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AIR FORCE HEALTH STUDY

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

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13. ABSTRACT *(Maximum 200 words)*

This report represents the results from an epidemiologic study to determine whether adverse health effects attributable to Herbicide Orange exist in Vietnam veterans who participated in Operation Ranch Hand. Data were analyzed for 12 clinical areas. The analysis focused on group differences between the exposed (Ranch Hand) and unexposed (Comparison) cohorts, as well as on the association of each health-related endpoint with extrapolated initial and current serum dioxin levels. Findings in this report reveal a consistent relationship between dioxin and body fat that was initially noted in the analysis of the 1987 examination results. Cholesterol and the cholesterol to HDL ratio were found to be associated with current serum dioxin levels. Evidence for a possible association between glucose intolerance, impaired insulin production, and dioxin exposure was revealed, but cause and effect remain to be established. Also revealed was a significant association between selected peripheral pulses and dioxin exposure, and a significant difference in self-perceived health status between Ranch Hands and Comparisons (although possible due to bias). Other health endpoints revealed no consistent patterns within or across clinical areas that were suggestive of health detriment due to dioxin exposure

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NOTICE

This report presents the results of the 1992 followup of the Air Force Health Study, the fourth examination in a series of epidemiologic studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of the 1982 Baseline study, the 1985 followup study, and the 1987 followup study were presented in four reports: the Baseline Morbidity Study Results (24 February 1984), the Air Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987 Followup Examination Results (16 January 1990), and the Air Force Health Study Serum Dioxin Analysis of 1987 Examination Results (7 February 1991).

Given the relationship of the 1992 followup to the previous studies, portions of these documents have been reproduced or paraphrased in this report. In addition, portions of the Air Force Health Study Statistical Plan for the 1992 Followup (23 December 1993) have been used in the development of this report. The purpose of this notice is to acknowledge the authors of these previous study reports and documents.

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Epidemiologic Research Division
Armstrong Laboratory
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EXECUTIVE SUMMARY

1992 FOLLOWUP EXAMINATION REPORT

The Air Force Health Study (AFHS) is an epidemiologic investigation to determine whether adverse health effects exist in Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971, and whether these adverse health effects can be attributed to occupational exposure to Herbicide Orange (and its dioxin contaminant). A comparison group was formed from Air Force veterans who flew or maintained C-130 aircraft in Southeast Asia (SEA) during the same time period as those who served in the Ranch Hand units. The Baseline study was conducted in 1982, and followup studies were performed in 1985, 1987, and 1992. Additional evaluations are planned for 1997 and 2002. This report presents the results from the statistical analyses of the data from the 1992 followup examination.

In the Baseline study, each living Ranch Hand was matched with a randomly selected Comparison based on age, race, and military occupation. At each followup study, noncompliant Comparisons were replaced from the set of living Comparisons, matched by age, race, military occupation, and self-perception of health. Participation throughout each examination cycle and at the 1992 followup examination remained high. Eighty-three percent (n=952) of the 1,148 eligible Ranch Hands and 77 percent (n=912) of the 1,191 eligible Original Comparisons participated in the 1992 followup examination and questionnaire process. Ninety-one percent of living Ranch Hands and 92 percent of living Comparisons who were fully compliant at the Baseline examination returned for the 1992 followup examination. In total, 2,233 study subjects (952 Ranch Hands and 1,281 Comparisons) participated in the 1992 followup examination.

This report presents conclusions drawn from the statistical analyses of more than 300 health-related endpoints in 12 clinical areas: general health, neoplasia, neurology, psychology, gastrointestinal, dermatology, cardiovascular, hematology, renal, endocrine, immunology, and pulmonary. Data were collected from medical records review, previous examination cycles, and the physical and laboratory examinations and questionnaire administered at the 1992 followup. The analyses focused on group differences between the exposed (Ranch Hands) and unexposed (Comparisons) cohorts, as well as on the association between serum dioxin levels and each health-related endpoint among the Ranch Hands.

Six statistical models were used to evaluate the relationship between the health status of study participants and their dioxin exposure. The first model (Model 1) examines contrasts between Ranch Hands and Comparisons using group as a proxy for exposure and does not incorporate serum dioxin measurements. However, it is assumed in this model that all Ranch Hands were exposed and all Comparisons were not. Each of the following five models incorporates estimates of serum dioxin in either initial or current form. Current serum dioxin is measured as of the 1987 examination. Initial serum dioxin is extrapolated from the current serum dioxin measurement to time of duty in SEA. The second model (Model 2) examines estimated initial serum dioxin levels, extrapolated from current serum dioxin measurements and assuming first-order kinetics and a constant dioxin decay rate. The

third model (Model 3) categorizes the Ranch Hand cohort according to serum dioxin levels and contrasts each Ranch Hand category with the Comparisons having background serum dioxin levels. The remaining three models (Models 4, 5, and 6) use three different measures of current serum dioxin: lipid-adjusted, whole-weight, and whole-weight adjusted for total lipids respectively. These three models assume nothing about serum dioxin elimination, but may not be good surrogates for exposure if elimination rates differ among individuals.

In the General Health Assessment, the Ranch Hand and Comparison cohorts seem comparable by all objective indices; however significant group differences, although possibly biased, were evident in self-perceived health status. Participants who knew they possessed an elevated dioxin level or whose occupation implied a greater risk for exposure may consciously or subconsciously have perceived their health to be poorer than their Comparisons. Percent body fat and sedimentation rate displayed significant associations with current serum dioxin levels, but the biological significance is uncertain.

In the Neoplasia Assessment, Ranch Hands had a slightly higher prevalence of benign and malignant skin neoplasms than Comparisons, as in previous examinations, but these group differences are not statistically significant for the 1992 study, although they were significant in previous examinations. Consistent with all previous examinations, none of the analyses revealed any significant group differences in the prevalence of systemic malignancies or an increased risk of any systemic malignancy in association with serum dioxin levels in Ranch Hands. At the end of a decade of surveillance, Ranch Hands and Comparisons appear to be at equal risk for the development of all forms of neoplastic disease, and there is no evidence to suggest a positive dose-response relationship between body burden of dioxin and neoplastic disease.

In the Neurological Assessment, the prevalence of historical neurological disorders was similar in the Ranch Hand and Comparison cohorts. In the analyses of the physical examination variables, Ranch Hand enlisted groundcrew, the occupational category with the highest levels of dioxin, had significantly more cranial nerve index abnormalities than Comparison enlisted groundcrew, but there was no evidence of a dose-response relationship in the serum dioxin analyses. Based upon indices aggregating dysfunction of various peripheral nerves, and upon the results of vibrotactile testing, a subclinical neuropathic effect may be developing in Ranch Hand veterans, although it has not manifested itself in any increase in clinical pathology and the results are not statistically significant. The analyses employing current serum dioxin yielded inconsistent results. A positive association was noted in relation to the cranial nerve motor variable smile and the peripheral nerve variables pin prick and patellar reflex, while inverse dose-response patterns were defined for smell and the Babinski reflex. In summary, the Neurological Assessment found the prevalence of neurological disease to be comparable between the Ranch Hand and Comparison cohorts, and showed no consistent evidence of a dose-response effect with serum dioxin levels.

In the Psychological Assessment, Ranch Hands exhibited higher psychological distress than Comparisons for the anxiety, obsessive-compulsive behavior, paranoid ideation, somatization, and global severity index scores in the Symptom Check List-90-Revised (SCL-90-R) inventory. A significant group contrast also was exhibited for the verified condition of other neuroses. However, when Ranch Hands were categorized according to

serum dioxin levels, significant group differences were found only in the contrasts of Ranch Hands having background serum dioxin levels versus Comparisons, and the serum dioxin analyses did not support a dose-response relationship. The differences in the Ranch Hand and Comparison cohorts together with the lack of an effect attributable to dioxin suggest that factors other than dioxin exposure continue to contribute to a relatively small, but notable, number of Ranch Hand SCL-90-R test score abnormalities. The possibility that a small subset of physically or psychologically vulnerable Ranch Hands may have suffered psychological injury in the context of their exposure to dioxin cannot be definitively ruled out at this time.

In the Gastrointestinal Assessment, the laboratory analyses revealed no biologically significant differences between the Ranch Hand and Comparison cohorts. The serum dioxin analyses indicated that estimated initial dioxin exposure was generally not associated with historical liver disorders or laboratory measurements. However, current dioxin levels were highly associated with lipid-related health indices, as well as some of the hepatic enzymes and proteins. Alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), serum triglycerides, and serum cholesterol revealed significant positive associations with current serum dioxin levels and a negative association was revealed between current serum dioxin and the cholesterol to high-density lipoprotein (HDL) cholesterol ratio. Analyses of the historical and clinical examination variables revealed no evidence of any overt hepatic disease related to the current body burden of dioxin. However, the elevated liver function tests in relation to current dioxin, though not clinically significant on an individual basis, are indicative of the presence of hepatocellular toxins as the result of dioxin exposure and may cause liver damage in conjunction with other toxins such as alcohol consumption. In summary, the gastrointestinal data reflect no apparent increase in organ-specific morbidity in Ranch Hands relative to Comparisons, nor do they reflect an association with serum dioxin levels. Although a subclinical dioxin effect on lipid metabolism cannot be excluded, some of the results may be related in part to body habitus and percent body fat.

The Dermatologic Assessment showed no significant differences between Ranch Hands and Comparisons. The analyses of extrapolated initial and current serum dioxin did not provide evidence of a dose-response effect. However, Ranch Hands with current serum dioxin levels above background level demonstrated a lower occurrence of an abnormal dermatology index than Comparisons, and the dermatology index exhibited a significant negative association with current serum dioxin in Ranch Hands. In the four examination cycles to date (Baseline, 1985, 1987, and 1992), no cases of chloracne have been detected. Therefore, there is no consistent evidence to suggest an adverse dioxin effect on the dermatologic system at doses received by the Ranch Hand cohort in SEA.

In the Cardiovascular Assessment, the verified historical indices were similar in Ranch Hands and Comparisons. Several of the electrocardiograph (ECG) indices, including right bundle branch block (RBBB), non-specific ST- and T-wave changes, and arrhythmias, displayed significant positive associations with current serum dioxin levels, but none of these endpoints also displayed a group difference between Ranch Hands and Comparisons to confirm the dose-response relationship. In the longitudinal analyses of the pulses endpoints, Ranch Hands were slightly more likely than Comparisons to develop peripheral pulse deficits over time, although there was no consistent evidence of a dose-response relationship from the

analyses using calculated initial serum dioxin levels as a measure of exposure. Ranch Hands were found to be at slightly greater risk than Comparisons for the development of selected peripheral pulse deficits which, based on the analysis of hypertension, ST- and T-wave changes, and the increase in the number of deaths caused by diseases of the circulatory system among Ranch Hand nonflying enlisted personnel, suggests some effects from dioxin.

In the Hematologic Assessment, only platelet count exhibited significant associations with the herbicide exposure indices. Ranch Hands in the enlisted flyer and enlisted groundcrew categories possessed statistically significant higher mean platelet counts than Comparisons. Ranch Hands with high extrapolated initial dioxin levels also had significantly greater mean platelet count measurements than Comparisons. These results are consistent with those from the 1987 examination, but the biological significance is uncertain. Based on the analyses of white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), and total platelet count, there is no longer evidence that a subclinical inflammatory reaction may exist in Ranch Hands, as was conjectured from previous examinations. There is no evidence from the current study to suggest an association between hematopoietic toxicity and prior dioxin exposure.

In the Renal Assessment, no significant group differences or association with serum dioxin were noted in the history of urinary tract disease. Although the prevalence of microhematuria (urinary red blood cell (RBC) counts) was similar in both groups, Ranch Hands with the highest levels of extrapolated initial serum dioxin had a significantly higher prevalence of microhematuria than Comparisons, and the analyses employing current serum dioxin yielded results consistent with a dose-response effect. However, the longitudinal analyses indicated that the prevalence of microhematuria has decreased in the Ranch Hand cohort at each of the last two cycles. The Ranch Hands most highly exposed to dioxin, the enlisted groundcrew, had twice the prevalence of pyuria as Comparisons, but the similar prevalence in Ranch Hands with low and high levels of serum dioxin does not support a dose-response effect. In general, no consistent evidence for any detriment to the renal system, with the possible exception of hematuria, was found to be related to the body burden of dioxin.

In the Endocrine Assessment, analyses of thyroid functions did not reveal significant differences between the Ranch Hand and Comparison cohorts, and the prevalence of diabetes mellitus in the two groups was not significantly different. Consistent with the 1987 examination, a significant inverse dose-response relationship between current serum dioxin and total serum testosterone in Ranch Hands was detected, but the clinical significance is uncertain. Significant results relating to the development of diabetes were limited to the current serum dioxin analyses. Fasting glucose in diabetics and 2-hour postprandial glucose in nondiabetics were positively associated with current serum dioxin levels and fasting glucose in nondiabetics was inversely associated with current serum dioxin. Similarly, though not statistically significant, serum insulin was inversely associated with current dioxin in diabetics and positively associated with current dioxin in nondiabetics. Although cause and effect remain to be established, these results imply a possible association between dioxin exposure and glucose metabolism and insulin production in diabetics.

The Immunologic Assessment did not reveal any relationship between dioxin exposure and physiologic abnormalities that could be considered clinically significant. The mouse stomach kidney (MSK) smooth muscle antibody, rheumatoid factor, and the lupus panel summary index displayed inverse associations with dioxin exposure, but did not support a dose-response relationship. A marginally significant positive association was found between serum IgA concentrations and extrapolated initial dioxin levels which, coupled with continuity over time, suggests a possible relationship that should be further evaluated because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction.

The Pulmonary Assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort relative to the Comparison cohort or in relation to body burden of dioxin. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be at an increased risk, relative to Comparisons, with respect to the history of bronchitis and thorax and lung abnormalities, but there was no evidence from the serum dioxin analyses to confirm a dose-response relationship. The ratio of observed FEV_1 to observed FVC in Ranch Hands revealed a significant relationship with initial dioxin that was consistent with a dose-response effect, but the changes in the ratio were slight and of doubtful physiologic significance.

Based on the statistical findings of the 1992 examination and subject to interpretive considerations and clinical evaluation, the following conclusions have been drawn.

1. Glucose Intolerance: The results indicate a statistically and potentially clinically significant association between serum dioxin and glucose intolerance. This association exhibits a dose-response relationship, and is present both for non-diabetic individuals (as manifested by elevated insulin levels) and diabetic individuals (as manifested by increased prevalence and severity of diabetes and decreased age of onset). This association was found with type II diabetes only. This association was also present longitudinally and occurs in other epidemiological studies in addition to the AFHS.

2. Cardiovascular Mortality: There is a statistically significant increase in cardiovascular mortality in the most heavily exposed subgroup, the enlisted groundcrew. This association persists longitudinally throughout the three examination cycles. Inclusion of this group with lesser exposed Ranch Hand subgroups results in a statistically nonsignificant overall relative risk. Less clinically severe criteria for altered cardiac functions including ECG findings of prior myocardial infarction, non-specific ST- and T-wave changes, and RBBB displayed significant positive associations with dioxin, although these associations did not cause significant group differences between all Ranch Hands and all Comparisons. Peripheral vascular function variables displayed significant subgroup differences for both the enlisted groundcrew and the high current dioxin category in relation to the Comparisons. Both groups had a greater prevalence of new pulse deficits arising since the 1985 followup examination than did their Comparisons.

