case. In the third instance, the Comparison mean was higher than the mean of the Ranch Hands; however, both means were within the normal range. The adjusted analyses without the group-by-covariate interactions supported the findings of the unadjusted analyses; the renal status of the Ranch Hands and Comparisons was generally similar.

ENDOCRINE ASSESSMENT

INTRODUCTION

The human endocrine system is not considered to be a major target of chlorophenol or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. This is not so in animals, however. A wide range of endocrine abnormalities in many species has been induced experimentally by TCDD and includes hypoglycemia, hypothyroxinemia, reduced progesterone levels, and increased testosterone levels, the latter presumably reflecting decreased liver catabolism due to parenchymal liver damage or an inhibition of the cytochrome P-450 system.

DISCUSSION

The historical and laboratory data collected in the endocrine assessment provide a valid reflection of thyroid, gonadal, and pancreatic functions by indices that are well established in clinical practice.

As would be expected, comparison of the current historical data with those of the 1985 followup revealed an increase over time in the incidence of thyroid disease, with similar trends in both the Ranch Hand (n=55 in 1985 vs. n=93 in 1987) and Comparison (n=78 in 1985 vs. n=113 in 1987) groups.

An increase in the presence of thyroid nodules as a result of advancing age is well documented in autopsy and ultrasound studies. However, a decrease was detected in thyroid abnormalities in the 1987 followup (n=592 abnormal) versus the 1985 followup (n=773 abnormal). Prior to the 1987 examination, an attempt was made to reduce interobserver variability among the examining physicians by employing more uniform techniques of palpation and by defining more objective endpoints for palpable abnormalities. Comparison of the data revealed virtually identical trends in both the Ranch Hands (342 abnormal in 1985 vs. 258 abnormal in 1987; 34% vs. 26% incidence) and Comparisons (431 abnormal in 1985 vs. 334 abnormal in 1987; 33% vs. 26% incidence).

Though not reported in the endocrine assessment, several additional physical findings beyond simple palpation are recognized as relevant to the clinical evaluation of thyroid and gonadal function. Body habitus, ocular and integumentary signs, and deep tendon reflexes are among the variables that were included in the general health, neurological, and dermatologic examinations, and are reported in those sections respectively.

Of the two laboratory variables used, the triiodothyronine (T_3) uptake, though far less sensitive than the serum thyroid stimulating hormone (TSH), assumes importance as the only index common to all three physical examination cycles. In the current study, as in the Baseline and 1985 followup, no significant differences were detected between the Ranch Hand and Comparison groups. Further, the few covariate associations defined fail to document any consistent clinical trends over time.

In lacking a lower limit of normal, the radioimmunoassay (RIA) technique of serum TSH determination is not sensitive to hyperthyroid states. Nonetheless, the current 1987 followup data can be validly compared with those from

the 1985 followup, which exhibited significant differences between Ranch Hands and Comparisons for both the unadjusted and adjusted analyses. For the 1987 followup, the Ranch Hand group was found to have TSH levels that were marginally higher than the TSH levels of the Comparisons in both the unadjusted and adjusted analyses (unadjusted: 1.01 2IU/ml vs. 0.97 2IU/ml; adjusted: 0.96 2IU/ml vs. 0.93 2IU/ml).

With respect to gonadal function, no significant group differences were found, and two established clinical correlations were confirmed. With advancing age, a gradual decline in serum testosterone levels would be expected and was evident only in those participants born in or before 1922.

The correlation between testosterone levels and obesity is less well defined. While extremes of obesity (i.e., in excess of 100% of ideal body weight) are usually associated with gonadal suppression, no consistent relationship has been defined between serum testosterone and percent body fat. Further, the apparent differences in serum testosterone levels may in fact reflect changes in sex hormone binding globulin rather than the biologically active-free fraction. Finally, the finding of slightly lower testosterone levels in Type B individuals is of doubtful clinical significance but consistent with the increased frequency of endomorphic body habitus in this personality type. The earlier examinations in this series found that the Ranch Hands had higher levels of testosterone than did the Comparisons, a difference that is no longer evident.

An expected incidence of overt diabetes mellitus and of glucose intolerance was documented in the current study with no significant group differences defined. In ambulatory medicine, the 2-hour postprandial blood sugar has replaced the traditional glucose tolerance test as a screen for diabetes. Consistent with the insulin resistance that occurs in Type II diabetes, strong covariate associations were defined relating glucose intolerance to age and percent body fat. Independent of weight, a 10-15 percent incidence of glucose intolerance will occur by age 70. For each decade over age 40, there is an increase in the 2-hour postprandial blood sugar of 10-15 mg percent, and an average increase of 5.0 mg percent per decade in the fasting blood sugar.

The results of the endocrine assessment confirmed numerous associations that would be expected in clinical practice, and no significant or clinically relevant group differences were found.

SUMMARY

Table 13 summarizes the results of Ranch Hand and Comparison group contrasts for the 10 variables examined in 1987 to assess the endocrine system.

Two variables were constructed from the review-of-systems questionnaire and the health interval questionnaire to determine the thyroid status for each participant. No significant group difference was noted for both the self-administered response to current thyroid function and the interviewer-administered response to history of thyroid disease.

TABLE 13

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Endocrine Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
<u>Questionnaire</u>					
Current Thyroid Function (Self- Administered)	NS	--	--	--	
History of Thyroid Disease (Interviewer Administered)	NS	--	--	--	
<u>Physical Examination</u>					
Thyroid Gland	NS	--	--	--	
Testes	NS	--	--	--	
<u>Laboratory</u>					
T ₃ % Uptake	NS	NS	NS	NS	
TSH	NS	NS*	NS	NS*	RH>C
FSH	NS	NS	NS	NS	
Testosterone	NS	NS	****	NS	
2-Hour Postprandial Glucose	NS	NS	NS	NS	
Composite Diabetes Indicator	NS	--	** (NS)	--	

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

--Analysis not performed or not applicable.

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

RH>C: Higher prevalence rate or mean in Ranch Hands than in Comparisons.

****: Group-by-covariate interaction ($p \leq 0.01$).

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table 0-2 in the main report for a detailed description of this interaction.

The thyroid gland and the testes were evaluated at the physical examination. The percentage of abnormalities did not differ significantly between groups for either organ.

Six laboratory examination variables were analyzed to assess current endocrine function: T_3 uptake, TSH, follicle stimulating hormone (FSH), testosterone, 2-hour postprandial glucose, and a composite diabetes indicator. Each variable was analyzed in continuous and discrete forms, except for the composite diabetes indicator, which was only analyzed discretely.

No significant unadjusted group differences were found for any of these variables. However, the Ranch Hand TSH mean was marginally significantly higher than the Comparison mean ($p=0.099$). A statistically significant TSH difference was noted in the 1985 followup. The only change in findings after adjustment for significant covariates was due to the presence of four group-by-covariate interactions for testosterone discretized. Initial stratification by occupation revealed no significant group differences for the officer and enlisted flyer cohorts. Further stratification by personality type and age for the enlisted groundcrew cohort detected no significant strata, but results from this analysis were limited due to sparse data in many cells (in several strata the abnormally low testosterone values were either all Ranch Hands or all Comparisons). Although no significant group differences were found for the laboratory test variables, the direction of the unadjusted results showed that Ranch Hands consistently had more abnormalities than Comparisons. These trends are discussed in the interpretive considerations section.

Results from the exposure index analyses generally did not support a herbicide effect. For T_3 uptake, TSH, FSH, and 2-hour postprandial glucose, there were no statistically significant findings. Unadjusted testosterone means differed significantly for the officer cohort, exhibiting a pattern consistent with a decreasing dose-response relationship; after covariate adjustment, this difference became nonsignificant. Adjusted results were significant for the enlisted flyer cohort, but did not indicate a dose-response effect since the highest levels were found in the medium exposed group. Testosterone results for the enlisted groundcrew were not significant. The enlisted groundcrew and officer cohorts showed increasing dose-response patterns for diabetes, but the association was not significant. In contrast, a significant result ($p=0.010$) was found for the enlisted flyer cohort but was due to most diabetics falling in the medium exposure category.

Longitudinal analyses for T_3 uptake, TSH, and testosterone showed no significant group differences from the Baseline to the 1987 followup examination.

In conclusion, statistical analysis of the 10 endocrinologic variables did not reveal any significant group differences. The Ranch Hand TSH mean was marginally significantly higher than the Comparison mean; at the 1985 examination, a significant difference was found. Means for the other variables were very similar between groups. For all laboratory examination variables, the percentage of abnormalities was higher for the Ranch Hand group than for the Comparison group, but not statistically significant. The significant differences in testosterone and 2-hour postprandial glucose found in the 1985 examination were no longer evident.

