Wolfe, et al., "Air Force Health Study. 1987 Follow up Examination Results," (1990)

No manifestations of porphyria cutanea tarda were reported in this study of study of Air Force personnel involved in the herbicide spraying operations in Vietnam.

Air Force Health Study

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

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This report represents the results of the health assessment of the 955 Ranch Hands and the 1,299 Comparisons who participated in the 1987 followup examination of the Air Force Health Study. The purpose of the study is to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides. The Ranch Hands continue to manifest slightly more abnormalities than the comparisons, although the results do not suggest an adverse effect due to exposure to herbicides and their dioxin contaminant. Reanalysis using dioxin body burden levels and continued medical surveillance are indicated. In summary, there is not sufficient evidence at this time to support a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

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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 exposurerelated 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 troups 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 carinogens 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 exposurea. 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 recorda. 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

	Ranch Hand			Comparison		
Stratum	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 lwithin 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.

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*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	
Questionnaire					
Self-Perception of Health	NS	--	NS	--	
Physical Examination					
Appearance of Illness/Distress	NS	--	NS	--	
Relative Age	NS	--	NS	--	
Percent Body Fat	NS	NS	NS	NS	
Laboratory					
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 interspecies 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 agerelated 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 fibro sarcoma 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 exposurerelated 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				
Behavior				
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]
Cell Type				
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]
Basal Cell Carcinoma by Location/Site				
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
Melanoma by Location/Site				
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]	--	
Sun Exposure-Related Malignant Skin Neoplasms by Location/Site				
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	--	
Basal Cell Carcinoma of the Ear, Face, Head and Neck by Occupation				
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
Sun Exposure-Related Malignant Skin Neoplasms of the Ear, Face, Head, and Neck by Occupation				
Officer	V	NS*	--	RH>C[d]
	VS	NS	--	
Enlisted Flyer	V	NS	--	
	VS	NS	--	
Enlisted Groundcrew	V	NS	--	
	VS	NS	--	
Conditional Analyses				
Skin Neoplasm Conditioned on Neoplasm	V	NS*	--	RH>C[d]
	VS	NS*	--	RH>C[d]
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	--	
Multiple Basal Cell Carcinoma				
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*	--	RH>C[d]

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				
Behavior				
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	--	
Malignant Systemic Neoplasms by Location/Site				
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
Malignant Systemic Neoplasms by Location/Site (continued)				
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	--	
Conditional Analyses				
Malignant Systemic Neoplasm	V	NS	--	
Conditioned on All Systemic	VS	NS	--	
Skin and Systemic				
All Skin and Systemic Neoplasms Combined	V	0.032	--	RH>C[d]
	VS	NS*	--	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 ($p>0.10$).
[a]No suspected neoplasms.
NS*: Borderline significant ($0.05<p\leq0.10$).
[b]No neoplasms for either Ranch Hands or Comparisons.
[c]No verified neoplasms.
[d]These 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 exposurerelated 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]

[a]Baseline participants: 1,045 Ranch Hands, 1,224 Comparisons.

[b]1985 followup participants: 1,016 Ranch Hands, 1,293 Comparisons.

[c]1987 followup participants: 995 Ranch Hands, 1,299 Comparisons.

[d]Nonblacks 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.

[e]Baseline p-value based on chi-square test; 1985 and 1987 followup p-values based on Fisher's exact test.

[f]Adjusted 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.