3. Serum Lipid Abnormality: There is a highly significant positive statistical association between dioxin and cholesterol, dioxin and triglycerides, and dioxin and the cholesterol-HDL ratio in most models using either current dioxin levels or dioxin levels

extrapolated to the end of the tour of duty in SEA. In such models, the correlation between HDL cholesterol and dioxin was highly significant and negative. These lipid findings were consistent with the 1987 findings, but were not consistent with the 1982 examination when serum cholesterol in Ranch Hands was significantly lower than in Comparisons.

4. Liver Enzymes: Both lipid-adjusted and whole-weight current dioxin showed elevated mean aspartate aminotransferase (AST), ALT, and GGT associations. For ALT and GGT, this association was highly significant. This association had not been present in previous examinations. Although these elevations were statistically significant, mean enzyme levels remained well within normal limits and the prevalence of abnormally elevated liver enzymes was not statistically increased. Thus, although this laboratory finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

5. Increase in IgA: A marginally significant increase in IgA with increased serum dioxin was found. This paralleled similar findings of increased IgA, first noted in the 1987 followup. Although this elevation was marginally significant, mean IgA levels remained well within normal limits, and the prevalence of significant abnormally elevated IgA was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

6. Decrease in Serum Testosterone: A statistically significant inverse effect was seen between total serum testosterone and current dioxin in Ranch Hands. This paralleled similar findings first noted in the 1987 followup. Although this decrease was statistically significant, mean serum testosterone levels remained well within normal limits, and the prevalence of abnormally low serum testosterone was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

7. Decrease in MSK and Lupus Panel Positives: Significant and marginally significant decreases in the prevalence of positive reactions to MSK, lupus, and rheumatoid factor tests in relation to dioxin were seen in the 1992 followup. When present, these tests are indicative of potential autoimmune disorders. Their absence is therefore not normally considered pathologic, but the decreased prevalence could nonetheless indicate some degree of immune suppression. More specific tests of immune suppression were not significantly associated with dioxin.

8. No Significant Difference in Incidence or Prevalence of Neoplastic Disease: It has been theorized that dioxin can act as either an inducer or promoter of neoplastic disease. A detailed analysis of all forms of neoplastic disease over the course of a decade show no significant group differences in the incidence of benign or malignant neoplasms, including those neoplasms most often associated with herbicide exposure in the Ranch Hand population (e.g., Hodgkin's Disease, non-Hodgkin's lymphoma, soft tissue sarcoma). In the 1992 followup, there was again no significant group differences. The marginally significant differences in site-specific incidence that were found, more often favored a decrease in relative risk associated with dioxin exposure rather than an increased risk. As previously stated, because of its size, this study does lack power to ascertain modest increases in relative risk for uncommon neoplasms. As the population continues to age, the combination

of an increase in background rate of neoplastic disease, increased time for latent effects of past exposure, and increased time of total exposure may combine to increase the power of this study to determine neoplastic effects.

In summary, glucose intolerance, serum lipid abnormality, and cardiovascular abnormality and mortality are areas demonstrating associations that, if causality were established, would represent the most important dioxin-associated health problems seen in the AFHS to date. These three areas appear to have the greatest magnitude of effect in terms of absolute increase in risk, in common areas known to contribute to years of potential life lost and to overall healthcare costs. Clearly, there are biological interrelationships among all three of these variables that will make the task of establishing causality, as well as establishing primary versus secondary causality, challenging. From a public health perspective, these three areas demand the greatest attention.

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CHAPTER 1

INTRODUCTION

This chapter briefly describes the background of the Air Force Health Study (AFHS) and provides an overview of the study design, the morbidity component, and the purpose and format of this report. Additionally, this chapter provides considerations that should be made when interpreting the results provided in this report.

BACKGROUND

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). This program, code-named Operation Ranch Hand, dispersed approximately 19 million gallons of herbicides on an estimated 10 to 20 percent of South Vietnam (1,2) from 1962 to 1971. Of the 19 million gallons dispersed, approximately 11 million gallons were "Agent Orange," the primary defoliant of the six herbicides used in the program.

From the start, Operation Ranch Hand was scrutinized intensely due to the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to issues of health in 1977. Numerous claims of exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, and subsequent perceived adverse health effects among U.S. military service personnel 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 the White House to conduct a health study on the Ranch Hand population, the aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The prevailing reasons behind the study commitment included the availability of a population with 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 pledge to care for the Air Force community.

The U.S. 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 Study Protocol was published (3). When the School of Aerospace Medicine was reorganized in 1990, the Armstrong Laboratory assumed responsibility for the AFHS.

Since 1978, numerous 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 to what extent each individual was exposed). Unfortunately, in many of the human studies, population identification and exposure estimation, which are critical for a valid study, have often been scientifically elusive.

Studies of serum dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD) levels have shown 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 population. The results of that study clearly demonstrated that substantial elevated levels of dioxin could still be found in the serum of some Ranch Hands, as opposed to the absence of elevated levels of dioxin found in U.S. Army ground troops by the CDC (4,5). If dioxin should cause an adverse health effect, based on the principle of dose-response, the Ranch Hands should manifest more, or earlier evidence of adverse health.

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 nonconcurrent aspect of the design results from Ranch Hand exposure over time between 1962 and 1971. 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. At the outset of the study, a Comparison group was identified consisting of veterans assigned to Air Force units operating C-130 cargo aircraft in Southeast Asia (SEA). Using a computerized selection procedure to identify Comparisons with similar characteristics to each Ranch Hand, a maximum of 10 Comparisons for each Ranch Hand was selected, matching on age, race, and military occupation. After personnel record reviews, each Ranch Hand determined to be eligible and fully suitable for study had an average of 8.2 matched Comparison subjects.

In the 1992 followup study, 952 of the 1,148 eligible Ranch Hands (83%) participated. Of the 1,195 eligible Original Comparisons, 912 (76%) participated, while 369 of the 567 replacement Comparisons (65%) invited to the 1992 followup chose to take part. Four Ranch Hands, 20 Original Comparisons, and 37 Replacement Comparisons participated for the first time at the 1992 followup examination. Complete information on the selection and participation of study participants can be found in Chapter 5 of this report, Study Selection and Participation.

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 mortality 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 19,080 veterans in the Comparison population.

MORBIDITY COMPONENT

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. The morbidity study followup comprises sequential questionnaires, medical record reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002.

The Baseline morbidity assessment, conducted in 1982, disclosed only minor differences between the Ranch Hands and Comparisons, and those differences were not traditional indicators of dioxin-related disease. The sustained commitment to pursue the Herbicide Orange question to its scientific conclusion was demonstrated by the conduct of the first two morbidity followups in 1985 and 1987. These followup examinations provided the opportunity to confirm or refute some of the Baseline findings and to explore subtle longitudinal changes. In the followup examinations, the mental and physical health status of the participants during the time interval since the Baseline study was assessed. The results of the followups showed a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline study in 1982. There was not sufficient evidence to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

For the Baseline and the 1985 and 1987 followup studies, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). During the 1987 physical examination, the Air Force initiated a collaborative study with CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (4,6,7). The measurement of serum dioxin levels led to a thorough statistical evaluation to assess dose-response relationships between dioxin and approximately 300 health-related endpoints in 12 clinical areas. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands, as well as contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels of serum dioxin (8). The analysis of dose-response relationships based on serum assays provided an important enhancement from the previous AFHS investigations. This was the first large-scale study of dose-response effects based on an accurate measurement of current dioxin.

In 1992, the third followup was initiated. During a 2½-year period, data were collected, automated, and analyzed. As in 1985 and 1987, this followup study was conducted by Science Applications International Corporation (SAIC) in conjunction with Scripps Clinic and Research Foundation (SCRF), and National Opinion Research Center (NORC), working as a team with the Air Force. The analysis of data collected at the 1992 followup is the basis for this report.

PURPOSE OF THE REPORT

The subject of this report is the 1992 morbidity followup to the AFHS. The objective of the morbidity followup is to continue the investigation of the possible long-term health effects following exposure to TCDD. This report describes the procedures and results of the third morbidity followup of the AFHS.

This report is written primarily for clinical epidemiologists, clinicians, and biostatisticians so that they may fully evaluate the data and analytic techniques. Familiarity with the Study Protocol and prior mortality and morbidity reports is essential to a full understanding of this 20-year study. The report format has been established to be complete, rigorous, and straightforward on all issues so that maximum scientific credibility will be maintained. The intent of the background sections of the clinical chapters is to provide a broad overview of the literature with respect to dioxin endpoints. It is important to note that all statistical analyses in this report were prescribed by the Air Force and none are ad hoc analyses.

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ORGANIZATION OF THE REPORT

This report is organized as follows:

- Chapter 1 (Introduction) provides summary background information on the AFHS and discusses specific technical items and issues that may affect the different clinical area assessments.

- Chapter 2 (Dioxin Assay) describes the procedure used to draw blood for the serum dioxin measurements, the analytical method used to determine the dioxin level from the serum, and the quality control (QC) procedures associated with the serum dioxin data.

- Chapter 3 (Questionnaire Methodology) gives an overview of the development and implementation of the participant questionnaires.

- Chapter 4 (Physical Examination Methodology) describes the conduct and content of the physical examinations.

- Chapter 5 (Study Selection and Participation) presents the methods by which participants were selected and scheduled and also presents a discussion of the participant replacement strategy and the factors known or suspected to influence study participation. Sources of potential bias also are discussed.

- Chapter 6 (Quality Control) provides an overview of the specific quality assurance (QA) and QC measures developed and used throughout the 1992 followup.

- Chapter 7 (Statistical Methods) documents the statistical methods used in the individual clinical area assessments, and the statistical procedures and results of the half-life analyses performed by the Air Force.

- Chapter 8 (Covariate Associations with Estimates of Dioxin Exposure) examines the associations between exposure (Ranch Hand, Comparison, and measures of dioxin exposure) and the individual covariates used in the different clinical assessments.

- Chapters 9 through 20 present the results and medical discussions of the statistical analyses of the dependent variables for each clinical area. Each chapter also contains a brief overview of pertinent scientific literature. The 12 clinical chapters are as follows:

  - Chapter 9: General Health Assessment
  - Chapter 10: Neoplasia Assessment
  - Chapter 11: Neurological Assessment
  - Chapter 12: Psychological Assessment
  - Chapter 13: Gastrointestinal Assessment
  - Chapter 14: Dermatologic Assessment
  - Chapter 15: Cardiovascular Assessment
  - Chapter 16: Hematologic Assessment
  - Chapter 17: Renal Assessment
  - Chapter 18: Endocrine Assessment
  - Chapter 19: Immunologic Assessment
  - Chapter 20: Pulmonary Assessment

- Chapter 21 (Conclusions) summarizes the findings and medical discussions of the 12 clinical areas.

- Chapter 22 (Future Directions) summarizes the anticipated future activities and discusses possible modifications to the existing instruments and methodologies used to investigate the association between health status and dioxin exposure.

INTERPRETIVE CONSIDERATIONS

In the interpretation of results from any epidemiologic study, no single result should be evaluated in isolation or at face value, but rather in the context of the overall study design, the data collection procedures, the data analysis methods, and the approach to evaluating results. This especially applies to the AFHS. This effort is a large-scale, prospective

observational study in which thousands of measurements are generated on each participant, and those measurements and diagnoses are subjected to extensive statistical analyses entailing the testing of thousands of individual hypotheses. Each positive result should be scrutinized relative to other findings in this and other studies and relative to the statistical methods used and the medical and scientific plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the assertion that there is no effect.

In this section, critical considerations in the evaluation of results from this study are reviewed. These considerations include study design and modeling considerations, information bias, consistency of results, strength of association, biological plausibility, interpretation of nonsignificant results, interpretation of graphics, extrapolation to other populations, and summarizing results. Other interpretive considerations, such as adjustments to analyses for covariates and interactions, multiple testing, trends in results within a clinical area, and power limitations, are discussed in greater statistical detail in Chapter 7, Statistical Methods.

Study Design and Modeling Considerations

Biased results will be produced if the assumptions underlying any of the statistical models are violated. Six models are used in this report to analyze the health effects of herbicide exposure in Vietnam. The first model contrasts the exposed population (Ranch Hands) with an unexposed group (Comparisons). The second model evaluates the relationship between estimated serum dioxin levels from the time of exposure (i.e., initial dioxin) with each health endpoint. The group contrast model is extended in the third model so that the Ranch Hand group is divided into three categories depending on current and estimated initial levels of serum dioxin, and each category is contrasted with the Comparison group. The final three models evaluate the associations between current serum dioxin levels and each health endpoint. The following current dioxin measurements are used in models four through six: lipid-adjusted current dioxin, whole-weight current dioxin, and whole-weight current dioxin with adjustment in the model for total lipids respectively. The parameters of these six models are summarized in Table 1-1.

As in any epidemiologic study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis that both groups are equal, due to possible misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Current dioxin data indicate that 40 percent of the Ranch Hands have background serum dioxin levels (10 ppt or less). These Ranch Hands either were never exposed or their initially elevated serum dioxin levels may have decayed to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether or not Ranch Hands currently having background dioxin levels had elevated levels in the past.

The model analyzing the association of health endpoints with extrapolated initial dioxin levels also is vulnerable to bias, because it directly depends on two invalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life (7.1 years). If dioxin elimination is first-order, but some

Table 1-1.
Parameters of Exposure Assessment Models

Model	Cohort(s)	Subset of Cohort	Exposure Characterized By:	Covariates in Analysis (not including endpoint-specific covariates)
1	Ranch Hands and Comparisons	All participants	Group (Ranch Hands versus Comparisons and military occupation	--
2	Ranch Hands	Lipid-adjusted current dioxin measurement >10 ppt	Extrapolated initial dioxin	PBF at time of duty and PBF change
3	Ranch Hands and Comparisons	RH: Current dioxin measurement C: Lipid-adjusted current dioxin measurement ≤10 ppt	Group (Ranch Hands versus Comparisons); Ranch Hands categorized according to current and estimated initial dioxin levels	PBF at time of duty and PBF change
4	Ranch Hands	Current dioxin measurement	Lipid-adjusted current dioxin: (102.6*whole-weight current dioxin/total lipids)	--
5	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	--
6	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	Total lipids

Note: RH = Ranch Hands.
C = Comparisons.
"PBF at time of duty" = Percent body fat at the time of duty in SEA.
"PBF change" = Change in percent body fat from the time of duty in SEA to the date of dioxin draw.

Ranch Hands have a shorter half-life than others, then there would have been misclassification of initial dioxin exposure. If the clinical endpoint is not associated with a factor that affects the elimination rate (e.g., relative weight change), then estimates of the relative risk for common diseases associated with low and high levels of initial dioxin, in general, will be biased toward unity. However, if the clinical endpoint is associated with a factor that affects the elimination rate, then the relative risk will be biased away from unity.