IMMUNOLOGIC EVALUATION

INTRODUCTION

Overt damage to organs of the immune system and depressed immunologic function have been noted in a variety of animals exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). As the fields of immunology and immunotoxicology have grown within the past 10 years, a significant spectrum of subtle immunotoxic effects has also been described in animals, but for many possible reasons, comparable adverse effects have not been consistently recorded in exposed human individuals or cohorts.

Thus, an intensive search is under way to ascertain the effects of TCDD on the human immune system, particularly with respect to the development of cancer. Most ongoing dioxin morbidity studies in the United States have incorporated comprehensive laboratory assessments of the immune system.

DISCUSSION

Immunologic competence was assessed by analysis of data from cell surface marker studies, immunoglobulin quantitation, functional stimulation assays, and skin tests for delayed hypersensitivity response on a randomized subset of the study population. The tuberculin skin test is the prototype test for DCH. This test has been used throughout the 20th century as the traditional method of diagnosing infection with Mycobacterium tuberculosis in individual patients, contacts of diseased individuals, occupational groups, and epidemiologic studies of populations.

The absence of a response to a series of skin test antigens is usually indicative of an impaired immune defense mechanism (anergy). Anergy can occur in elderly individuals in the setting of certain viral, bacterial, and fungal infections; or with advanced protein deficiency, underlying malignancy, or treatment with corticosteroids and other immunosuppressive agents. Skin tests for DCH are occasionally used to test for anergy as a prognostic indicator in individuals in compromised states such as the acquired immunodeficiency syndrome or those at risk of infection following surgery.

Skin tests for DCH are subject to numerous variables including the dose and method of administration of the antigen and the techniques employed in reading and interpreting the response. Following quality control concerns over the 1985 skin test data, stringent protocols were established to ensure consistent methods and interpretation. In the current study, a premium was placed on uniform and consistent methods and interpretation. There was a 92 percent concordance between readers and duplicate interpretations by the same reader. More than 99.6 percent of the sample population had interpretable skin tests. The 94.9 percent incidence of intact DCH is consistent with clinical experience in the general population. Analysis of the data suggested interactive effects of cigarette and alcohol use. Clarification of the observed group difference in the composite skin test diagnosis must await the analysis of the quantitative serum dioxin results.

Cell surface marker studies for CD2 (total T cell), CD4 (helper T cell), CD8 (suppressor T cell), CD25 (activated T cells), CD20 (total B cell), CD14 (monocytes), and HLA-DR positive cell populations were analyzed. The CD4/CD8 ratio was calculated and also analyzed. Both the unadjusted and adjusted analyses of the various cell surface markers measured did not indicate significant group differences between Ranch Hands and Comparisons. Significant covariate associations with age were found for CD2, CD4, CD8, CD20, and HLA-DR cells. These variables consistently decreased with increasing age, which is consistent with established clinical findings. Statistically significant race and alcohol associations were found for CD20 and CD14. Overall, cell surface marker counts increased with cigarette smoking. The clinical significance of these findings is unknown.

Functional stimulation assay data analyzed include the unstimulated and stimulated responses for both the PHA and MLC assays. No significant unadjusted or adjusted group differences between Ranch Hands and Comparisons were found for either the PHA or MLC assays. Both PHA and MLC responses appeared to decrease with age. Race appeared to affect PHA response, but biologic significance was difficult to evaluate given the lack of established clinical endpoints associated with these differences and the lack of a consensus as to what the normal range is for these assays. Implications of mild to moderate increases and decreases are not known. The ability to respond to a challenge with increased cell counts and functional reactions is desirable but a hyperactive response may not be desirable since it might indicate a constantly challenged immune system.

Other functional stimulation assay data evaluated included the net responses for the natural killer cell assays (with and without the addition of Interleukin 2 as a response stimulator). Unadjusted analyses for both natural killer cell assays revealed no significant Ranch Hand and Comparison differences; however, there was a significant group-by-race interaction for both assays. When analyzing the data within each racial grouping, there was a statistically significant difference between Black Ranch Hands and Black Comparisons.

The adjusted group contrast analysis for the four natural killer cell variables and the MLC net response variable each contained group-by-race interactions. The clinical significance of these findings is not apparent.

The exposure index analyses failed to reveal any consistent trends in the many variables analyzed. For the adjusted analyses, many exposure index-by-covariate interactions were found. These interactions primarily involved the covariates of cigarette smoking, age, and alcohol use. Final interpretation of these data must await the results of the serum TCDD assays and the development of interpretive criteria for these immunologic assays.

As seen in the 1985 followup, there were no significant group differences for either the unadjusted or adjusted analyses of any of the laboratory immunologic variables examined. Consistently decreasing values for the cell surface markers and functional stimulation assays were associated with increasing age, while increases in lifetime smoking were usually associated with increases in the values of those variables. Longitudinal analysis of the CD4/CD8 ratio results did not reveal a significant group difference over time.

The immunologic assessment of laboratory data revealed no statistically significant differences between the Ranch Hand and Comparison populations. Covariate associations with age and lifetime smoking were noted in the adjusted analyses of these immunologic tests. The finding of a group difference in the proportion of participants possibly abnormal on the composite skin test diagnosis is of interest and will be reevaluated in the context of quantitative serum dioxin levels. Overall, there appears to be no indication of impaired immunologic competence in the Ranch Hand group versus the Comparison group over time.

SUMMARY

For the 1987 followup immunologic assessment, a number of unadjusted and adjusted analyses were performed using physical examination (composite skin test diagnosis) and laboratory examination data (cell surface marker studies, TLC, quantitative immunoglobulin measurements, and functional stimulation tests). The results of the Ranch Hand and Comparison group contrasts performed using the physical examination and laboratory examination data are summarized in Table 14.

For the composite skin test diagnosis, the unadjusted group contrast of the relative frequency of participants with possibly abnormal composite readings was significantly greater ($p=0.019$) for the Ranch Hands than the Comparisons. The adjusted model for the composite skin test results contained a significant group-by-lifetime cigarette smoking history interaction. Because of this interaction, the skin test results were analyzed for group differences through stratification of lifetime cigarette smoking history. Ranch Hands who smoked for over 10 pack-years had a significantly greater frequency of individuals with possibly abnormal skin test results than Comparisons with the same lifetime cigarette smoking history ($p=0.005$). Without the cited interaction, a significant adjusted group difference ($p=0.011$) remained.

For the cell surface marker studies of the 1987 followup, there were no significant group differences for either the unadjusted or the adjusted analyses. Except for CD25, the same cell surface marker variables were analyzed in both the 1985 and the 1987 followup studies. The 1985 followup unadjusted analyses for group differences were not significant. The 1985 followup adjusted analyses were not significant for CD4, CD8, and the CD4/CD8 ratio; the remaining 1985 followup cell surface marker variables had significant group-by-covariate interactions in the adjusted models.

Unadjusted and adjusted group contrasts were not significant for TLC.

For each of the quantitative immunoglobulins (IgG, IgA, and IgM), the unadjusted and adjusted group contrasts were not significant.

For the functional stimulation tests of the 1987 followup study, unadjusted and adjusted analyses were performed on a number of measures pertaining to responses after mitogen stimulation with phytohemagglutinin (PHA), mixed lymphocyte culture (MLC) responses to stimulation from donor lymphocytes, and natural killer cell assay (NKCA) and natural killer cell assay with Interleukin 2 (NKCI).

TABLE 14.

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

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<u>Physical Examination</u>				
Composite Skin Test Diagnosis	D	0.019	** (0.011)	RH>C
<u>Laboratory Examination: Quantitative Studies</u>				
CD2 Cells	C	NS	NS	
CD4 Cells	C	NS	NS	
CD8 Cells	C	NS	NS	
CD20 Cells	C	NS	NS	
CD14 Cells	C	NS	NS	
CD25 Cells	D	NS	--	
	C	NS	NS	
HLA-DR Cells	C	NS	NS	
CD4/CD8 Ratio	C	NS	NS	
TLC	C	NS	NS	
IgG	C	NS	NS	
IgA	C	NS	NS	
IgM	C	NS	NS	
<u>Laboratory Examination: Functional Stimulation Tests</u>				
Unstimulated PHA Response	C	NS	NS	
PHA Net Response: Day 1				
Concentration 1	C	NS	** (NS)	
Concentration 2	C	NS	NS	
Concentration 3	C	NS	NS	
PHA Net Response: Day 2				
Concentration 1	C	NS	NS	
Concentration 2	C	NS	NS	
Concentration 3	C	NS	NS	
Overall PHA Net Response	C	NS	NS	
Maximum PHA Net Response	C	NS	NS	
Unstimulated MLC Response	C	NS	NS	
MLC Net Response	C	NS	** (NS)	
NKCA 50/1 Net Response	C	NS	** (NS)	
NKCA 50/1 Percent Release	C	NS	** (NS)	
NKCI 50/1 Net Response	C	NS	****	
NKCI 50/1 Percent Release	C	NS	****	

TABLE 14. (continued)

Overall Summary Results of Unadjusted and
Adjusted Analyses of Immunologic Variables

D: Discrete analysis performed.

** (0.011): Group-by-covariate interaction ($0.01 < p < 0.05$); significant ($p=0.011$) when interaction is deleted.

RH>C: More abnormalities in Ranch Hands than in Comparisons.

C: Continuous analysis performed.

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

--Analysis not done.

** (NS): Group-by-covariate interaction ($0.01 < p < 0.05$); not significant when interaction is deleted; refer to Table P-3 in the main report for a detailed description of this interaction.

****: Group-by-covariate interaction ($p \leq 0.01$); refer to Table P-3 in the main report for a detailed description of this interaction.

For the PHA responses, the group contrasts were performed for each of the following: unstimulated PHA responses for 2 harvest days concurrently; net responses to PHA at each of three concentrations on two different days; all PHA net responses concurrently for the six concentration and day combinations; and the maximum of the six PHA net responses.

For the 1987 followup, as in 1985, the unadjusted and adjusted group contrasts of the unstimulated PHA responses were not significant.

For the PHA net response for day 1, the unadjusted group contrast at each of the three concentration levels was not significant. The adjusted group contrasts of the PHA net response for day 1 at concentration levels 2 and 3 were also not significant. However, the adjusted analysis of the PHA net response for day 1 at concentration level 1 had a significant group-by-current alcohol use interaction. For participants having over four drinks per day, Comparisons had a significantly greater net response to PHA for day 1 at concentration level 1 than Ranch Hands ($p=0.024$). For the PHA net response for day 2 at each of three concentration levels, the unadjusted and adjusted group contrasts were not significant. For the 1985 followup data, both the unadjusted and the adjusted group contrasts of the PHA net response did not exhibit significant group differences.

The unadjusted and adjusted simultaneous contrast of the six PHA net responses was not significant. The unadjusted and adjusted analyses of the maximum PHA net responses were not significant for the Ranch Hand versus Comparison group contrasts.

For the unstimulated MLC response, both the unadjusted and the adjusted group contrasts were not significant. For the MLC net response, the unadjusted group contrast was not significant and the adjusted analysis had a significant group-by-race interaction. Because of this interaction, group contrasts were performed within race strata. Among Blacks, the Ranch Hands

had a marginally significantly lower average MLC net response than the Comparisons ($p=0.059$). An interaction with smoking history was seen in 1985.

For the NKCA and NKCI, 50/1 net responses and 50/1 percent releases were analyzed. In the Ranch Hand and Comparison group contrasts, the unadjusted analyses were not significant. For each of the adjusted analyses of the NKCA and NKCI variables, there was a significant group-by-race interaction. Because of these interactions, the NKCA 50/1 net responses and the 50/1 percent releases were analyzed within race strata. Black Ranch Hands had a borderline significantly greater average net response than Black Comparisons ($p=0.065$), and Black Ranch Hands had a significantly higher average percent release than their Comparisons ($p=0.031$). Deleting these interactions yielded nonsignificant group contrasts. For the NKCI assay, the group contrasts were also examined by race because of the significant group-by-race interaction. Black Ranch Hands had a significantly greater mean net response for NKCI than did the Black Comparisons ($p=0.007$). Black Ranch Hands had a significantly greater average percent release of NKCI than Black Comparisons ($p=0.008$), and nonblack Ranch Hands had a marginally significant lower average than nonblack Comparisons ($p=0.069$).

The unadjusted exposure index analysis of the composite skin test diagnosis was not significant for the enlisted flyers and for the enlisted groundcrew, and it was borderline significant ($p=0.090$) for the officers. For the adjusted exposure index analysis, officers had a significant exposure index-by-lifetime cigarette smoking history interaction and a significant exposure index-by-current alcohol use interaction. For enlisted flyers, there was a significant exposure index-by-lifetime alcohol history interaction. For enlisted groundcrew, there was a significant exposure index-by-lifetime alcohol history interaction and a significant exposure index-by-current alcohol use interaction.

For the exposure index analysis of the cell surface marker measures, the unadjusted analysis generally showed no significant difference for each occupation. For the adjusted exposure index analyses of an individual cell surface marker variable, an exposure index-by-covariate interaction was generally found for at least one occupation. For the most part, the interactions involved the covariates of age, lifetime cigarette smoking history, current alcohol use, or lifetime alcohol history.

The unadjusted and adjusted exposure index analyses of TLC were not significant for officers and enlisted flyers. For the enlisted groundcrew, the unadjusted exposure index analysis was not significant, and the adjusted analysis contained a significant exposure index-by-lifetime cigarette smoking history interaction.

In general, the unadjusted exposure index analyses of the immunoglobulins were not significant for each occupation. For officers, the adjusted exposure index analysis of IgG was significant ($p=0.032$). For enlisted groundcrew, there was a significant exposure index-by-lifetime cigarette smoking history interaction for IgG. For officers and enlisted groundcrew, the adjusted exposure index analyses of IgA had significant exposure index-by-current cigarette smoking and exposure index-by-lifetime alcohol history interactions, respectively. The adjusted exposure index analyses of IgM were not significant.

For the exposure index analysis of the unstimulated PHA responses, the unadjusted and adjusted analyses for officers and for enlisted flyers were not significant. For enlisted groundcrew, the unadjusted exposure index analysis was not significant and the adjusted analysis contained significant interactions between the exposure index and both alcohol use covariates. For the PHA net responses for day 1 at each of three different concentration levels, the unadjusted and adjusted exposure index analyses were generally not significant for the three occupations. The exceptions occurred for enlisted flyers at concentration level 2 on the adjusted analysis ($p=0.053$), and for enlisted flyers at concentration level 3 on the unadjusted and the adjusted analyses ($p=0.067$ and $p=0.056$, respectively). For the PHA net responses for day 2 at each of three concentration levels, the unadjusted analyses were not significant for the three occupations. For the adjusted exposure index analyses of the PHA net responses for day 2, a significant exposure index-by-age interaction was found for the enlisted groundcrew at concentration level 1 and a significant exposure index-by-current cigarette smoking interaction was found for the officers at concentration level 3. For the simultaneous analysis of the six PHA net responses, neither the unadjusted nor the adjusted analysis was significant for each occupation. Similarly, neither the unadjusted nor the adjusted exposure index analysis of the maximum PHA net response was significant for each occupation.

The unadjusted exposure index analyses of the unstimulated MLC responses were not significant for each occupation. For the adjusted exposure index analysis of the unstimulated MLC responses, the enlisted flyers had a significant exposure index-by-age interaction, and the officers and the enlisted groundcrew displayed no significant difference for exposure index. For the MLC net responses, both the unadjusted and the adjusted exposure index analyses were not significant for each occupation.

The unadjusted exposure index analyses of the NKCA and NKCI net responses and percent releases were not significant for each occupation. For the exposure index adjusted analysis of the NKCA net response, the enlisted flyers had a significant exposure index-by-lifetime cigarette smoking history interaction. For the exposure index adjusted analyses of the NKCA and the NKCI percent release, the enlisted groundcrew had significant exposure index-by-age interactions. Overall, the exploration of covariate interactions in the exposure index analyses detected scattered increases and decreases in cell count and functional assays that are impossible to interpret in the absence of a consensus as to what is abnormal for these measures of immunity.

The longitudinal analysis of the CD4/CD8 ratio results for the 1985 and 1987 followup examinations did not exhibit a significant group difference over time.

The immunologic assessment of laboratory data revealed no statistically significant differences between the Ranch Hands and Comparisons. The finding of a group difference in the proportion of participants possibly abnormal on the composite skin test diagnosis is of interest and will be reevaluated in the context of the quantitative serum dioxin levels. Overall, there appears to be no indication of clinically relevant impaired immunologic competence in the Ranch Hand group versus the Comparison group over time.

PULMONARY DISEASE

INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

Acute exposure to chlorophenols, phenoxy herbicides, and TCDD have caused the traditional acute symptoms of cough, nasal/lung irritation, shortness of breath, and, occasionally, bronchitis. These symptoms have been noted almost exclusively in industrial workers and not in individuals experiencing casual contact. Long-term sequelae arising from the acute symptom stage in ill individuals have not been generally known because of minimal followup and surveillance of the pulmonary symptoms.

Further, due to the profound effect of smoking on pulmonary function, great emphasis must be placed on the collection of highly accurate, detailed, and validated smoking data as an adjustment variable.

DISCUSSION

While the presence of pulmonary disease is often evident based on a careful history and physical examination, definitive diagnosis usually requires the collection of data from a number of other sources. The standard radiographic examination of the chest and pulmonary function studies are routinely ordered and were included as variables in the Air Force Health Study examination. In addition, because the lung is often involved secondarily in numerous infectious, inflammatory, and neoplastic disorders, the assessment of pulmonary disease should include the type of comprehensive multisystem review conducted in this examination cycle and reported in other sections.