The half-life of dioxin has been found to change significantly with percent body fat and age in the 337 Ranch Hands having paired dioxin measurements above 10 ppt; one derived from serum drawn in 1982 and the other from serum drawn in 1987 (9). Half-life increased significantly with higher levels of obesity and decreased significantly with weight gain and age. The constant 7.1 year half-life used in this report was derived from an earlier half-life study based on 36 subjects (6). The longer half-life estimate derived from 337 subjects was developed 3 years after the statistical plan for this report, too late for application to these data, because the statistical analyses summarized in this report had already begun. As a partial solution to the observed relationship of half-life to obesity and weight gain, analyses using estimated initial dioxin levels were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin (see Chapter 7, Statistical Methods).

The validity of the constant half-life assumption cannot be assessed until the half-life study is expanded to include dioxin measurements taken in 1992, giving three repeated dioxin measures for each of the Ranch Hands in the half-life study. These analyses are expected to be published in 1995. Dioxin measurements on multiple blood specimens taken from 20 males exposed during a factory explosion near Seveso, Italy (10), will be evaluated to further assess the first-order elimination assumption.

In order to account for the possible misclassification of exposure between groups, the third statistical model categorizes Ranch Hands into three levels of exposure: background levels of current dioxin, low levels of estimated initial dioxin, and high levels of estimated initial dioxin. Each Ranch Hand dioxin category is contrasted with Comparisons having background levels of current dioxin. Although this model is less dependent upon the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination assumptions are not valid. Also, the Ranch Hands with background levels of current serum dioxin (10 ppt or less) may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decayed to background levels. This will result in a bias towards the null hypothesis of no dioxin effect on the health endpoint.

In the analyses of this model in this report and in the Serum Dioxin Analysis of the 1987 Followup, a "checkmark pattern" has become prevalent. The checkmark pattern is defined as the occurrence of a lower percentage of abnormalities in the Ranch Hands with background dioxin levels than in background Comparisons, but a greater percentage of abnormalities in Ranch Hands with high levels of serum dioxin than in the Comparisons. A checkmark pattern is expected when there is a positive association between disease and dioxin in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This

circumstance could arise if there is a large degree of misclassification between the exposure groups (Ranch Hands and Comparisons) with regard to dioxin levels that conceal the difference between exposed and unexposed participants (11) (as may be the case with 40% of the Ranch Hands having background levels). As a corollary, the pattern is expected if body fat, but not dioxin, is associated with disease in Ranch Hands and the prevalence of disease in the two-exposure groups is nearly equal. This circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat (as is the case because the group means on body fat are nearly equal). A second corollary is that the checkmark pattern is expected when disease is associated with both dioxin and body fat in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This last circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat and dioxin (as is the case for the reasons described above).

The three models that analyze associations between current serum dioxin and health endpoints are less subject to bias than the previous models. However, current serum dioxin levels may not be good measures of exposure if serum dioxin elimination rates differ among individuals. Current serum dioxin levels also were extrapolated from 1992 measurements to 1987 for participants without current serum dioxin levels measured in 1987. Therefore, these current dioxin measurements are subject to the potential bias from the half-life and first-order elimination assumptions that also affect the initial dioxin estimates.

Information Bias

Information bias, represented by the over-reporting of disease symptoms, was minimized by verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands may be more verifiable because they may have been seen by physicians more often than Comparisons; this would be revealed by group differences in the quantity and content of medical records. Because there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, however, if it exists, would affect only estimates of health effects used in the models contrasting Ranch Hands and Comparisons because Comparison data were not used in models assessing associations between health effects and dioxin. Information bias due to errors in the data introduced through data entry or machine error is negligible. All laboratory results were subject to strict QC procedures, historical data were verified completely by medical record review, and medical data were subjected to strict QC standards (Chapter 6, Quality Control).

Consistency of Results

Adverse health effects in Ranch Hands attributable to herbicide or dioxin should be confirmed by internally and externally consistent findings. An internally consistent finding does not contradict other findings in the report, and an externally consistent finding has been previously established by other research. All statistically significant findings in this report were subjected to clinical review and were compared to published results from other research to identify consistent findings.

Strength of Association

Ideally, an adverse effect, if it exists, would be revealed by a strong association between categorized dioxin and a disease condition; that is, by a statistically significant relative risk greater than 2.0 for Ranch Hands with high categorized dioxin levels relative to the Comparisons (12). Statistically significant relative risks less than 2.0 are generally considered to be less important than larger risks because relative risks less than 2.0 can easily arise due to unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2.0 and 5.0 are epidemiologic guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as initial or current serum dioxin measurements).

Biological Plausibility

The assessment of biological plausibility requires consideration of the feasibility, in biological terms, of the exposure under study to produce the effect of interest. While a lack of biological credibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results are subjected to medical review and confirmation from previously published results in order to identify consistent and biologically plausible results.

Interpretation of Nonsignificant Results

In this study, a lack of significant results relating dioxin to a particular disease only means that the study is unable to detect a relationship between dioxin and health. This does not imply that a relationship may not exist, but that, if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relationship between dioxin and health. The AFHS was not designed to establish safety. Rather, this study was designed to determine whether a hazard existed for the exposed personnel. Determination of safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample-size criteria for proof of safety and hazard in studies of environmental and occupational exposures (13).

Graphics

Scatterplots of selected continuous health endpoints were included as aids to interpretation. The graphics alone are not sufficient to assess the relationship between dioxin and health. For example, a trend may be seen in a plot, but it could be statistically nonsignificant because the number of abnormalities is small. On the other hand, a statistically significant result can be clarified by the graphics, especially if the result depends on a few data points that appear far from the main cluster.

Extrapolation to Armed Forces Ground Troops

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is difficult because Ranch Hand and ground troop exposure situations were very different. Based on serum dioxin testing results done by CDC (7) and others (14), nearly all ground troops tested have current levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from levels in men who never left the United States (with mean dioxin levels of 4.2 ppt and 4.1 ppt respectively). The AFHS subgroup most like the ground troops in terms of current dioxin levels are Ranch Hands who currently have background levels of dioxin (10 ppt or less). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the "Background" Ranch Hand versus Comparison contrast. However, extrapolating the results of these analyses to Vietnam veterans still should be made cautiously. There may be demographic distinctions between the "Background" group of Ranch Hands and other Vietnam veterans that may be related to health. Also, if Ranch Hands with background levels of current serum dioxin showed a significant health detriment relative to Comparisons, but there was no significant detriment for Ranch Hands with high serum dioxin levels, the biological plausibility of such an effect would be questionable, because this would not indicate a dose-response effect. In general, the analyses in this report found that Ranch Hands with background levels of current serum dioxin did not show a significant health detriment relative to Comparisons. This was particularly true for the analyses that exhibited a statistically significant health detriment in Ranch Hands with high levels of current serum dioxin.

Summary of Results

A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful summary tabulation. Such summaries can be 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 (e.g., psychological scales and indices developed from combining multiple variables). In addition, such tabulations combine endpoints that are not comparable. For example, diminished sense of smell is of less medical importance than the presence of a malignant neoplasm. Nevertheless, the AFHS presents a summary of all statistical results (see Appendix Q-1). However, these summaries can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

CHAPTER 1
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CHAPTER 2

THE DIOXIN ASSAY

PARTICIPANTS SELECTED FOR DIOXIN MEASUREMENT

Participants at the 1992 physical examination eligible to have blood drawn for the dioxin assay were assigned to one of three categories: previous participants with a quantifiable dioxin result who were selected for an additional blood draw to advance pharmacokinetic studies (1), previous participants returning to the 1992 physical examination with no prior dioxin blood draw or no previously quantifiable dioxin results, and first-time participants. Table 2-1 shows the number of participants eligible for the 1992 dioxin blood draw belonging to each category by exposure group (Ranch Hand, Comparison). Table 2-1 also gives the number of actual dioxin assay results observed by participant category and exposure group.

A total of 835 participants in the 1992 examination were invited for the blood draw. Blood samples from 62 participants were unavailable for analysis at Centers for Disease Control (CDC). Table 2-2 displays the reasons for this reduction. Five participants not meeting eligibility criteria had blood drawn inadvertently. Sixteen participants were medically deferred, 34 refused, 2 had unsuccessful blood collection, 2 eligible participants were inadvertently omitted, and 3 participants were excluded when their unit bags broke during processing. Samples for the remaining 773 participants were shipped to CDC.

SAMPLE ACQUISITION

Blood was drawn from volunteers for the serum dioxin assay on the morning of the second day of the 1992 physical examination cycle. The participants fasted after midnight (water was allowed); samples were drawn with a 15-gauge needle into a blood pack unit without anticoagulant. The blood pack units had been previously tested by CDC and found to be free of dioxin contamination. Participants selected for the immunology studies had 250 ml of blood drawn; all others had 350 ml of blood drawn. After the drawing, the bags were clamped, labeled, placed upright at room temperature, and the samples allowed to clot for 7 hours.

The clotted samples were centrifuged for 15 minutes at 4,500 RPM at a temperature of 4°C to 10°C. The serum was then transferred from the spun unit bag to transfer packs (also dioxin-free) by a plasma extractor. The transfer packs then were spun for 15 minutes at 4,500 RPM. The serum was then placed into four Wheaton bottles: two 4-ounce bottles for the serum dioxin analysis, a 5 ml bottle for the lipid profile, and a 10 ml bottle for reserve serum. Samples were cataloged and stored at -20°C or less until shipment. Appendix A-1 contains the detailed procedures used by the Scripps Clinic and Research Foundation (SCRF) for the dioxin blood collection and processing. Frozen samples were packed in dry ice in styrofoam boxes and shipped twice weekly from SCRF, La Jolla, California, to Brooks Air Force Base, Texas. At Brooks Air Force Base, inventory was taken and the specimens were stored at -70°C until shipment to CDC. All samples were coded so that the group status of each specimen (Ranch Hand, Comparison) was unknown to the CDC staff.

Table 2-1.
Participants Eligible for the 1992 Dioxin Blood Draw

Participant Category	Number Eligible			Number Results		
	RH	C	Total	RH	C	Total
Returning participants with previous quantifiable dioxin result selected for another blood draw	341	47	388	329	44	373
Returning participants with no previous dioxin blood draw or no previous quantifiable dioxin result	103	211	314	91	194	285
Participants new to study	38	90	128	35	80	115
Total	482	348	830	455	318	773

RH = Ranch Hand.
C = Comparison.

Table 2-2.
Participants Invited for the 1992 Dioxin Blood Draw and Reasons for Participant Sample Exclusions

Distribution of Sample Exclusion	Ranch Hand	Comparison	Total
Total Invited	483	352	835
Less:			
• Inadvertent Additional Draws (Did not meet Eligibility Criteria)	(1)	(4)	(5)
Total Selected for Blood Draw	482	348	830
Less:			
• Medically Deferred	(8)	(8)	(16)
• Refused	(16)	(18)	(34)
• Attempted, Unsuccessful	(1)	(1)	(2)
• Inadvertent Omissions	(1)	(1)	(2)
• Bag Broke	(1)	(2)	(3)
Total Specimens Sent to CDC	455	318	773

ANALYTICAL METHOD

The serum samples were analyzed for dioxin in groupings consisting of a method blank, three unknown samples, and a quality control (QC) pool sample (2,3). Cholesterol esters, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined in duplicate by standard methods. Total phospholipids were determined in duplicate by modifying the Folch et al. procedure (4,5). Fresh cholesterol was determined in duplicate by an enzymatic method (6). For each analysis, the mean result of duplicate analyses was used to calculate the concentrations of total lipids using the summation method (7), low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol (8).

QUALITY CONTROL

Quality assurance (QA) was maintained with matrix-based materials well-characterized for dioxin concentration and isotope ratios to ensure that the analytical system was in control. QC charts were maintained for each of these materials (five serum pools). The concentration in the QC sample from each analytical run was required to be within established 99-percent confidence limits (9,10). The unlabeled and carbon-13 labeled internal standard isotope ratios were required to be within 95-percent confidence limits. All analytical runs for the dioxin and lipid measurements were in control. No dioxin was detected in the blanks (on-column injection of 100 femtograms from a standard solution produces detectable signals greater than three times the background noise).

DATA DESCRIPTION

CDC delivered whole-weight and lipid-adjusted dioxin concentrations to the Air Force, together with the total sample weight, weights of lipid fractions, total lipid weight, detection limit, quantitation limit, and all associated QC information, including results from blank samples. The lipid-adjusted dioxin concentration is a calculated quantity based on the whole-weight dioxin concentration and the total lipid weight. Details of the calculation are discussed subsequently in this chapter.

The analyses in this report are based in part on 522 of the total 773 assay results. These 522 results were available at the commencement of the statistical analyses, and the additional 251 dioxin assay results were received after the statistical analysis began. Table 2-3 provides the results of the 1992 physical examination blood draws by exposure group and result comment (i.e., the notes on dioxin result). This table is divided into two descriptive sections: the 522 results used in the analyses in this report and the 251 assay results received after the commencement of the statistical analyses. The third section of the table provides totals. Additional statistics on these 251 assay results are given later in this chapter.

The dioxin data base is a combination of the dioxin assay results from the 1987 and 1992 examination. Figure 2-1 shows the number of dioxin blood draw results by year, and exemplifies the high percentage of study participants who have dioxin measurements. Of the 2,233 fully compliant participants, 1,970 (88.2%) had blood drawn in 1987; 545 of these 1,970 participants who had blood drawn in 1987 also had blood drawn in 1992. Figure 2-2

Table 2-3.
Result Comments for 1992 Blood Draw Assays

Result Comment	Ranch Hand	Comparison	Total
	Assays Available Before the Commencement of the Statistical Analysis (n=522)		
G	366	92	458
GND	3	15	18
GNQ	2	2	4
NR	32	10	42
Total	403	119	522
	Assays Available After the Commencement of the Statistical Analysis (n=251)		
G	46	149	195
GND	5	31	36
GNQ	1	13	14
NR	0	6	6
Total	52	199	251
	Total of 1992 Blood Draw Assays (n=773)		
G	412	241	653
GND	8	46	54
GNQ	3	15	18
NR	32	16	48
Total	455	318	773

G = Good result.
GND = Good result, below limit of detection.
GNQ = Good result, below limit of quantitation.
NR = No result.

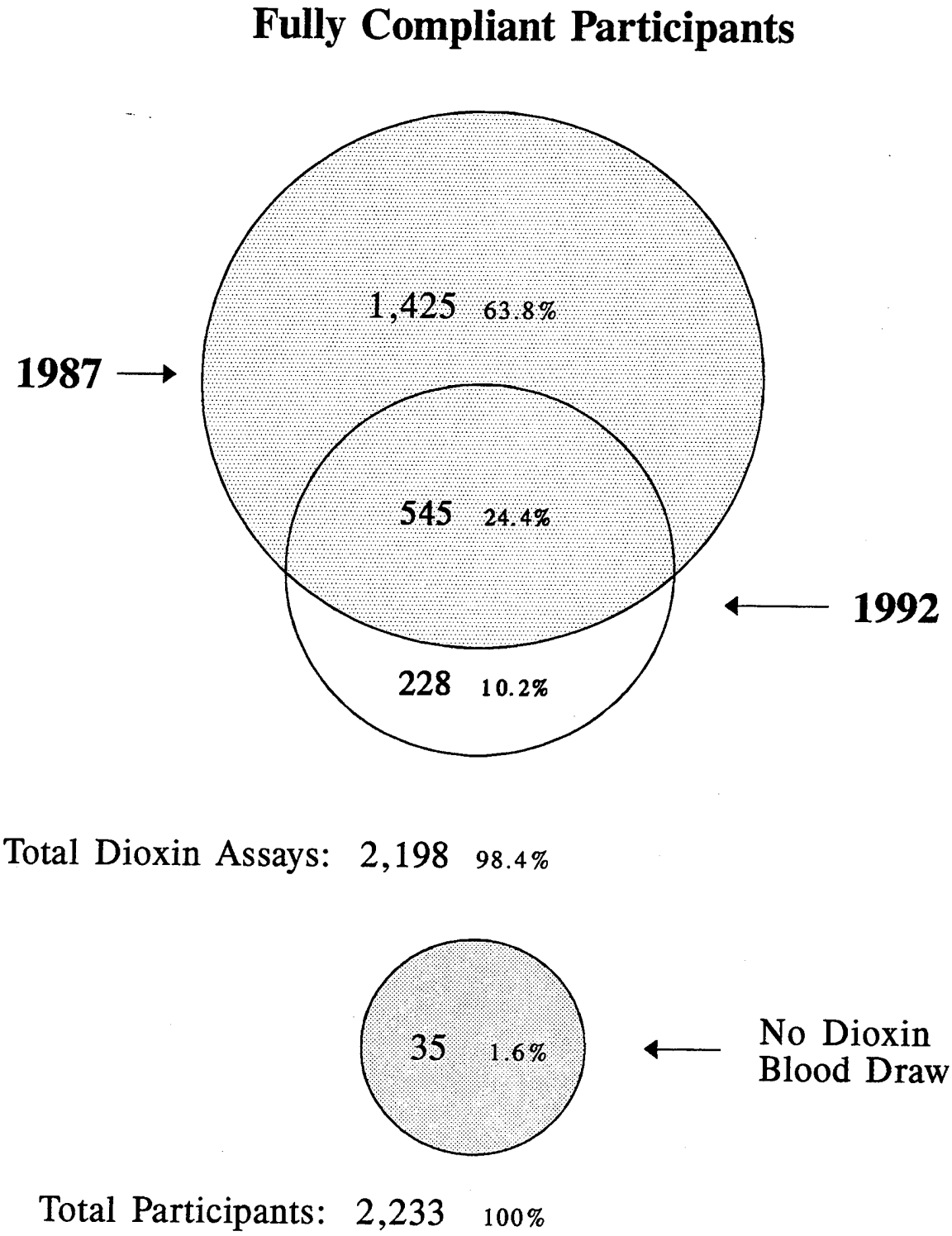


Figure 2-1. Dioxin Results for 2,233 Fully Compliant Participants at the 1992 Physical Examination

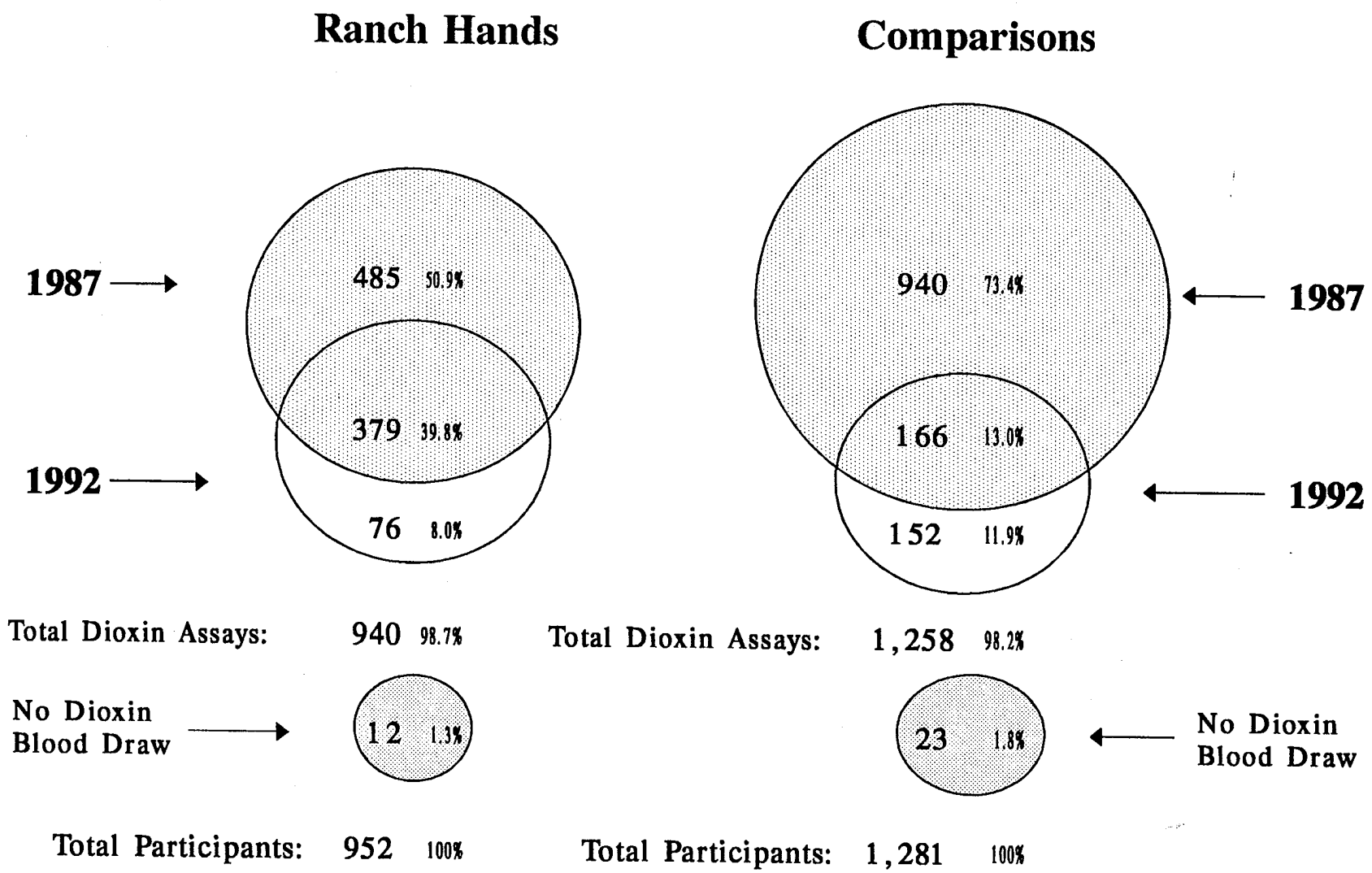


Figure 2-2. Dioxin Results for 952 Fully Compliant Ranch Hands and 1,281 Fully Compliant Comparisons at the 1992 Physical Examination

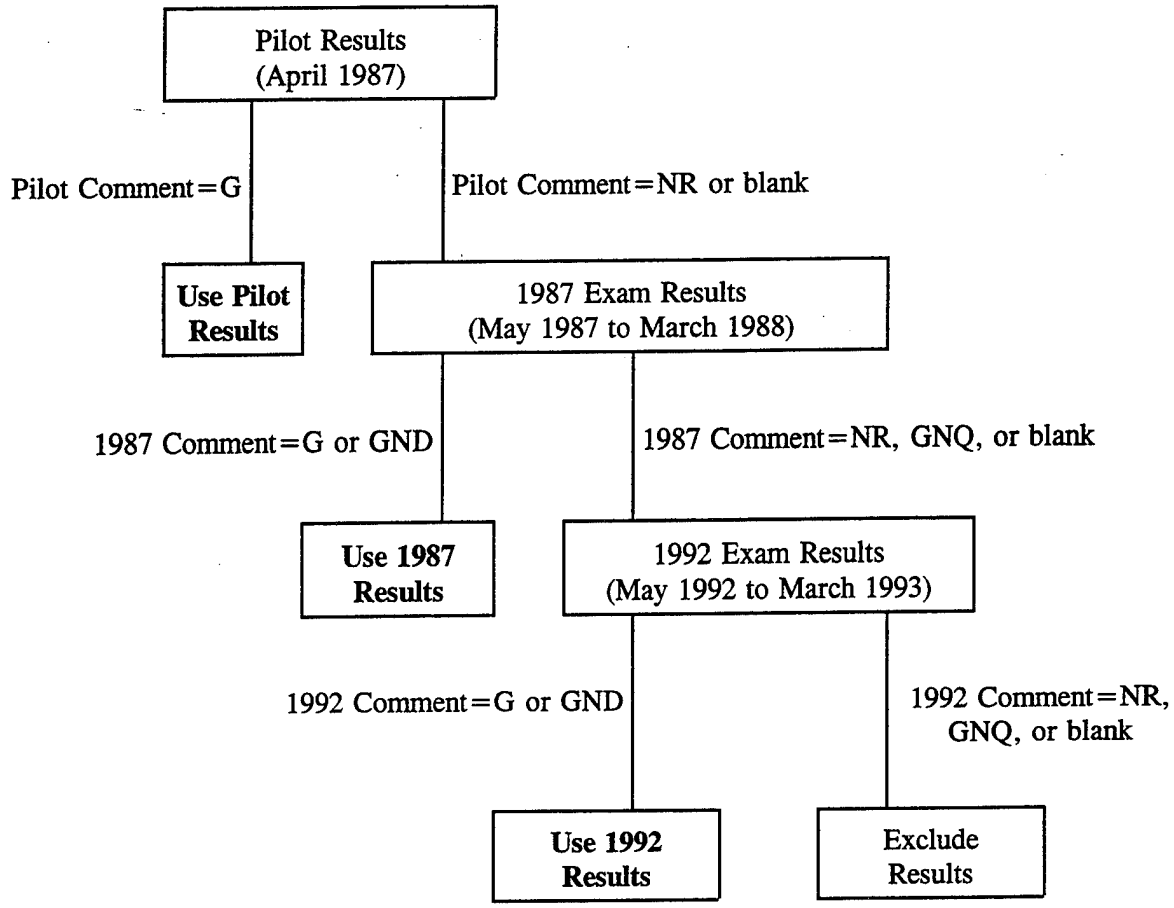
shows the number of dioxin blood draws by both year and exposure group. Almost 70 percent of those participants assayed twice were Ranch Hands (379 out of 545).

Participants may have been assayed for any combination of three events: the pilot study conducted in April 1987 (9), the 1987 followup examination (May 1987 to March 1988), or the 1992 followup examination (May 1992 to March 1993). The majority of participants had an assay in 1987, either in conjunction with the pilot study or the 1987 followup examination. Consequently, 1987 was designated as the reference point for current dioxin assays. When a participant had multiple assay results, first priority was given to the 1987 pilot-study dioxin results, second priority was given to results derived from serum collected at the 1987 physical examination, and third priority was given to the 1992 results. Figure 2-3 outlines this decision process. If a quantifiable pilot-study assay was available, it was used. Otherwise, a 1987 assay (if available and quantifiable) or a 1992 measurement was used. For use in models based on current dioxin, if the 1992 measurement was used (n=83 for samples used for the statistical analyses), the level was extrapolated to 1987 levels when the 1992 dioxin concentration surpassed 10 ppt (n=34). These extrapolated lipid-adjusted dioxin values were calculated using a first-order decay model with a half-life of 7.1 years and a background level of 4 ppt. Levels at or below 10 ppt were not extrapolated because the first-order decay model was not considered to be valid at background levels (lipid-adjusted current dioxin levels $\leq$10 ppt). Details on the extrapolation method are given in Chapter 7, Statistical Methods.

Of the 2,233 fully compliant participants at the 1992 physical examination, 952 were Ranch Hands and 1,281 were Comparisons. Of the 2,233 participants, 35 never had blood drawn for a dioxin assay (see Figure 2-1). Forty-four participants had missing dioxin results (result comment=NR) or nonquantifiable dioxin results (result comment=GNQ). A total of 2,154 participants, consisting of 930 Ranch Hands and 1,224 Comparisons, had quantifiable dioxin measurements. Of these 2,154 participants, 1,980 were available at the commencement of the statistical analyses (894 Ranch Hands and 1,086 Comparisons). The remaining 174 assays (36 Ranch Hands and 138 Comparisons) were received after the start of the statistical analysis. Table 2-4 summarizes the sample-size reduction by exposure group and further classifies the 2,154 participants according to their availability for statistical analysis. Participants with missing or nonquantifiable dioxin results are cross-classified in Table 2-5 by result comment and exposure group.

Lipid-Adjusted and Whole-Weight Current Dioxin Measurements

Serum dioxin is defined as the serum concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Its relationship with dioxin concentrations in other compartments, such as adipose tissue, is a subject of continuing research. Serum dioxin, as analyzed in this report, can be expressed as a lipid-adjusted or a whole-weight measurement. The lipid-adjusted dioxin measurement, also called "current dioxin body burden," is a derived quantity calculated from the formula ppt = ppq·102.6/W, where ppt is the lipid-adjusted concentration, ppq is the actual weight of dioxin in the sample (also known as whole-weight dioxin) in femtograms, 102.6 corrects for the average density of serum, and W is the total lipid weight of the sample (10). The correlation between the serum lipid-adjusted concentration and adipose tissue lipid-adjusted concentration of dioxin has been observed to be 0.98 in 50 persons from Missouri (11). Using the same data, Patterson et al. calculated the



G = Good result.
GND = Good result, below limit of detection.
GNQ = Good result, below limit of quantification.
NR = No result.

Figure 2-3. Decision Process for Determination of Dioxin Results for Analysis

Table 2-4.
Dioxin Blood Draw Results

Summary of Sample-Size Reduction and Participant Availability	Ranch Hand	Comparison	Total
Fully Compliant to 1992 Physical Examination	952	1,281	2,233
Less: No Blood Draw for Dioxin at any Physical Examination	(12)	(23)	(35)
Participants Fully Compliant to 1992 Physical Examination with a Dioxin Assay	940	1,258	2,198
Less: Missing or Nonquantifiable Results (Good result, but below limit of quantitation or No Result)	(10)	(34)	(44)
Participants with Quantifiable Dioxin Results	930	1,224	2,154
Available Before the Commencement of the Statistical Analysis	894	1,086	1,980
Available After the Commencement of the Statistical Analysis	36	138	174

Table 2-5.
Dioxin Blood Draw Results with Missing or Nonquantifiable Results

Result Comment				
1987 Assay	1992 Assay	Ranch Hand	Comparison	Total
	GNQ	1	7	8
	NR	4	4	8
GNQ		1	2	3
GNQ	GNQ	1	7	8
GNQ	NR	0	7	7
NR		2	2	4
NR	GNQ	0	1	1
NR	NR	1	4	5
	Total	10	34	44

GNQ = Good result, below level of quantification.
NR = No result.

partitioning ratio of dioxin between adipose tissue and serum on a lipid-adjusted basis as 1.09 (95% C.I. = [0.97, 1.21]). On the basis of these data, a one-to-one partitioning ratio of dioxin between lipids in adipose tissue and lipids in serum cannot be excluded. Measurements of dioxin in adipose tissue generally have been accepted as representing the body-burden concentration of dioxin. The high correlation between serum dioxin levels and adipose-tissue dioxin levels in their study suggests that serum dioxin is also a valid measurement of dioxin body burden.