Historical information on the occurrence of pulmonary disease must be interpreted with caution in the absence of medical record verification. Many of the cardinal symptoms of lung disease, including dyspnea, chest pain, and exercise intolerance, are common to cardiovascular disease as well (particularly ischemic heart disease) and are frequently misinterpreted as to cause. Wheezing, assumed by the patient to be indicative of asthma, may in fact be reflective of hemodynamic compromise in congestive heart failure. A positive purified protein derivative skin test, indicative of subclinical tuberculous infection, may be erroneously interpreted and reported as prior active infection. "Pneumonia" and "pneumonitis" are often confused by patients in relating the medical history.

The physical examination variables studied can provide valuable clues to the presence of pulmonary disease. In lacking specificity, however, these data are often of limited utility in confirming a specific diagnosis. Wheezes and hyperresonance, for example, will occur in obstructive airway disease in

asthma or in emphysema secondary to cigarette use. Dullness to percussion, a finding common to many disorders, will occur in consolidation from atelectasis, infections, pleural thickening, or pleural effusion.

In view of the limitations of the history and physical examination noted above, added emphasis is placed on screening laboratory data in the diagnosis of respiratory disease. The chest x ray, when normal, is highly reliable in excluding pulmonary parenchymal disease, though several exceptions must be recognized. Solitary lesions less than 6 millimeters, miliary granulomatous infection, and early interstitial disease, among others, may be present but not detectable radiographically. On the other hand, the chest x ray may reveal an early occult malignancy in an asymptomatic patient and thus afford an opportunity for cure.

Spirometry has been used as a clinical tool to measure static lung volumes and to detect respiratory disease for over a century. Dynamic indices, relating changes in lung volume to time, were first developed over 50 years ago and, with computerization, have been refined to a high degree of accuracy and reproducibility. To be valid, spirometry requires that particular attention be paid to technician training and, with proper coaching, to eliciting the full cooperation of the patient. In any longitudinal study emphasis must be placed on the use of identical techniques to ensure comparability of data.

In broad terms, the spirometric indices evaluated in this chapter are designed to measure lung volume (vital capacity) and respiratory air flow (FEF). Static lung volume is principally determined by height and is independent of weight, while dynamic volume measurements depend in part on physical strength. Accordingly, all indices require correction for age and gender. Further, as confirmed in the present study, normal values for whites cannot be applied to other ethnic groups.

In clinical practice, respiratory disease can be divided into two broad categories. "Restrictive" disease is characterized by reduced vital capacity as seen in interstitial fibrosis or reduced lung volume after surgical resection. In "obstructive" airways disease, usually emphysema associated with cigarette use, there is abnormal prolongation of the flow-dependent indices [forced expiratory volume in one second (FEV1), forced expiratory volume in two seconds (FEV2), forced expiratory volume in three seconds (FEV3), and maximum forced expiratory flow (FEFmax)].

With few exceptions, the dependent variable-covariate associations found in the statistical analyses, confirm observations that are well established in clinical practice. With advancing age, an increased incidence of respiratory disease would be expected and was confirmed by history, on physical examination, and in the laboratory. The age-related decline in vital capacity is considered "physiologic" over time and will occur independent of acquired pulmonary disease.

The cause of the increased incidence of bronchitis and pneumonia in non-blacks is uncertain and cannot be explained on the basis of any previously established genetic or ethnic susceptibility. Differential access and use of medical care may play a role. In contrast, Blacks were found to be at detriment by all spirometric indices.

In the exposure index analyses, the ratio of FEV1 to forced vital capacity (FVC) revealed similar trends in the enlisted flyer and enlisted groundcrew cohorts. Although the data may reflect some herbicide-related health detriment, two confounding variables must be taken into consideration. As an index reflective of obstructive airways disease, the FEV1 will diminish with increased cigarette smoking over time. Secondly, as an effort-dependent index, the FVC is subject to performance bias and requires a fully compliant participant in order to be valid. Even in those studies considered technically adequate, the self-perception of prior herbicide exposure could introduce subtle bias sufficient to affect the results. It will be important to reexamine the FEV1/FVC ratio data when the body burden of herbicide can be defined more objectively by serum levels.

As expected, current and lifetime cigarette use were associated with significant abnormalities in all variables examined. Enlisted participants, with greater lifetime and current cigarette exposure, were at detriment relative to officers.

Finally, though limited to a single variable, the longitudinal analysis revealed no significant difference in the Ranch Hands versus the Comparisons. These observations will be greatly strengthened by longitudinal analysis of the spirometric variables in future examination cycles.

Data collected in the pulmonary assessment provide a valid reflection of lung function in the population under study. There was a similar incidence of respiratory disease and similar respiratory function in the Ranch Hand and Comparison groups.

SUMMARY

The 1987 pulmonary assessment was based on five questionnaire variables, seven variables from the physical examination, and eight laboratory variables. The results of the Ranch Hand and Comparison contrasts are summarized in Table 15.

The five questionnaire variables were based on self-reported data for the occurrence of the following conditions: asthma, bronchitis, pleurisy, pneumonia, and tuberculosis. There were no differences identified between the Ranch Hands and the Comparisons based on the unadjusted analyses. The results of the adjusted analyses supported this finding for asthma, bronchitis, and pleurisy. Due to the low number of participants reporting tuberculosis, no adjusted analysis was conducted. In the adjusted analysis of pneumonia, there was a significant interaction between group and lifetime cigarette smoking history ($p=0.004$). Stratifying by the covariate showed that a significantly higher percentage of Comparisons in the heavy cigarette smoking category reported pneumonia than heavy smoking Ranch Hands ($p=0.005$).

TABLE 15.

**Overall Summary Results of Unadjusted and Adjusted
Group Contrast Analyses of Pulmonary Variables**

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<u>Questionnaire</u>				
Asthma	D	NS	NS	
Bronchitis	D	NS	NS	
Pleurisy	D	NS	NS	
Pneumonia	D	NS	****	
Tuberculosis	D	NS	--	
<u>Physical Examination</u>				
Thorax and Lung Abnormalities	D	0.020	NS*	RH>C
Asymmetric Expansion	D	NS	--	
Hyperresonance	D	NS*	** (NS)	RH>C
Dullness	D	NS	--	
Wheezes	D	NS	NS	
Rales	D	NS	NS	
X-Ray Interpretation	D	NS	** (NS)	
<u>Laboratory</u>				
FVC	C	NS	NS	
FEV ₁	C	NS	** (NS)	
FEV ₂	C	NS	** (NS)	
FEV ₃	C	NS	NS	
FEFmax	C	NS	NS	
Ratio of Observed FEV ₁ to Observed FVC	C	NS	NS	
Loss of Vital Capacity	D	NS	NS	
Obstructive Abnormality	D	NS	NS	

D: Discrete analysis performed.

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

****: Group-by-covariate interaction ($p \leq 0.01$); refer to Table Q-2 in the main report for a detailed description of this interaction.

--: Analysis not done.

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

RH>C: Higher prevalence rate in Ranch Hands than in Comparisons.

** (NS): Group-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Table Q-2 in the main report for a detailed description of this interaction.

C: Continuous analysis performed.

The physical examination variables of the pulmonary assessment were: thorax and lung abnormalities, asymmetric expansion, hyperresonance, dullness, wheezes, rales, and x-ray interpretation. The Ranch Hands had significantly more thorax and lung abnormalities than the Comparisons based on the unadjusted analysis ($p=0.020$). After adjusting for age, occupation, current cigarette smoking, and lifetime cigarette smoking history, the difference was borderline significant ($p=0.072$).

There was only one participant--a Comparison--with asymmetric expansion. No significant difference was detected in the unadjusted analysis, and due to the low number of participants with this condition, no adjusted analysis was conducted.

The unadjusted analysis of hyperresonance showed a borderline difference between the two groups with a higher prevalence rate among the Ranch Hands ($p=0.100$). In the adjusted analysis, there was a significant group-by-occupation interaction ($p=0.017$). Stratifying by occupation revealed that the Ranch Hand enlisted flyers had a significantly higher rate of hyperresonance than the Comparison enlisted flyers ($p=0.006$). Without the group-by-occupation interaction in the model, no difference between the two groups was detected.

There was a total of three participants diagnosed with dullness of the lungs: two Ranch Hands and one Comparison. No difference was found in the unadjusted analysis. Due to the low prevalence rate of dullness, no adjusted analysis was performed.

Neither the unadjusted nor adjusted analyses for wheezes and rales detected a difference between the Ranch Hands and the Comparisons.

No significant difference between the two groups was identified based on the unadjusted analysis of x-ray abnormalities. In the adjusted analysis, there was a significant group-by-race interaction ($p=0.023$). Exploring the interaction by stratifying on race showed a borderline significant difference between the Black Ranch Hands and the Black Comparisons, with the Ranch Hands having more x-ray abnormalities ($p=0.068$). Without the interaction in the model, no significant difference was found.