Figures 2-4 and 2-5 show the distribution of serum lipid-adjusted current dioxin for the 894 Ranch Hands and 1,086 Comparisons whose results were used in analyses of current dioxin versus health in this report. The 95th, 98th, and 99th percentiles of serum lipid-adjusted current dioxin distribution for Ranch Hands were 101.7, 156.2, and 200.5 ppt respectively; percentiles for the corresponding Comparisons were 8.5, 10.2, and 13.5 ppt. Figure 2-6 compares distributions of the logarithm (base 2) of serum lipid-adjusted dioxin concentrations for Ranch Hands and Comparisons.

Table 2-6 summarizes, by military occupation and exposure group, the serum lipid-adjusted dioxin results among the 894 Ranch Hands and 1,086 Comparisons whose results were used in analyses of dioxin versus health in this report. Serum whole-weight dioxin results are presented in Table 2-7.

Dioxin Results Provided After the Commencement of the Statistical Analyses

CDC provided the remaining 251 dioxin results after the commencement of the statistical analyses (see Table 2-3). Of these 251 additional results, 52 belonged to Ranch Hands and 199 belonged to Comparisons. Of the 52 additional Ranch Hand results, 51 were quantifiable (result comment=G or GND) and one was nonquantifiable (result comment= GNQ). The median current dioxin level for these 51 Ranch Hands was 5.1 ppt. Ranch Hand dioxin levels ranged between 0 ppt and 110.7 ppt; the first and third quartiles were 3.2 ppt and 8.8 ppt. All 51 quantifiable results fell between the minimum and maximum observed for the 894 Ranch Hands whose data were used in this report. Of the 199 additional Comparison results, 180 were quantifiable (result comment=G or GND) and 19 were nonquantifiable (13 had a result comment of GNQ, and 6 had a result comment of NR). For the 180 quantifiable Comparison results, the median was 3.1 ppt, the range was between 0 ppt and 13.8 ppt, and the first and third quartiles were 2.1 ppt and 4.7 ppt. All 180 quantifiable results fell between the minimum and maximum observed for the 1,086 Comparison results used in this report.

Of the 51 additional quantifiable Ranch Hand results, 15 belonged to Ranch Hands who had a previous quantifiable 1987 dioxin result. Similarly, of the 180 additional quantifiable Comparison results, 42 belonged to Comparisons who had a previous quantifiable dioxin result; these additional results are included in Tables 2-6 and 2-7. Inclusion of the 15 Ranch Hand and 42 Comparison 1992 assay results (had they been received before the commencement of the statistical analysis) would not alter the analysis because, when a participant had multiple assays, priority was given to 1987 results. The remaining 174 (36 Ranch Hand and 138 Comparison) quantifiable results were not included in analyses of dioxin versus health in this report; these individuals were included in the overall group contrasts (Ranch Hand versus

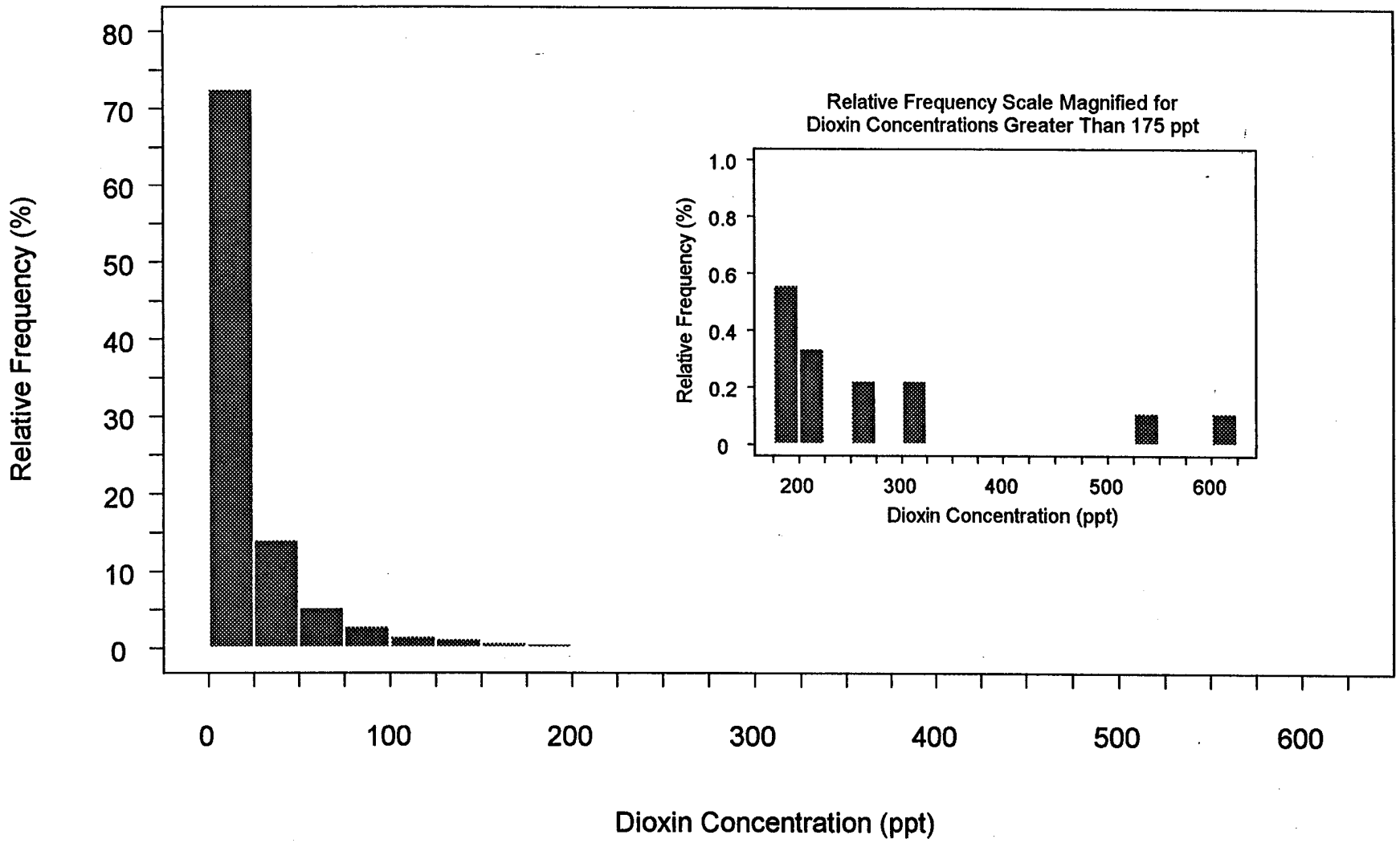


Figure 2-4. Relative Frequency Distribution of Lipid-Adjusted Dioxin Concentrations for 894 Ranch Hands

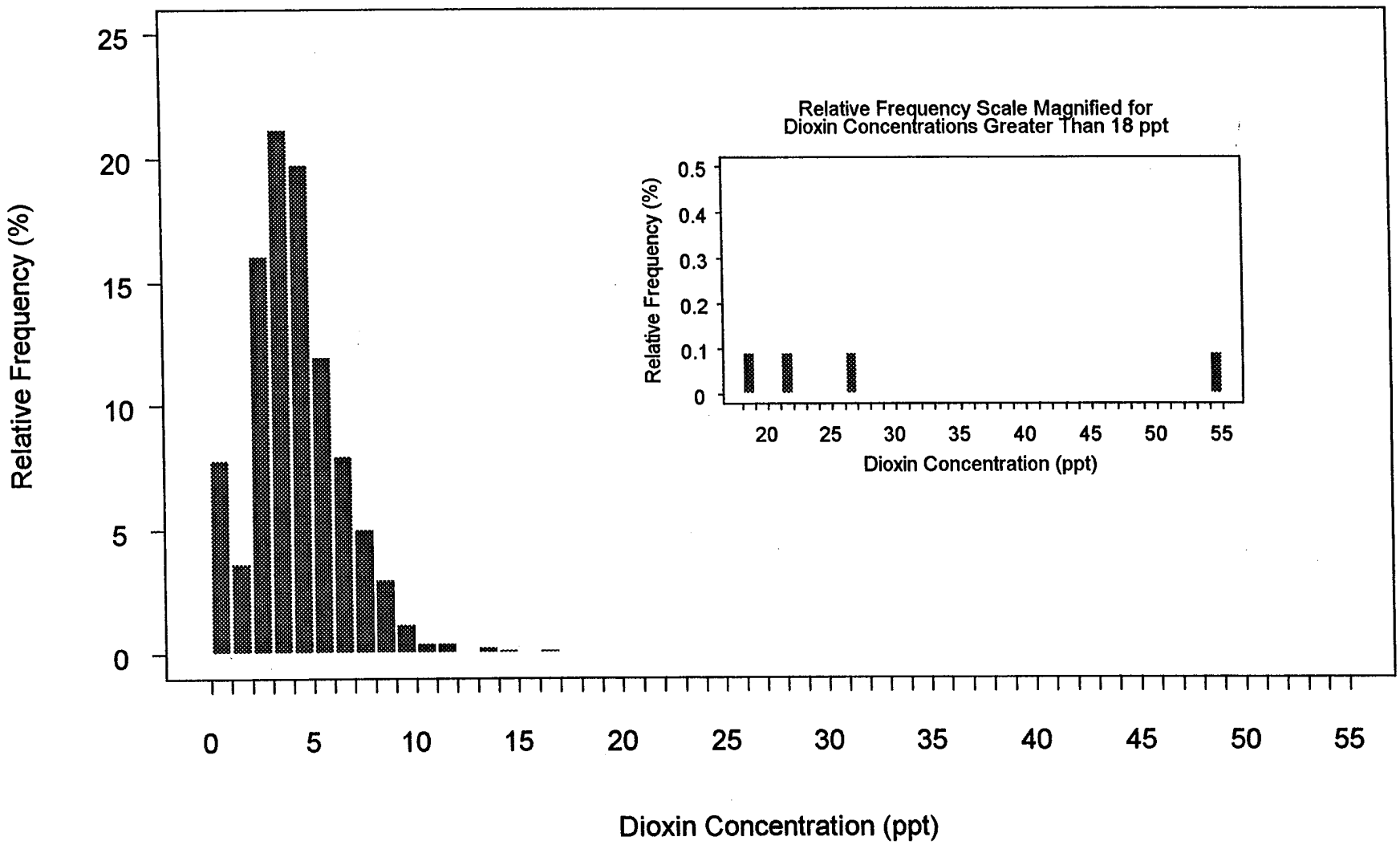


Figure 2-5. Relative Frequency Distribution of Lipid-Adjusted Dioxin Concentrations for 1,086 Comparisons

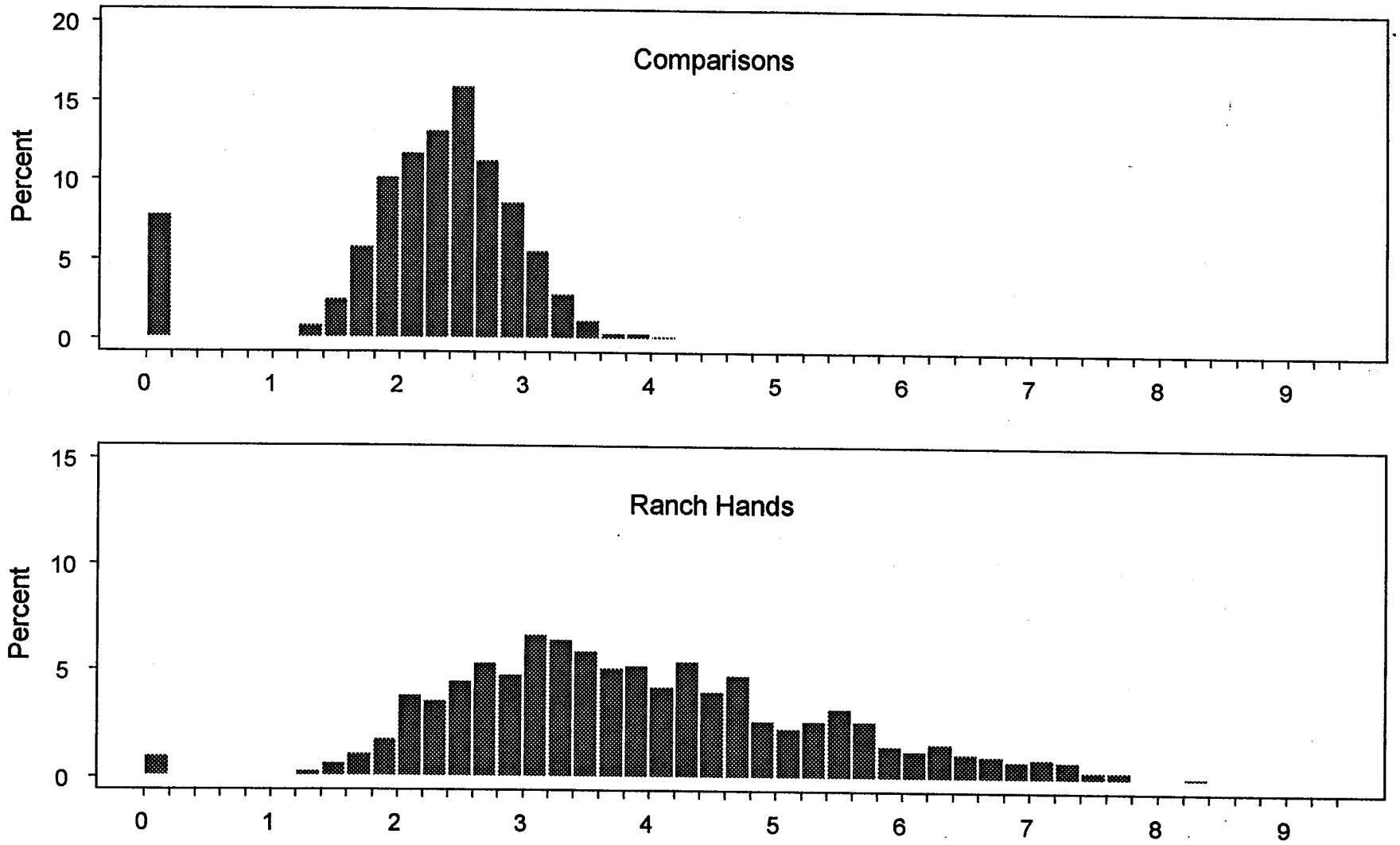


Figure 2-6. Relative Frequency Distribution of the Logarithm (Base 2) of Lipid-Adjusted Dioxin Concentrations

Table 2-6.
Lipid-Adjusted Dioxin Result Summary of 894 Ranch Hands and 1,086 Comparisons Used in the Statistical Analysis

	Ranch Hand			Comparison		
Military Occupation	n	Median	Range	n	Median	Range
Officer	348	7.7	0-36.0	420	4.4	0-18.5
Enlisted Flyer	150	17.8	0-195.5	174	4.0	0-12.8
Enlisted Groundcrew	396	24.1	0-617.8	492	4.0	0-54.8
Total	894	12.5	0-617.8	1,086	4.1	0-54.8

Table 2-7.
Whole-Weight Dioxin Result Summary of 894 Ranch Hands and 1,086 Comparisons Used in the Statistical Analysis

	Ranch Hand			Comparison		
Military Occupation	n	Median	Range	n	Median	Range
Officer	348	45.0	0-332.0	420	25.0	0-158
Enlisted Flyer	150	98.4	0-1,537.8	174	25.3	0-181
Enlisted Groundcrew	396	148.0	0-5,433.0	492	22.0	0-318
Total	894	74.8	0-5,433.0	1,086	24.0	0-318

Comparison), however. Additional analyses of malignant systemic cancer and serum insulin were subsequently performed with the inclusion of the 174 dioxin results, to determine whether the inclusion of these dioxin results would alter the conclusions. Appendix A-2 contains the results of the additional analyses.