The eight laboratory variables of the pulmonary assessment were: FVC, FEV1, FEV2, FEV3, FEFmax, ratio of observed FEV1 to observed FVC, loss of vital capacity, and obstructive abnormality. For six of the eight variables, no significant difference was detected between the Ranch Hands and the Comparisons in both the unadjusted and adjusted analyses. These six variables were: FVC, FEV3, FEFmax, ratio of observed FEV1 to observed FVC, loss of vital capacity, and obstructive abnormality.

No significant difference was identified in the unadjusted analysis of FEV1. This result was supported by the adjusted analysis without the significant group-by-age interaction ($p=0.037$). When the interaction was explored, the Ranch Hands born between 1923 and 1941 were found to have a significantly lower adjusted mean than the Comparisons in the same age category ($p=0.022$). However, the Ranch Hands who were born in or before 1922 had a marginally higher adjusted mean than the Comparisons in that category ($p=0.081$).

The results of the analyses of FEV2 were similar to the results of FEV1. No difference between the two groups was detected based on the unadjusted analysis. In the adjusted analysis, there was a significant interaction between group and age ($p=0.042$). Of the participants born between 1923 and 1941, the Ranch Hands had a significantly lower adjusted mean FEV2 than the Comparisons ($p=0.017$). Among the participants who were born in or before 1922, a borderline significant group difference was found with the adjusted mean of the Comparisons being lower than the adjusted mean of the Ranch Hands ($p=0.070$).

Although the results were primarily not significant or borderline significant, the relative risk was greater than 1 or the mean of the Ranch Hands was less favorable than the mean of the Comparisons in 17 of the 20 unadjusted analyses. In general, this pattern was repeated in the adjusted analyses, where the models were adjusted for the effects of cigarette smoking; again, however, the results were primarily not significant. Trends such as these are discussed in the section on interpretive considerations.

Longitudinal analyses showed no changes over time between groups for the ratio of observed FEV1 to observed FVC. The exposure index analyses detected significant results suggestive of a dose-response relationship infrequently, and no pattern in the results emerged. Exposure index-by-covariate interactions observed were primarily with the two smoking covariates.

In conclusion, 14 variables demonstrated nonsignificant results in both unadjusted and adjusted Ranch Hand versus Comparison group contrasts. Two variables exhibited a significant or borderline significant result affecting the Ranch Hands in either the unadjusted or adjusted analyses. The Ranch Hands had more thorax and lung abnormalities than the Comparisons based on the unadjusted analysis; after adjustment for age and current cigarette smoking, the difference was borderline significant. A borderline significant difference in hyperresonance was found in the unadjusted analysis, and a group-by-occupation interaction was present in the adjusted analysis. Four additional variables were nonsignificant in unadjusted analyses with a group-by-covariate interaction present in the adjusted analyses. Of the five interactions, two variables showed a significant detriment to the Ranch Hands, one a significant detriment to the Comparisons, and two variables demonstrated mixed results; that is, significant or borderline significant results were present for both Ranch Hands and Comparisons, depending on which covariate stratum was examined. Without the group-by-covariate interactions in the final model, no significant effects due to group were seen. Although the pulmonary health of the two groups was reasonably comparable, assessment of the pulmonary function should be included in the future examinations.

INTERPRETIVE CONSIDERATIONS

INTRODUCTION

Careful consideration of bias, interactions, consistency, multiple testing, dose-response patterns and the exposure index, power limitations, strength of association and biologic credibility is essential to the

interpretation of these data. Problems inherent in the evaluation of negative results and the summarization of these data should also be considered.

CONSISTENCY

Ideally, an adverse health effect in Ranch Hands attributable to herbicide or dioxin exposure would be revealed by internally and externally consistent findings. A finding would be regarded as internally consistent if it did not contradict prior information, other findings, or medical knowledge. For example, the finding of increased femoral pulse abnormalities is not consistent with the lack of increased posterior tibial pulse abnormalities in Ranch Hands. Further, the lack of interaction with occupation is not consistent with known patterns of dioxin levels in Ranch Hands. A finding would be externally consistent if it had been previously established either in theory or empirically as related to exposure. The observed excess of basal cell carcinoma in Ranch Hands is externally inconsistent since there is no prior evidence that basal cell carcinoma is related to dioxin or herbicide exposure. It is also internally inconsistent because there is no evidence that basal cell carcinoma relative risk is greater among enlisted ground personnel than the relative risk among officers.

MULTIPLE TESTING

The lack of a predefined medical endpoint has necessitated the consideration of literally hundreds of dependent variables. Each dependent variable is analyzed many different ways to accommodate covariate information and different statistical models. In the hypothetical case that Ranch Hand physical health is the same as that of the Comparisons, about 5 percent of the many statistical tests of hypotheses shown in this report should be expected to detect a group difference (produce p-values less than 0.05). The observation of significant results due to multiple testing, even when there is no group difference, is known as the multiple testing artifact and is common in large studies. Unfortunately, there is no statistical procedure available to distinguish between those statistically significant results that arise due to the multiple testing artifact and those which may be due to a bona fide herbicide effect. Instead, the authors have relied on reasoned consideration of strength of association, consistency, dose-response patterns and biologic credibility to weigh and interpret the findings.

DOSE-RESPONSE PATTERNS AND THE EXPOSURE INDEX

Ideally, a dose-response effect would be represented by an increasing trend in disease prevalence from a low rate among Ranch Hands with low exposure to a high rate among Ranch Hands with a high exposure. A dose-response effect may be expected to occur regardless of the presence or absence of a group difference.

Epidemiologic studies of health effects after environmental or occupational exposure to toxic chemicals or substances have generally relied upon indirect measures of exposure, termed exposure indices, to assess dose-response. For example, a study of respiratory cancer mortality in Montana smelter miners

exposed to airborne arsenic trioxide and sulfur dioxide used the number of years of employment as an exposure index for an individual miner. With it, a statistically significant dose-response effect was demonstrated. In the aborted Centers for Disease Control (CDC) study of health effects in US Army troops potentially exposed to Agent Orange in Vietnam, study investigators derived several exposure indices in terms of troop locations, known half-lives of dioxin in soil and on plant leaves, and the dates and spray paths of Ranch Hand aircraft. The study was canceled after their exposure indices failed to correlate with current dioxin levels in assay study subjects. In the Air Force Health Study, each Ranch Hand's dioxin exposure was metricized as the product of the gallons of herbicide sprayed during his tour and the dioxin concentration of that herbicide divided by the number of Ranch Hands in his job category during his tour. This exposure index has so far failed to reveal consistent dose-response effects and is not correlated with current dioxin body burden in Ranch Hands.

The AFHS exposure index was based on the best information available during the design phase of this study. The gallons sprayed, dioxin concentrations and personnel figures are considered accurate. The index is based on the logic that exposure should increase with increased spraying or if fewer men in an occupational category become available to do the work. Similarly, it was reasoned that exposure should decrease as spraying decreased or as more men became available to do the work. The validity of this index is limited, however, since the gallons sprayed and personnel figures are not specific to an individual Ranch Hand's assigned base in Vietnam or to his specific daily work schedule. The AFHS exposure index is probably more accurate than the indices attempted by the CDC because the Ranch Hands were much closer to the herbicide than the Army and because recorded troop locations were somewhat inaccurate. Indirect exposure indices based on work history and demographic information have demonstrated significant dose-response effects in studies of long term occupational exposure with moderate to high relative risks. Such indices have failed to demonstrate significant effects or have failed to correlate with direct measures of exposure, such as the dioxin assay, when exposures are short in duration, are of less than industrial intensity or when the relative risk is small.

Fortunately, the development of the serum dioxin assay and its application to Ranch Hands and Comparisons has obviated our concern about the calculated exposure index.

TRENDS

An assessment of consistent and meaningful trends is an essential element of the interpretation of any large study with multiple endpoints, clinical areas, and covariates. However, caution must be exercised in the interpretation of trends.

Increased abnormalities or adverse means for the Ranch Hands across medically related variables within a clinical area might indicate an exposure effect. In this case, it is important to note that there is moderate to strong correlation between endpoints. Hence, the strength of the group differences must also be considered in assessing the extent of the suspected exposure effect.

Based on preliminary results, current dioxin levels are strongly associated with occupation. Thus, strong, statistically significant differences between groups in means or percent abnormalities for different occupations (i.e., group-by-occupation interactions) would be indicative of a dose-response effect. In this situation, one would expect to see a steadily increasing relative risk or difference between means as occupational exposure increased (i.e., officers less than enlisted flyers less than enlisted ground-crew). Under these assumptions, significant interaction with occupation could be due to the absence of a true effect, or the power limitations of the statistical test for interactions.

An increasing trend in differences between groups in means or disease rates with levels of a covariate (other than occupation) could also indicate an exposure effect. For example, an increased relative risk for hepatic disease with increased levels of alcohol consumption could be due to an indirect causal relationship between exposure and hepatic disease through alcohol consumption. In assessing potential indirect causal relationships, it is important to consider the strength of the group differences and consistency of both the results with related endpoints and findings over time (i.e., 1982 Baseline, 1985 followup, 1987 followup examinations).

Based on the calculated exposure index, increasing trends in Ranch Hand disease rates with increasing levels of exposure within occupational category would be expected in the presence of an exposure effect. However, preliminary results of serum dioxin assays of the Ranch Hands indicate that the calculated exposure index is not a good measure of actual dioxin exposure. Thus, the results of the exposure index analysis should be interpreted with caution.

POWER LIMITATIONS

The fixed size of the Ranch Hand cohort limits the ability of this study to detect group differences. This limitation is most obvious with regard to specific types of cancer, such as soft tissue sarcoma and non-Hodgkins lymphoma, which are so rare that fewer than one case is expected in each group and, therefore, this study has virtually no statistical power to detect low to moderate group differences regarding them. On the other hand, these sample sizes are sufficient to detect very small mean shifts in the continuously distributed variables. For example, with regard to IgG, this study has approximately 90 percent power to detect a mean shift of 1 percent. The detection of significant mean shifts without a corresponding indication of increased Ranch Hands abnormalities or disease is considered to be of little importance or an artifact of multiple testing. This study has good power to detect relative risks of 2.0 or more with respect to diseases occurring at prevalences of at least 5 percent in the Comparison group, such as heart disease and basal cell carcinoma.

In an attempt to overcome the lack of power to detect group differences for specific types of systemic cancer, all kinds of systemic cancer were combined into a single variable. It is still possible, however, that an increased risk could exist for a particular rare type of cancer and that increased risk would be missed in this study.

STRENGTH OF ASSOCIATION

Ideally, an adverse effect, if it exists, would be revealed by a strong association between group and a disease condition, that is, by a statistically significant relative risk greater than 2.0. Statistically significant relative risks less than 2.0 are considered of less importance than larger risks because relative risks less than 2.0 can easily arise due to unperceived bias or confounding; relative risks greater than 5.0 are less subject to this concern. Relative risks greater than 5.0 were generally not found in this study.

BIOLOGIC CREDIBILITY

The assessment of biologic credibility requires consideration of the question: Is it understood in biologic terms how the exposure under study could produce the effect of interest? While lack of biologic credibility or even a contradiction of biologic knowledge can sometimes lead to dismissal of a significant result as spurious, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it has proven all too easy to propose credible biological mechanisms relating most exposures to most cancers. Thus, while pertinent, the response to this question is not especially convincing one way or the other.

SUMMARIZATION OF RESULTS

Many interpreters will attempt to tally statistically significant results across clinical areas and study cycles. A study of this scope having a multitude of endpoints and no prescribed strength of association to declare an effect meaningful, demands and at the same time defies meaningful summary tabulation. Such summaries are misleading because they ignore correlations between the endpoints, correlations between study cycle results, and the nonquantifiable medical importance of each endpoint. In fact, many endpoints are redundant in an effort not to "miss" anything. Additionally, such tabulations combine endpoints that are not medically comparable. For example, sense of smell is of less medical importance than the presence of malignant neoplasm. Nevertheless, given the lack of adequate summary statistics, the tally of significant results will occur. Such summaries can be misleading and must be carefully interpreted.

CONCLUSION

The interpretation of the AFHS requires careful consideration of potential biases, interactions, consistency of results, the multiple testing artifact, dose-response patterns and the exposure index, power limitations, strength of association and biologic credibility. Additionally, any assurances of safety drawn from these data are not scientifically valid and should be avoided. The AFHS is large enough to establish hazard (for disease prevalences on the order of 5%), but is not large enough to establish safety. Simple tabulations of positive results can be misleading.

SUMMARY OF CONCLUSIONS

INTRODUCTION

This section summarizes the conclusions drawn from the statistical analyses that have been conducted on the Air Force Health Study data base. The 1987 followup was the logical extension of the 1982 Baseline and the 1985 followup, building upon the strengths of the previous studies and utilizing the data collected at the Baseline, 1985 followup, and 1987 followup. The high level of participation that characterized the Baseline and 1985 studies was maintained through the 1987 followup.

STUDY PERFORMANCE ASPECTS

Of the 2,919 study subjects who were eligible to attend the 1987 followup, 2,853, or 97.7 percent, were located and asked to participate in the 1987 followup. Participation in the 1987 followup was high. In total, 2,294 study subjects (995 Ranch Hands and 1,299 Comparisons) were fully compliant. This represented compliance rates of 84 percent and 75 percent for Ranch Hands and Comparisons, respectively. Of the living study subjects who were fully compliant at Baseline, 92.2 percent of the Ranch Hands and 93.2 percent of the Comparisons returned to participate in the 1987 examination. Of the 2,853 invited study subjects, 531 (171 Ranch Hands and 360 Comparisons) refused to participate. One Ranch Hand and 27 Comparisons (all new to the study) agreed to complete the Baseline questionnaire, but failed to attend the physical examination and were thus partially compliant.

Study participation was analyzed to assess the potential for compliance bias. The negative findings suggested that there has been no change in the way new and replacement Comparisons self-selected for entry into the 1987 followup from the Baseline and 1985 studies. Based on analysis of telephone interview data, there appeared to be little selection bias due to nonparticipation.

POPULATION CHARACTERISTICS

Overall, the Ranch Hands and Comparisons had similar personal characteristics and lifestyle habits. No significant differences were found in age, race, occupation, education, current military status, and individual income. Although current and lifetime alcohol use were similar for the two groups, significantly more Comparisons than Ranch Hands reported that they drank wine both at the time of the physical examination and during their lifetimes; however, the current and lifetime wine consumption means were similar for both groups. Ranch Hands smoked significantly more cigarettes per day than the Comparisons at the time of the physical examination, but there was no difference between the groups on lifetime cigarette smoking, current cigar and pipe smoking, and recent and past marijuana smoking habits. In general, risk-taking behavior of the Ranch Hands and Comparisons was comparable.

In addition to the characteristics and habits summarized above, analyses were conducted to detect group differences on all other variables that were candidate covariates in the adjusted analyses of clinical endpoints. In general, the groups were similar for these variables as well.

PATTERNS OF RESULTS

The conclusions reached in this report were carefully considered using the criteria of consistency, specificity, coherence, strength, and plausibility as they apply to the interpretation of group differences. To form an overall assessment, patterns of results that emerged from the clinical evaluations were examined. Few significant group differences were noted for the proportion of abnormalities. In general, the positive associations did not aggregate in the clinical areas of prime concern; some of the statistically significant group differences noted at Baseline or at the 1985 followup examination have disappeared and only a few new associations have emerged. The longitudinal analyses were primarily negative. The unadjusted results have been concordant with the adjusted results, both in terms of the magnitude and statistical significance of the group differences. Associations between the covariates and the dependent variables generally behaved as expected. No consistent pattern of group-by-covariate interactions emerged, and the exposure index analyses were generally not significant and did not support a dose-response relationship. Dose-response relationships were not emphasized in reaching final conclusions because of the acknowledged limitations of the calculated exposure index used in this report. Dioxin body burden levels will be analyzed in a subsequent report and will provide a more valid indicator of the level of exposure.

CLINICAL ASPECTS

This section provides the conclusions from the analyses of the 12 clinical areas. The results for the dichotomous and continuous variables are summarized in Appendix R of the main report.

General Health

General health in the Ranch Hand and Comparison groups was assessed by five measures (self-perception of health, appearance of illness or distress, relative age, percent body fat, and the erythrocyte sedimentation rate). There were no significant group differences, either unadjusted or adjusted for covariates (age, race, occupation, and, in the case of self-perception of health and sedimentation rate, personality type), nor any significant group-by-covariate interactions for self-perception of health, appearance of illness or distress, relative age, or percent body fat. There was little difference in the geometric mean values of erythrocyte sedimentation rate in the two groups, but the Ranch Hand group had a significantly higher percentage of individuals with an abnormal sedimentation rate (>20 mm/hr) than the Comparisons. However, only three participants (two Ranch Hands and one Comparison) were found to have rates in excess of 100 mm/hr. One participant (a Comparison) proved to have lung cancer and died in early 1989. For neither of the two Ranch Hands was a diagnosis established during the course of the

1987 followup. Exposure index analyses did not detect any consistent dose-response relationships. Longitudinal analyses revealed a similar decline in both groups over time in the percentage of individuals reporting their health as fair or poor. For sedimentation rate, there was a significant difference between groups in the change from Baseline to the 1987 followup examination, with a relatively greater number of Ranch Hands than Comparisons shifting from normal at Baseline to abnormal at the followup examination. The clinical meaning of this observation is unknown.