SUMMARY

In summary, 91 percent of the 1,281 fully compliant Comparisons and 96 percent of the 952 fully compliant Ranch Hands at the 1992 physical examination had dioxin assay results. Eighty-five percent of the 1,281 Comparisons and 94 percent of the 952 Ranch Hands had quantifiable results used in the statistical analyses in this report. Additional dioxin results became available after the commencement of the statistical analyses. These additional data were incorporated into several analyses, documented in Appendix A-2, which had little effect on the analysis results provided in this report.

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CHAPTER 3

QUESTIONNAIRE METHODOLOGY

This chapter describes the development and implementation of the two participant questionnaires used in the 1992 followup to the Air Force Health Study (AFHS): the 1992 Interval Questionnaire and the 1982 Baseline Questionnaire.

The 1992 participant Interval Questionnaire was designed to capture the participant's health history in the interval since participation in previous followups. Data collection was comparable to the Baseline and to the 1985 and 1987 followup efforts—the questionnaire was similar and administered using the same face-to-face methodology to almost the same population. In the 1982 Baseline study, interviews were conducted in the participants' homes; in 1985, 1987, and 1992 studies, the followup interviews were conducted at the physical examination site. The latter method was more efficient and subject to better quality control (QC).

Since some study subjects did not participate in the 1982, 1985, and 1987 studies, and other participants were new to the study, the same Baseline Questionnaire used during the Baseline examination was administered to these new participants. The National Opinion Research Center (NORC), a social science research center at the University of Chicago, developed and administered the questionnaire and scheduled participants.

QUESTIONNAIRE DEVELOPMENT

The goal of 1992 questionnaire development was to maintain, to the maximum extent possible, the question wordings, context, and procedures used in the 1982 Baseline study and the 1985 and 1987 followup studies, and to obtain data on new areas of inquiry added to the study for 1992. The central task of questionnaire development was to obtain interval histories on questionnaire items to update the information provided in previous followups (i.e., if the study subject participated in the 1987 followup, the 1992 Interval Questionnaire captured interval histories for the period 1987 to 1992. If the subject last participated in the Baseline study or the 1985 followup, the 1992 Interval Questionnaire captured interval histories from those dates until 1992).

The 1982 Baseline Questionnaire captured information on demographics, education, occupation, medical history, study compliance, toxic exposures, and reproductive history. In general, histories and one-time questions (where the response does not change over time) were obtained in the Baseline Questionnaire, which is completed for each participant the first time he participates in the study. For the 1985 followup, new questions on risk factors for skin cancer and personality type were added to the Interval Questionnaire. In addition, enhancements were made to the data collection procedures for birth defects and drinking habits, and questions were added to capture a more detailed smoking history.

In general, the 1987 Interval Questionnaire built on the changes made in the 1985 Interval Questionnaire, and was expanded to include a detailed drinking history and sleep

disorder questions. Since some of the study subjects did not participate in the 1985 followup, the 1987 Interval Questionnaire was structured to capture one-time questions added in 1985, such as ethnic background and smoking history, for "rejoining" participants (i.e., those who completed a previous questionnaire but did not participate in all cycles). All participants were asked questions to update their histories from previous interviews.

The 1992 Interval Questionnaire contained all of the questions in the 1987 Interval Questionnaire, and was further expanded to collect the following information:

- Whether the participant was ever occupationally exposed to heavy metals and vibrating power tools
- Family health history (with particular reference to diabetes, heart trouble, and heart disease)
- Whether the participant was ever diagnosed with diabetes and, if so, type, treatment received, and medications taken
- Whether the participant was ever vaccinated for Hepatitis B
- Intermittent claudication and vascular insufficiency
- The participant's normal level of physical activity.

These new questions for the 1992 followup were grouped in a separate booklet titled "Interval Supplementary Recording Booklet." In addition, participants completed a Diet Assessment Questionnaire developed by Walter Willett at Harvard University (1). The results of this questionnaire were used to evaluate participants' diet patterns and caloric intake.

A copy of the 1992 Study Subject Health Interval Questionnaire, including the Interval Supplementary Recording Booklet and the Diet Assessment Questionnaire, is provided in Appendix B. The 1992 Interval Questionnaire is the latest in the series of longitudinal AFHS questionnaires.

A longitudinal questionnaire is dependent on the respondent's ability to remember events and to place those events in time. Even when given a precise starting date, respondents frequently repeat information given earlier, neglect to report new information because they thought they had previously reported it, and otherwise misplace events in time or forget them completely. The best means of preventing such errors is through the use of "bounded recall," in which the respondent is reminded of information that he has already reported and asked to provide new information. Information sheets containing computer-generated summaries of key respondent answers given in previous interviews (either in the Baseline, or 1985 or 1987 followups) were used to provide bounded recall for participants. Among the data elements included were: date of birth, highest educational degree, military status at the last interview, marital status at the last interview, name of spouse or partner at the last interview, and a cumulative list of all children reported during previous interviews. To

ensure that the questionnaire provided accurate results, 10 men participated in a pretest examination, which had successful results.

INTERVIEWER TRAINING

In April 1992, NORC's field management and the Chicago office staff recruited and trained 11 interviewers to administer the Interval Questionnaires. Four of the interviewers had administered Interval Questionnaires previously in the 1987 followup. The onsite NORC staff were not informed of the exposure status of any study participant either before or after questionnaire completion. The site supervisor reported to the NORC Project Manager in Chicago at least once a week, and the Project Manager made quarterly visits to the site. The site supervisor observed at least one interview per interviewer each quarter, and either the supervisor or NORC's site editor reviewed and edited all questionnaires for completeness.

Three of the site interviewers were trained by the site supervisor to administer the Baseline Questionnaire to new participants. Two of those interviewers had administered the Baseline Questionnaire previously during the 1987 followup. Completed Baseline Questionnaires also were reviewed and edited for completeness by the site supervisor or site editor.

DATA COLLECTION

Upon arrival at the Scripps Clinic and Research Foundation (SCRF), the participant received a schedule including the time and place for the 1992 Interval interview (and, if appropriate, the Baseline interview), and an interviewer was assigned. In all of the personal interviews conducted for the AFHS, interviewers were required to ask questions exactly as written, were not allowed to interpret questions or inject personal commentary, and were not allowed to skip between sections of the questionnaire. They were also instructed to probe "don't know" answers at least once. During the interview, participants signed medical record release forms; if a participant did not have all of the information with him to complete the form during the interview, or if the medical records pertained to his now-adult children and required their signature, he was given blank forms and instructions to take home with him for return to the Air Force when completed.

CHAPTER 3
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CHAPTER 4

PHYSICAL EXAMINATION METHODOLOGY

The 1992 followup examination was provided to 2,233 invited and scheduled participants, who traveled to the examination site in La Jolla, California. The examination consisted of the following major elements:

- Review-of-systems questionnaire
- Psychological testing
- Physical examination
- Laboratory testing
- Specialized testing (e.g., phlebotomy for measurement of serum dioxin)
- Psychological and medical outbriefings.

The Combat Experience Questionnaire and skin, hair, and eye color determinations (components of the 1985 followup examination) were conducted for all participants who did not attend the 1985 or 1987 followup.

The Air Force carefully prescribed the details of the above examination elements. Clinical variations were neither desired nor authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical and contractual personnel prior to the start of the examinations. An important objective of the entire physical examination process was to ensure that bias was not created by any procedural change, and this objective was carried out successfully. The requirement to maintain blind examinations was particularly stringent. The clinical staff was prohibited from knowing or seeking information as to the group identity (i.e., Ranch Hand, Comparison) of any participant. At the end of the examination, each participant was asked to note on the critique form whether such information was sought by any member of the clinical or paramedical staff. Three participants indicated that an examining physician had asked them about specific duties in Southeast Asia (SEA); two of these participants later stated that they had not been questioned but rather had volunteered information in casual conversation. The third participant could not be identified because he chose to remain anonymous.

EXAMINATION CONTENT

Examination content, as designed by the Air Force, emphasized detection of medical endpoints suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In 1985, the Air Force used findings of the Baseline examination to direct refinement of the 1985 followup examination. Since the 1987 followup examination was initiated prior to the full analysis of the data from the 1985 examination, most modifications to the examination format and procedures were founded upon quality control (QC) issues and the desire to make the clinical content of the examination more responsive to the medical needs of the participants.

Based on the results of the 1987 followup examinations, the 1992 examination content was expanded to include additional testing for glucose-intolerant participants. Other additions to the examination content used updated medical testing equipment and procedures such as vibrotactile threshold, Doppler pulses, and testicular ultrasound. The general content of the 1992 physical examination and psychological test battery is shown in Table 4-1. The complete laboratory test series is displayed in Table 4-2.

As in the Baseline and the 1985 and 1987 studies, QC requirements for both laboratory testing and clinical procedures were extensive. Although details are provided in Chapter 6, the following categories summarize the extent of the emphasis on quality. For laboratory testing, single reagent lots and control standards were used when practical, duplicate specimens were routinely and blindly retested, testing overlaps were mandatory when test reagent lots were changed, and fast initial response cumulative sum (FIR CUSUM) were used to rapidly detect any subtle drift in test results over time. The Scripps Clinic and Research Foundation (SCRF) clinical team was carefully instructed to assure clinical quality. Quality control included the following elements:

- The examination process was pretested.
- Detailed clinical inspection techniques were employed by SCRF, Science Applications International Corporation (SAIC), and Air Force physicians and personnel.
- Preprinted mark-sense examination forms were used.
- Clinical quality assurance (QA) meetings were conducted to detect and correct problems.
- The examiners were unaware of the exposure status of the participants.

Based on the 1985 followup, clinical QC enhancements were made to improve measurement techniques in the 1987 followup and continued in the 1992 followup. The digit preference noted in systolic and diastolic blood pressure readings in the 1985 followup led to the use of automated blood pressure recording; all other parameters of the blood pressure readings (e.g., sitting position, three recordings, nondominant arm at heart level) were not changed. The 1987 skin-test-reading QC plan was continued. That plan included the following elements:

- Refresher training for readers.
- A reading of the four skin tests of all participants by both readers, each blind to the results of the other.
- Ten percent of all tests were reread by each of the readers, each blind to the previous reading.

Table 4-1.
Elements of the 1992 Followup Physical Examination

Elements	Remarks
General Physical Examination	Internist
Neurological Examination	Neurologist
Dermatologic Examination	Dermatologist
Electrocardiogram	Resting, 4-Hour Fasting and Nicotine Abstinence
Chest X-Ray, KUB, Testicular Ultrasound	Radiologist
Immunologic Studies	40% Random Sample
Skin Test Studies	80% Sample
Psychological Evaluation:	
Millon Clinical Multiaxial Inventory (MCMI)	
Symptom Checklist 90-Revised (SCL-90-R)	
Jenkins	
Pulmonary Function	Internist with Subspecialty in Pulmonary Disease
Audiometry Examination	Audiologist
Vision Screening and Tonometry	Technician
Patient Outbriefing and Discussion of Individual Results	Internist, Medical Diagnostician, and Ph.D. Psychologist
Vibrotactile Threshold	Technician
Doppler	Technician

Table 4-2.
Laboratory Test Procedures of the 1992 Followup Physical Examination

Day 1 Tests: Monday and Wednesday	
Sedimentation Rate	Alkaline Phosphatase
Prothrombin Time	Direct Bilirubin
Protein Profile	Total Bilirubin
Complete Blood Count (includes RBC indices)	High Resolution Electrophoresis
Creatinine	LDH
Creatine Phosphokinase	Glycated Hemoglobin
Urinalysis (including urobilinogen)	Hepatitis Panel*
Cholesterol	High-Density Lipoprotein Cholesterol
T-Cell Clones**	Triglycerides
Immunofixation***	Serum Amylase
Rapid Plasma Reagin	Stool Hemoccult
Lupus Panel (includes anti-thyroid antibodies)	Prostate-Specific Antigen
Flow Cytometry**	2-Hour Urinary Postprandial Glucose
Rheumatoid Factor	Glucagon
AST	Insulin
ALT	2-Hour Postprandial Glucose
GGT	Proinsulin****
Fasting Glucose	C-Peptide****
	Islet Cell Antibodies****

Day 2 Tests: Tuesday and Thursday	
Serum ACTH	Total Testosterone
Free Testosterone	Estradiol
Follicle Stimulating Hormone	Serum Luteinizing Hormone
Thyroid Stimulating Hormone	T_4
Sex Hormone Binding Globulin	Blood Draw for Dioxin*****

* Testing to be performed by Air Force.
** Participants scheduled for special immunology testing.
*** An immunochemical method for identifying monoclonal proteins in serum.
**** Testing to be performed only on known or newly diagnosed diabetics. Individuals with a 2-hour post-prandial glucose > 140 mg/dl are considered newly diagnosed.
***** Participants scheduled for dioxin testing by CDC.

- A weekly report citing numbers and proportions of participants with possible anergy, reversal of induration-erythema measurements, and untoward skin reactions or other reading problems (e.g., participant refusal).

In addition, skin test forms developed for the 1987 followup were used to facilitate accurate recording and transcription. Specific clinical criteria were formulated to require consultation with an allergist, and the skin test measurement criterion for possible anergy, consistent with current World Health Organization (WHO) guidelines, was adopted for the clinical interpretation of all skin test readings.

To encourage participation in future followup studies, participant rapport-building techniques were added in 1985; these included participant critique forms and recreational opportunities afforded to any accompanying family members. These were continued for the 1992 followup, and additional aspects, such as unscheduled time for the participant and a number of preventive medicine evaluations were added including tonometry, vision screening, audiometry, and occult blood testing.

In the 1992 followup, the preventive medicine examinations were expanded to include human immunosuppressant virus (HIV) testing, prostate-specific antigen (PSA) testing, and kidney, urethra, and bladder (KUB) x rays. Proctosigmoidoscopy, as well as treadmill tests, were made available to participants for a nominal fee, and accompanying family members were offered the opportunity to use the clinic facilities at a discounted rate.

CONDUCT OF EXAMINATIONS

All examinations, from May 1992 to March 1993, were conducted in accordance with the Examiner's Handbook, provided in Appendix C. Excluding weeks with national holidays, two groups of participants, averaging approximately 28 per group, were examined weekly.