Malignancy

The unadjusted analysis of all verified neoplasms indicated that the proportion of Ranch Hands with neoplasms was significantly greater than that of the Comparisons. After including suspected neoplasms with verified neoplasms, the Ranch Hand proportion was marginally greater than the Comparison proportion. The majority of malignant neoplasms observed in the Ranch Hands were basal cell carcinomas, a nonlife-threatening form of cancer. When the analysis was performed only on skin neoplasms for nonblack participants, significantly more Ranch Hands had skin neoplasms than did the Comparisons for both the verified and the verified and suspected diagnoses. A significantly greater proportion of Ranch Hands had verified malignant skin neoplasms than did the Comparisons. Given the presence of a neoplasm, a marginally significant higher proportion of Ranch Hands had skin neoplasms than did the Comparisons.

No significant group differences were found in the analyses of systemic neoplasms by number, behavior (malignant, benign, uncertain, or unspecified), or by location and site. Thus, the increase in overall malignancy was due to elevated relative risks for skin cancer and basal cell carcinoma. Also, given the presence of any systemic neoplasm, Ranch Hands and Comparisons did not differ significantly for malignant systemic neoplasms. The number of soft tissue sarcomas and non-Hodgkin's lymphomas were comparable in the two groups.

For unadjusted analyses of verified basal cell carcinoma, a borderline significant group difference was found. The unadjusted analysis of the verified and suspected basal cell carcinomas was not significant. After adjustment for covariates was performed, the group contrast was statistically significant for verified basal cell carcinoma and borderline significant for the verified and suspected diagnoses. Ranch Hands and Comparisons differed significantly on the frequency of participants with zero, one, or multiple verified basal cell carcinomas. Also, the Ranch Hands had a significantly higher percentage of participants with multiple verified basal cell carcinomas than did the Comparisons.

Sun exposure-related malignant skin neoplasms also exhibited group differences. Approximately 90 percent of the participants with sun exposure-related malignant neoplasms had basal cell carcinomas. For the unadjusted analysis, the group contrast was significant for the verified diagnoses and borderline significant for the combination of verified and suspected sun exposure-related malignant skin neoplasms. For the adjusted analyses of these neoplasms, the Ranch Hands and Comparisons differed significantly for both the verified and combined diagnoses. Verified neoplasms of the upper extremities for the sun exposure-related malignant skin neoplasms also exhibited a significant

unadjusted group difference. Examining the sun exposure-related malignant skin neoplasms by occupation produced a borderline significant group difference between the Ranch Hand and Comparison officers for verified malignancies of the ear, face, head, and neck.

The fixed size of the Ranch Hand cohort limits the ability of the study to detect group differences, particularly for the rare occurrences of soft tissue sarcoma and non-Hodgkin's lymphoma. The study has virtually no statistical power to detect low to moderate group differences for these malignancies. The study has good power to detect relative risks of 2.0 or more with respect to disease occurring at prevalences of at least 5 percent in the Comparison group, such as basal cell carcinoma.

Neurological Assessment

The neurological health of the Ranch Hand group was not substantially different from the Comparison group. Of the six questionnaire variables relating to neurological disease, the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological disease, such as Parkinson's disease and benign essential tremor. The statistical results of the group contrasts for 30 physical examination variables relating to cranial nerve function, peripheral nerve status, and central nervous system coordination processes were generally not significant. Unadjusted analyses disclosed marginally more balance/Romberg sign and coordination abnormalities for Ranch Hands than for Comparisons. Conversely, Ranch Hands had significantly fewer biceps reflex abnormalities than Comparisons. The adjusted analyses revealed a significant group-by-insecticide exposure interaction for the cranial nerve index (excluding neck range of motion). Stratified results showed a relative risk significantly greater than 1 for participants who had never been exposed to insecticides, and a relative risk marginally less than 1 for participants who had been exposed to insecticides. The adjusted analysis for coordination detected differences in the relative risks with occupation and insecticide exposure. Stratified analyses found a significant group difference for enlisted groundcrew who had never been exposed to insecticides. There were no significant differences for the other strata. Further investigation found a significant group difference for enlisted groundcrew after excluding the insecticide interaction, and a significant adjusted group difference overall after excluding both interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The trend of increasing abnormality in the enlisted groundcrew for coordination will be more fully evaluated in the analyses of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels. The exposure index analyses for each occupational cohort did not reveal significant differences supportive of a herbicide effect. The longitudinal analyses for the cranial nerve index and the central nervous system index were not significant.

Psychological Assessment

The psychological assessment was based on verified psychological disorders; reported sleep disorders; and two clinical psychological tests, the Symptom Check List-90-Revised (SCL-90-R) and the Millon Clinical Multiaxial Inventory (MCMI). The verified data on lifetime psychological disorders

showed no differences for psychoses, drug dependence, and anxiety. However, marginally more Ranch Hands than Comparisons had a verified history of alcohol dependence and other neuroses based on unadjusted analyses. The Ranch Hands reported experiencing great or disabling fatigue during the day and talking in their sleep more frequently than the Comparisons. No group differences were detected in the other 13 sleep disorder variables in the unadjusted analyses. Although no significant differences between the Ranch Hands and Comparisons were found in the unadjusted analyses of the 12 SCL-90-R variables, the Ranch Hands had marginally more abnormalities than the Comparisons for depression, somatization, and an index of the general severity of symptoms. The results of the unadjusted analyses of the MCMI scores revealed that the Ranch Hands had significantly higher mean antisocial and paranoid scores than the Comparisons. Marginally significant differences were identified on the narcissistic and psychotic delusion scores, where the mean score of the Ranch Hands exceeded that of the Comparisons. After adjustment for covariates, a significant difference remained on the narcissistic score. The Comparisons had a significantly higher mean dependent score than the Ranch Hands. Significant group-by-covariate interactions were frequently noted in the adjusted analyses, which made direct contrast of the two groups difficult. The exposure index analyses did not reveal evidence of consistent dose-response relationships.

Gastrointestinal Assessment

Overall, the gastrointestinal assessment did not find the health of the Ranch Hand group to be significantly different from the Comparison group. Group differences based on verified historical data from the questionnaire were not significant for eight categories of liver disease. No significant group difference was found for past or present occurrence of peptic ulcers. The prevalence of hepatomegaly diagnosed at the physical examination was also not significantly different between groups. The only significant finding from the laboratory examination variables was that the Ranch Hands had a higher mean alkaline phosphatase than the Comparisons. This was also noted at the 1985 followup examination. Group differences for the other laboratory variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], total bilirubin, direct bilirubin, lactic dehydrogenase, cholesterol, high density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, creatine kinase, and fasting glucose) were not significant. Stratified analyses to explore group-by-covariate interactions did not disclose any consistent pattern of significant group differences within a subgroup. The exposure index data often exhibited positive dose-response relationships, but results of the statistical analyses were generally not significant. The longitudinal analyses of AST, ALT, and GGT showed that the group differences did not change significantly between the Baseline examination and the 1987 followup examination.

Dermatologic Evaluation

Except for more Ranch Hands reporting at least one occurrence of acne during their lifetime than Comparisons, no significant group differences were detected in the dermatologic evaluation. Subsequent analysis of the occurrence of acne indicated that, for participants with no history of acne

before the start of the first Southeast Asia (SEA) tour, a higher percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour. However, the anatomic distribution of these lesions did not suggest chloracne as a cause. No cases of chloracne were diagnosed in the physical examination. Analyses were conducted on historical occurrence and duration of acne, six dermatologic disorders, a composite variable of other disorders, and a dermatology index of four disorders. All of these analyses found no significant group differences. Exposure index analyses did not reveal consistent patterns that supported an increasing dose-response relationship. The longitudinal analysis, based on the dermatology index, showed no significant differences between groups over time.

Cardiovascular Evaluation

The cardiovascular evaluation was based on reported and verified heart disease (essential hypertension, overall heart disease, and myocardial infarction) and measurement of central cardiac function and peripheral vascular function. Based on reported and verified hypertension and heart disease, the health of the two groups was similar. For reported/verified myocardial infarction, there was a statistically significant difference in the relative risk with family history of heart disease. The relative risk was less than 1 in those with no family history of heart disease and greater than 1 in those with a family history of heart disease, although neither of these within-stratum relative risks was statistically significant.

The assesement of the central cardiac function also found the groups to be similar, although significantly fewer Ranch Hands than Comparisons had bradycardia and more had arrhythmias (borderline significant). There were differences in the relative risk with levels of covariates for systolic blood pressure and nonspecific T-waves, but none of the relative risks was statistically significant in any particular stratum of individuals.

For the peripheral vascular function, significant or borderline differences were detected for five of the eight measurements. The Ranch Hands had a higher or marginally higher mean or percent abnormal for diastolic blood pressure (continuous), carotid bruits, femoral pulses, and dorsalis pedis pulses than did the Comparisons. (No difference between the two groups was detected in the discrete analysis of diastolic blood pressure.) The percentage of radial pulse abnormalities was marginally higher in the Comparisons than in the Ranch Hands. On the three pulse indices (leg, peripheral, and all pulses), the Ranch Hands had marginally or significantly higher percentages of abnormalities than the Comparisons. Arterial occlusive disease is often unilateral rather than bilateral and can affect large vessels proximally or smaller vessels distally in segmental fashion. Distal circulation may be maintained by good collateral vessels even in the presence of proximal, partial pulse deficits. The Doppler should be more reliable than palpation in such cases, but neither method is perfect. The peripheral pulses were measured by manual palpation in the 1987 followup and at Baseline, when differences were also detected. In the 1985 followup, pulses were assessed manually and by the Doppler technique, and the two groups were found to be similar. The exposure index analyses did not reveal consistent patterns suggestive of a dose-response relationship, except possibly for the presence of arrhythmias in the enlisted flyer cohort, where there were six abnormalities in the high

exposure-level category, compared to none in the medium and low exposure-level categories. Longitudinal analysis of electrocardiograph findings and combined mortality-morbidity analyses did not indicate excess cardiovascular risk in the Ranch Hands.

Hematologic Evaluation

The hematologic status of the Ranch Hand and Comparison groups was assessed by the examination of eight variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count. There were no statistically significant differences between the two groups for RBC, hemoglobin, hematocrit, MCV, MCH, and MCHC, in analyses either unadjusted or adjusted for the covariates of age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history. For WBC, the mean level was significantly greater in the Ranch Hands than in the Comparisons, but the magnitude of the difference was small. The difference was not statistically significant after adjustment for covariates, nor were significant differences detected in the percentage of individuals with abnormal values. Mean platelet counts were also significantly greater in the Ranch Hands than in the Comparisons, as was the percentage of individuals with abnormally high values. While these differences remained significant after adjustment for covariates, no platelet count was elevated into a pathologic range.

Exposure index analyses detected significant exposure level effects in the discrete analysis of hematocrit in the officer cohort, in the continuous analysis of MCV in the enlisted groundcrew, in the continuous analysis of MCHC in the enlisted flyers, and in the discrete analysis of platelet count in the enlisted flyers. Several exposure index-by-covariate interactions were also significant. Only the hematocrit and MCV findings were consistent with a dose-response relationship, however. Longitudinal analyses detected a significantly greater decrease in the mean platelet count from Baseline to the 1987 followup examination in the Ranch Hands than in the Comparisons, despite the higher overall mean count. The clinical importance of these observations is unclear.

Renal Assessment

Without adjustments for covariates, none of the variables of reported history of kidney disease/stones, urinary protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups. In general, these findings were supported by the adjusted analyses. Examination of the group-by-covariate interactions did not yield a consistent pattern to suggest renal detriment to either group. Lack of a group difference in the reported history of kidney disease/stones (consistent with the 1985 followup results) was in contrast with the Baseline findings, where Ranch Hands reported significantly more disease. A nonsignificant difference in the percentage of participants with urinary protein was also inconsistent with the Baseline examination, when the Comparisons had a marginally significant higher prevalence rate. Like the 1982 and 1985 studies, the exposure index analyses showed very little evidence

of a dose-response relationship. In the longitudinal analysis of blood urea nitrogen, no difference in the change over time was detected.

Endocrine Assessment

Findings from the endocrinologic assessment did not disclose any statistically significant differences between the Ranch Hand and Comparison groups. The percentage of participants who indicated problems with current thyroid disease was similar between groups, as were the percentages of thyroid and testicular abnormalities determined by palpation at the physical examination. Of the six laboratory examination variables that were examined (triiodothyronine percent [T_3 %] uptake, thyroid stimulating hormone [TSH], follicle stimulating hormone, testosterone, 2-hour postprandial glucose, and a composite diabetes indicator), the Ranch Hand TSH mean was marginally significantly higher than the Comparison TSH mean, a finding that was statistically significant at the 1985 followup examination. Ranch Hand and Comparison mean levels for the other laboratory variables, including testosterone, were similar. For all laboratory variables, the percentage of Ranch Hands with abnormal values was higher than the percentage of Comparisons with abnormal values, but none of these differences was statistically significant. Exposure index results generally did not support the presence of a herbicide effect. The enlisted groundcrew and officer cohorts exhibited increasing dose-response patterns for diabetes, but the associations were not significant. Conversely, the overall result for diabetes was significant for enlisted flyers, but was due to the presence of relatively more diabetics in the medium exposure category than in either the low or high categories. The longitudinal analyses for the T_3 % uptake, TSH, and testosterone did not show significant differences between groups in the changes over time.

Immunologic Evaluation

For the immunologic assessment of the 1987 followup examination, composite skin reaction test results were analyzed from the physical examination data, and various laboratory examination measurements from cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins were also analyzed. Ranch Hands had a higher frequency of individuals with possibly abnormal reactions on skin testing than the Comparisons. The analysis of the composite skin tests results, adjusting for covariate information, contained a significant group-by-lifetime cigarette smoking history interactions. Followup analyses showed that, among those individuals with the heaviest smoking histories, Black Ranch Hands had a higher frequency of possibly abnormal readings when contrasted with Comparisons. Within the other strata, there were no significant differences. The unadjusted analyses of the laboratory examination data indicated no significant group difference between Ranch Hands and Comparisons. For the adjusted analyses of the natural killer assay measurements with and without Interleukin 2, significant interactions between group and race were present. Exploration of these interactions revealed that the Black Ranch Hands had higher adjusted means than the Black Comparisons for the natural killer assay measures. The clinical significance of these findings is not apparent and does not point to any known clinical endpoints. In general, the immunologic assessment revealed no medically important differences between the Ranch Hands and Comparisons.

Pulmonary Disease

The pulmonary assessment was based on five self-reported respiratory illnesses, seven clinical observations, and eight laboratory measurements. No evidence of a herbicide effect was detected in the assessment of the reported respiratory illnesses. The health of the two groups was reasonably comparable based on the clinical and laboratory variables, although the Ranch Hands had a significantly higher percentage of thorax and lung abnormalities on examination than the Comparisons, based on the unadjusted analysis, and a marginally higher percentage after adjustment for covariates. No significant group differences were detected in the adjusted analyses without significant interactions involving group. Exploration of the group-by-covariate interactions did not reveal a consistent pattern indicating a herbicide effect. The adverse effects of smoking on pulmonary status were evident in all analyses.

CONCLUSIONS

In the 1987 followup, relatively few differences in health status were found between the Ranch Hands and Comparisons. No cases of chloracne or porphyria cutanea tarda, the most commonly accepted effects of dioxin exposure, were detected in this study. There was a single case of soft tissue sarcoma in each group and one case of non-Hodgkin's lymphoma in a Ranch Hand. The results do not indicate that the health of the Ranch Hands is related to herbicide exposure in Vietnam. Although few differences were noted, reanalysis of the data using the dioxin body burden levels and continued medical surveillance are warranted.

In summary, there is not sufficient scientific evidence at this time to support a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

FUTURE DIRECTIONS

The scope and complexity of the Air Force Health Study (AFHS) has required gradual refinement and correction to meet the challenges of changing technology and scientific direction, and to ensure continued participation of all participants.

The selection of procedures to be included in each of the followup physical examinations has been driven by the findings and experiences of the earlier phases of the study. Similarly, changes for the 1992 followup examination will be based on the findings covered in this report. The opportunity to measure dioxin accurately in the blood of study participants will significantly enhance the ability to identify relationships between dioxin and medical findings. It is anticipated that additional serum studies to further explore and characterize dioxin half-life will be performed as part of the 1992 examination.

Additional modifications to the examination format being considered for 1992 include enhanced assessments of psychological and neurological status. The evaluation of immune function will continue to be emphasized in the next examination and the current set of skin test reagents will be used; however, modifications may be made in the dosages of the antigens to reflect World Health Organization recommendations. Modifications to the battery of cell surface marker and functional studies may be made to reflect state-of-the-art laboratory practice. Similarly, advances in laboratory technology, such as the use of fluorometric enzyme assays for thyroid function, will be incorporated as well.

Statistical methodology in the longitudinal analyses will be modified so that data from all four physical examinations can be included in these important analyses. In addition, it is anticipated that a more complete characterization of sun exposure will be available through the use of data that describe the average hours of daily sunshine at each geographic location.

The next 12 to 16 months will see several significant milestones in the AFHS: (1) completion of the reanalysis of verified birth defect and reproductive outcome data; (2) reanalysis of the 1987 examination data in conjunction with the serum dioxin results; and (3) a mortality analysis of deaths through December 1989. These reports should provide information that will be useful in the resolution of the scientific and political questions surrounding the military use of Agent Orange in Vietnam.