A demanding logistics effort was required to contact, transport, and examine 2,233 study participants. Pre-examination contact consisted of making telephone calls to recruit participants, determine special requirements (e.g., wheelchair assistance, weekend examination schedule), and arrange transportation. Once scheduling was reasonably firm, the SAIC logistics coordinator sent each participant a detailed information package outlining dietary requirements, a stool occult blood testing kit (Hemoccult®), inbriefing schedules, important telephone numbers, a request for medical records, and local maps designating examination-site dining and recreational facilities.

Figures 4-1 and 4-2 outline participant flow for the first and second examination days. As depicted in these figures, each morning of the first 2 days, the current group of participants was transported to the SCRF clinic, having fasted and abstained from tobacco and caffeine since midnight the previous evening. In addition, alcohol was strictly prohibited from 72 hours before the first day of the examination through the second day of the examination. On the first day, each participant was given an individualized 3-day schedule outlining his medical, interviewing, and laboratory appointments. The schedule carefully noted the specific required periods of fasting and tobacco abstinence (see Figures 4-1 and

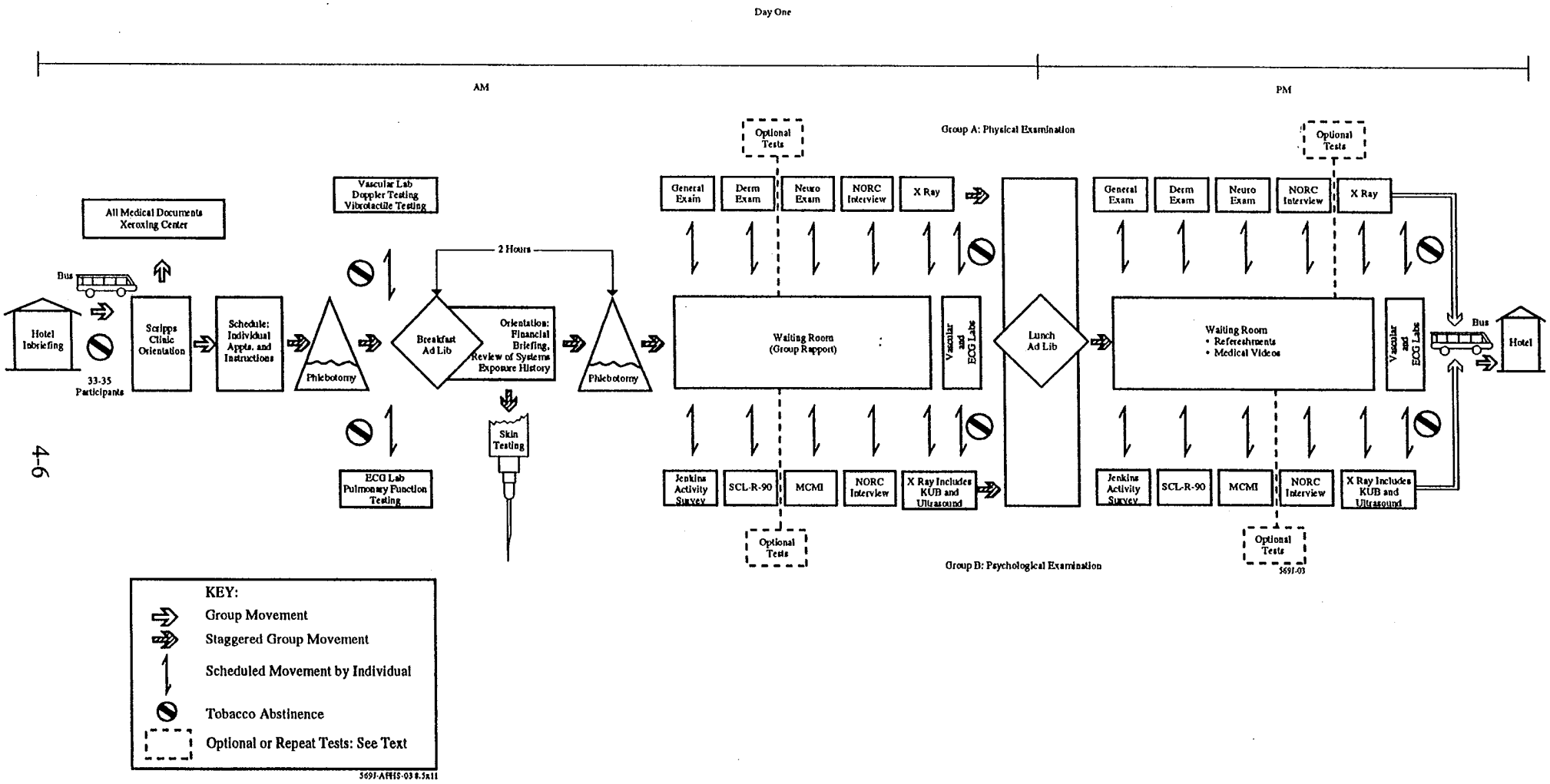

Figure 4-1. Flow Diagram of Day One Followup Interviews and Physical Examination

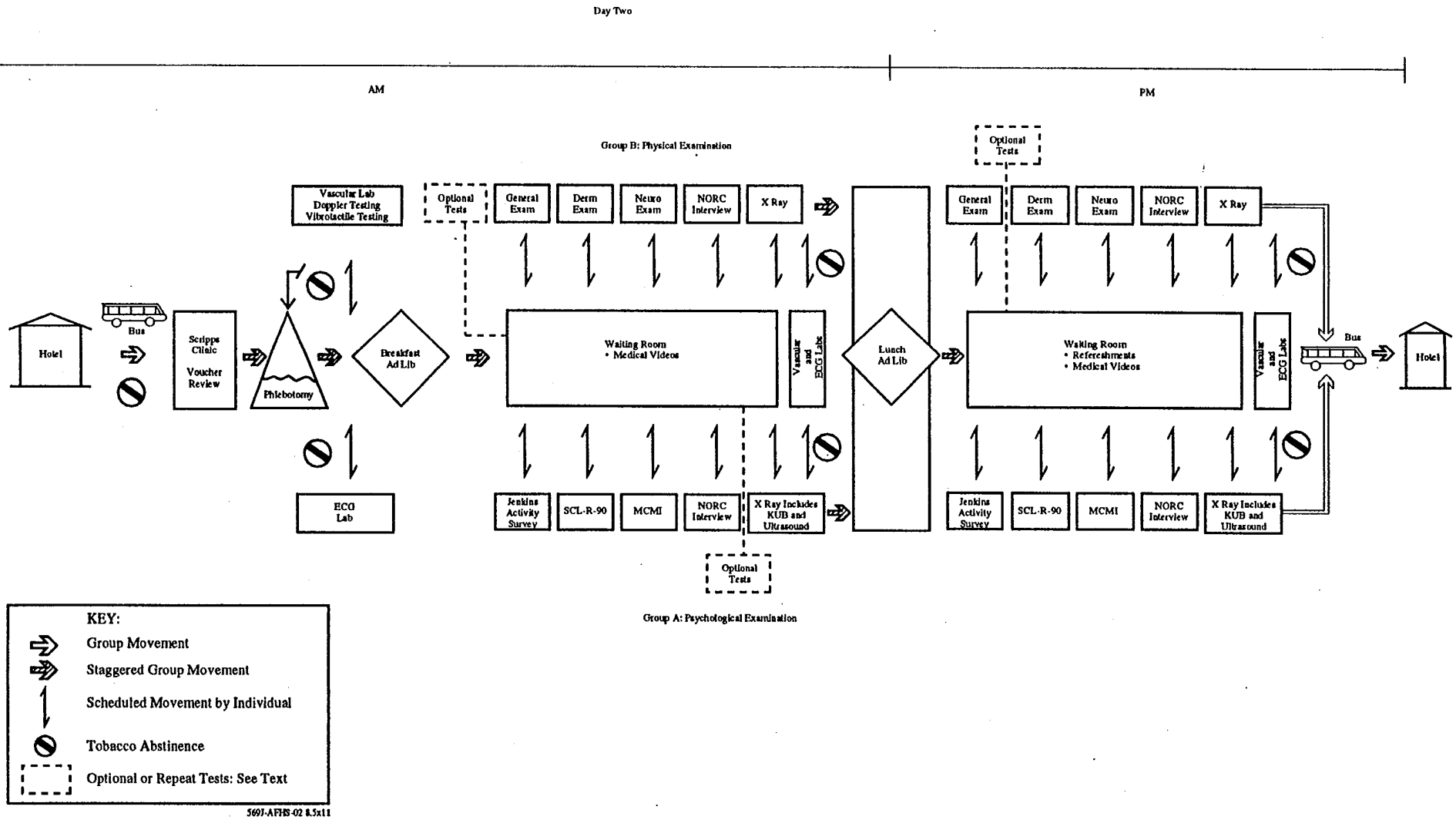

Figure 4-2. Flow Diagram of Day Two Followup Interviews and Physical Examination

4-2) for generalized periods in relation to electrocardiograph (ECG) testing. Although the clinic schedules were generally assigned at random, consideration was given to smokers and diabetics because of the fasting and abstinence restrictions.

As in the 1987 examination, schedules were printed with specific directions to aid participants in locating clinic departments, although for many tests, participants were escorted from the waiting room. Throughout the examination day, time was provided for waiting-room activities (i.e., renewal of past friendships, discussions of experiences in SEA, consumption of refreshments when permitted, and completion of paperwork). On the third day of the examination, skin tests were read, and the participants received outbriefings from a psychologist and medical diagnostician. Upon completion of these debriefings, the participants were paid their stipend, reimbursed for travel expenses, and transported to the airport.

As noted previously, the SCRF clinical team was specifically chosen for this project. In total, 15 board-certified physicians in internal medicine, neurology, and dermatology participated in the general, specialty, and diagnostic examinations. In addition to the 15, there were 13 radiologists, 5 allergists, 2 pulmonologists, and 2 cardiologists who performed tests and interpreted results. To reduce observer variability, turnover in the clinical and paramedical staffs was minimized during the 10 months of examinations. One SCRF physician served as the Project Medical Director, responsible for the scheduling, conduct, and QC of the examinations. All examining physicians were introduced to the mark-sense examination forms prior to the pretest examination. To minimize recording errors, the layout of the form was designed to parallel the flow of the clinical examination. Because data transcription was not permitted, each physician was responsible for filling in the bubbled form. To a large extent, the use of these mark-sense forms and subsequent QC measures were the primary reason for a clean clinical data set. A complete set of forms is provided in Appendix C.

As in the 1987 followup, special testing included delayed hypersensitivity skin tests and immunologic tests. Skin tests for four antigens were administered in a standardized manner: *Candida* (1:1,000 weight/volume, 0.1 ml intradermal), mumps (2 complement-fixing units), Trichophyton (1:1,000 weight/volume, 0.1 ml intradermal), and staph-phage lysate (6-9 x 10^6 colony-forming units of *S. aureus* and 0.5-5 x 10^7 staphylococcus bacteriophage plaque-forming units). Allergy-immunology nurse specialists measured the indurations by the standard pen method* at 48 hours after injections. For unusual cases of anergy or severe local reactions, physician consultation was provided. Detailed immunologic testing (see Table 4-2) was conducted on approximately 40 percent of the participants. These participants were identified by the last digit of their participant study identification number used for previous testing, thus establishing a longitudinal connection between examinations. Workload factors mandated blood draws on the second day for one-half of the selected

*Starting 1 to 2 cm away from the margin of the skin test reaction, a medium ball point pen is used to trace a line toward the center of the skin test reaction. When the line reaches the margin of area, resistance is incurred, and the line is stopped. A similar line is drawn from the opposite direction of the first line. The distance between the two lines is measured.

group. Because of the high proportion of adverse reactions at the first blood draw during the Baseline examination and the potential of these reactions to adversely effect the aviator status of many of the participants, reclining blood-bank chairs were used for all phlebotomy procedures. The chairs were introduced initially in the 1985 study and kept blood-draw incidents to a minimum. The individuals chosen for in-depth immunological testing were excluded from skin testing to avoid interference with the immunologic results. The immunologic tests were subjected to highly structured QC procedures set forth by the Air Force.

New testing introduced in the 1992 followup included: estradiol, rheumatoid factor, serum amylase, lupus panel, serum adrenocorticotropic hormone (ACTH), and glycated hemoglobin. In addition, known and newly diagnosed glucose-intolerant participants received C-peptide, proinsulin, and islet cell antibody tests.

CHAPTER 4
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CHAPTER 5

STUDY SELECTION AND PARTICIPATION

INTRODUCTION

During the design phase of the Air Force Health Study (AFHS), the authors of the Study Protocol (1) anticipated that a loss of participants between followups would pose the greatest threat to study validity. In particular, they expected differential compliance, with relatively more Ranch Hands choosing to return to the study than Comparisons, and with health differences of unknown character between refusing Ranch Hands and refusing Comparisons. In an attempt to partially correct the situation, the study design specified that refusing Comparisons would be replaced by Comparisons with the same values of the matching variables (age, race, rank, and military occupation) and the same health perception. In this way, the Replacement Comparisons would serve as surrogates for Comparisons who refused to participate. This method of replacement would tend to reduce bias resulting from refusal in the Comparison group and also would maintain group size. No corresponding strategy for the Ranch Hands was possible, because all Ranch Hands had been identified and invited to participate.

The first Comparison in each randomized matched set who was asked to participate in the Baseline questionnaire and physical examination was identified as the Original Comparison for his respective Ranch Hand (in accordance with the Study Protocol). If the Original Comparison was noncompliant (refused to participate, was partially compliant [completed the Baseline questionnaire but did not complete the Baseline physical examinations], or was unlocatable), a "Replacement" Comparison was invited in his place. Replacement Comparisons were identified as such in the data base to satisfy the Study Protocol requirement that they be contrasted based on health with the refusing Original Comparisons (also known as refusals). In the case of an unlocatable Original Comparison, this contrast is, of course, not possible. Original Comparisons who were partially compliant were replaced, but deceased Original Comparisons were not.

The statistical contrast of replacements and refusals was to be based on responses to a telephone questionnaire administered to refusals and to their potential replacements. This questionnaire assessed self-perception of health, days lost from work due to illness, and medication use, and was to serve as the basis for health matching required by the Study Protocol. Although the Study Protocol is not explicit on this point, it implies that the decision to include or exclude the replacements from the study should be based only on this contrast. A telephone questionnaire was administered to refusals at the Baseline and at the 1985 followup examination. At the 1987 followup examination, refusals were asked during the scheduling process for their self-perception of health. At the 1992 followup examination, schedulers attempted to obtain current perception of health compared to others their age from all participants contacted by telephone. Health-matching of replacements was not implemented at the Baseline but was implemented with the 1985, 1987, and 1992 followup examinations. Replacement Comparisons were matched to noncompliant (refusal, partially

compliant, or unlocatable) Original Comparisons with respect to age, race, rank, and military occupation at all examinations.

In this chapter, cumulative study compliance is summarized, and refusing Ranch Hands and Comparisons at the 1992 followup examination are contrasted with respect to reason for refusal and reported health status. All Ranch Hands and Comparisons were contrasted on reported health with adjustment for compliance (fully compliant or refusal). (Only fully compliant Ranch Hands and Comparisons are described with respect to reported health, medication, and work loss because no partial compliance occurred in 1992.) Scheduling patterns were compared by plotting cumulative compliance versus calendar time for Ranch Hands, Original Comparisons, and Replacement Comparisons. Adherence to the replacement algorithm for noncompliant Original Comparisons was investigated at the 1992 followup. Replacement Comparisons were contrasted with their corresponding Original Comparisons on reported health status. Ranch Hands and Comparisons who passively refused the 1992 followup examination (scheduled but failed to appear at the clinic) were contrasted with respect to reported health status. Statistical methods used in this chapter include log-linear models, stepwise logistic regression, and Pearson's chi-square statistic.

FACTORS KNOWN OR SUSPECTED TO INFLUENCE STUDY PARTICIPATION

A multitude of factors might influence study participation. These may be broadly classified as health, logistic, operational, publicity, or demographic factors. For example, health factors are thought to include self-perception of health as well as demonstrable health indicators, such as medication use and work days lost due to illness or injury. Logistic factors include distance to the examination site, reluctance to spend time away from family or job, income, and occupation. Demographic factors include flying status, age, race, or military duty status (active, retired, separated). Operational factors include any aspect of study operation that may cause differential compliance, such as differential treatment of participants during scheduling, physical examination, interview, or debriefing. Publicity factors are related to national attitudes and media presentations regarding the Agent Orange (Herbicide Orange) issue, the Vietnam War, veteran health care, or health care in general. Additionally, these considerations may affect people differently and, in particular, may influence Ranch Hands differently than Comparisons.

The decision to volunteer for this study, or any study, is admittedly complex, making statistical assessment of compliance bias difficult and necessarily crude in that many of the factors contributing to self-selection cannot be measured directly. Instead, compliance bias was investigated at the 1992 followup with respect to self-perception of health. Medication use and days lost from work due to illness or injury were taken from questionnaire and physical exam data, and therefore were available only for fully compliant participants. In 1992, no partial compliance (compliant to the questionnaire and noncompliant to the physical examination) occurred because both the physical examination and the questionnaire were administered at the exam site.

1992 FOLLOWUP SCHEDULING AND REPLACEMENT OPERATION

All Comparisons who had been invited to participate in the Baseline or 1985 or 1987 followups were invited to participate in the 1992 followup. If no previously invited Comparisons for a particular Ranch Hand agreed to participate in 1992, schedulers attempted to recruit a replacement from a matched set of up to 10 candidate Comparisons whose self-reported health status in 1992 (reported in the categories: excellent, good, fair, or poor) matched that of the noncompliant Original Comparison for that Ranch Hand. In 1992, as in both previous followup scheduling operations, replacements were matched to noncompliant Original Comparisons on the basis of reported health status in addition to the four matching variables (age, race, rank, and military occupation). The Replacement Comparisons were men who served in C-130 units in Southeast Asia (SEA) between 1962 and 1971, but who did not participate actively in the Baseline phase of the study. If a willing, health-matched (excellent, good, fair, poor) participant was not found in the matched set, self-reported perceptions of health status were dichotomized into excellent or good, and fair or poor categories, and matched to the dichotomized health status of the noncompliant Original Comparison. If this second method for identifying a suitable replacement failed, no replacement was made.

There were two exceptions to the replacement strategy. First, the Study Protocol required that the noncompliant Original Comparisons report their health status during the 1992 scheduling effort so that they could be used to recruit Replacement Comparisons with the same health status. Occasionally, Original Comparisons refused to talk or respond. In those cases, Replacement Comparisons for each Original Comparison were recruited in the (random) order in which they were listed in the Air Force data file. Second, as previously mentioned, no replacement was made if the Original Comparison for the Ranch Hand was deceased.

The scheduling process had three objectives:

- Maximize participation rates (both in the 1992 followup and future followups).
- Ensure that Ranch Hands and Comparisons were recruited using the same procedures and with the same effort.
- Ensure that, whenever possible, at least one Comparison was examined for each Ranch Hand.

These objectives led to a set of conflicting priorities: maximizing participation rates meant giving each potential participant every opportunity and encouragement to participate (without being so persistent as to lose the cooperation of unwilling respondents in future followups). This careful approach had to be balanced against the need to quickly identify uncooperative Comparisons and eliminate them from the scheduling process so that they could be replaced. Potential participants were given the following priorities in the scheduling process:

- Participants who requested specific examination dates from the Air Force prior to the beginning of the study were contacted first to accommodate those requests.

- Participants listing their occupations as "teacher" during their previous interviews, and those residing outside of the United States at the time of the 1992 study, were contacted next due to their probable travel time constraints.

- Participants who had been fully compliant at previous followups were given third priority.

Three attempts were made to convert potential participants who initially refused over the telephone to volunteer for the study. A minimum of 4 weeks was allowed between conversion attempts. If the three attempts were unsuccessful, the participant was considered a final refusal and replaced when appropriate. The only exceptions to this rule were participants who had either shown themselves hostile to the study in previous followups (in which case they were not contacted in 1992), or who were so vehement in their refusal to initial scheduling contacts in 1992 that efforts to recruit them were terminated after the first or second refusal conversion attempt. Participants who broke three examination appointments were considered final refusals. Participants unwilling to commit to an examination appointment after six contacts also were considered final refusals.

Small adjustments were made to the scheduling process as the study proceeded to accommodate specific situations and the approaching end of the scheduling period. Because of the lack of success of most third refusal conversion attempts, this last attempt was changed to a request for health status only (as this information was required for the replacement process). A month before the end of scheduling, the time between conversion attempts was reduced to 2 weeks, and within the last 2 weeks of data collection, the number of conversion attempts was reduced to two. Some potential participants could not be contacted directly because other household members either refused for them, or refused to bring them to the telephone. A maximum of six contacts with such "gatekeepers" was attempted before the participant was considered a refusal. This number was reduced to four during the last 2 weeks of scheduling. At that time, participants were eliminated from the scheduling process and replaced, if appropriate, after three contacts with the participant himself, four contacts with a "gatekeeper," or three messages left on his answering machine without any response. Potential participants who were designated as final refusals at any stage in the scheduling process were provided with the toll-free number for the study, and allowed to volunteer to participate at any time.

The percent completing the 1992 physical examination is plotted by calendar date in Figure 5-1 for Ranch Hands, Original Comparisons, Replacement Comparisons, and all Comparisons. These patterns are similar to those seen at previous followups.

1992 FOLLOWUP COMPLIANCE

Of the 1,148 eligible Ranch Hands, 952 (82.9%) participated in the 1992 followup examination while 912 (76.3%) of the 1,195 eligible Original Comparisons participated. Of the 567 Replacement Comparisons eligible for the 1992 followup, 369 (65.1%) chose to

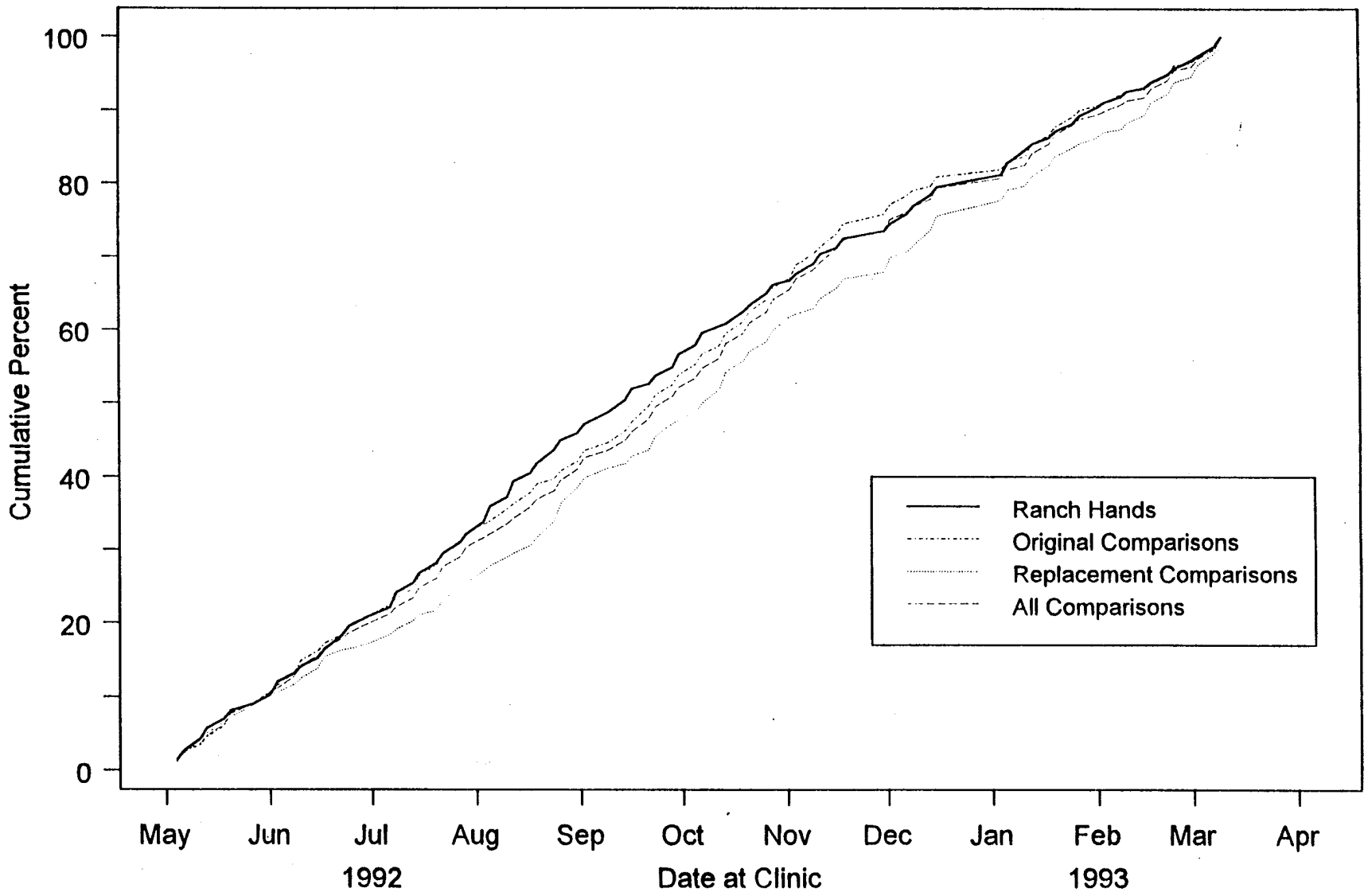

Figure 5-1.
Percent Completed Physical Examination, by Calendar Date

attend the examination. Table 5-1 provides counts for the Ranch Hands. Total Comparison counts are summarized in Table 5-2. Original Comparison counts are presented in Table 5-3 and Replacement Comparison counts are provided in Table 5-4. Within the Comparison tables, the "New to Study" rows include potential Replacement Comparisons who were found to be deceased when contact was attempted. These same deceased potential replacements are then accounted for in the rows marked "Died." Undefined categories are indicated by dashes. For example, dashes appear when partially compliant participants at Baseline could not be partially compliant at a later examination because partial compliance only occurred when a participant agreed to the Baseline questionnaire but refused to attend the physical exam. As stated previously, no partial compliance occurred in 1992 because both the Baseline questionnaire and physical examination were given at the same site. However, there were two participants who took the physical exam but refused to complete the questionnaire. Ninety-one percent of living Ranch Hands and 92 percent of living Comparisons who were fully compliant at the Baseline examination returned for the 1992 followup.

Four Ranch Hands, 20 Original Comparisons, and 37 Replacement Comparisons were fully compliant and examined for the first time at the 1992 followup examination. Table 5-5 describes these newly compliant participants in terms of their compliance at the Baseline, 1985, and 1987 followup studies. Two of the four newly examined Ranch Hands had refused all three previous examinations; the other two Ranch Hands were partially compliant at one previous examination and had refused two previous examinations. Eighteen of the 20 new Original Comparisons and 17 of the 37 new Replacement Comparisons had refused at least one of the previous exams. One new fully compliant Original Comparison was unlocatable in both 1985 and 1987. Three new fully compliant Replacement Comparisons were new to the study in 1987, but were only partially compliant at the 1987 followup examination. One of the new Original Comparisons and 17 of the new Replacement Comparisons were new to the study at the 1992 followup.

CORRECTIONS TO PREVIOUSLY REPORTED STUDY COMPLIANCE TOTALS

Several changes were made to the cell counts shown in Table 5-1 through Table 5-4 so that they now differ from compliance tables presented during previous examination cycles (in particular, Table 5-1 through Table 5-4 of the 1987 Followup Report). The differences fall into two categories:

- Corrections made to the Baseline compliance status of several individuals carried throughout each of the three followup examinations

- Corrections to followup compliance classification errors made during previous reporting cycles.

The following corrections affect the Ranch Hand study compliance reported in Table 5-1.

- The Partial Compliance column (PC) at Baseline decreased from 129 (in the 1987 Followup Report) to 127, and the Refusal column (R) at Baseline increased from 32 (in the 1987 Followup Report) to 34. Two individuals who refused to complete the

Table 5-1.
Baseline Compliance and Followup Disposition of Ranch Hands at the Baseline, 1985, 1987, and 1992 Examination

Time Period	Disposition	Baseline Compliance					
		FC	PC	R	UNL	NS	Total
Baseline		***1,045***	***127***	***34***	***2***	***--***	***1,208***
Between Baseline & 1985 Followup	New to Study	--	--	--	--	9	9
	Died	(10)	(9)	(0)	(0)	(0)	(19)
1985 Followup	***Eligible***	***1,035***	***118***	***34***	***2***	***9***	***1,198***
	Contact Attempted	1,035	118	34	2	9	1,198
	Subject Unlocatable	(27)	(12)	(0)	(0)	(0)	(39)
	Refused	(37)	(67)	(29)	(1)	(0)	(134)
	Partially Compliant	--	--	(5)	(0)	(4)	(9)
	Fully Compliant	**971**	**39**	**0**	**1**	**5**	**1,016**
1985 Followup	***Eligible***	***1,035***	***118***	***34***	***2***	***9***	***1,198***
Between 1985 & 1987 Followup	New to Study	--	--	--	--	4	4
	Died	(12)	(2)	(1)	(0)	(0)	(15)
1987 Followup	***Eligible***	***1,023***	***116***	***33***	***2***	***13***	***1,187***
	Contact Attempted	1,023	116	33	2	13	1,187
	Subject Unlocatable	(8)	(10)	(2)	(0)	(0)	(20)
	Refused	(71)	(69)	(27)	(1)	(3)	(171)
	Partially Compliant	--	--	(1)	(0)	(0)	(1)
	Fully Compliant	**944**	**37**	**3**	**1**	**10**	**995**
1987 Followup	***Eligible***	***1,023***	***116***	***33***	***2***	***13***	***1,187***
Between 1987 & 1992 Followup	New to Study	--	--	--	--	(0)	(0)
	Died	(35)	(2)	(2)	(0)	(0)	(39)
1992 Followup	***Eligible***	***988***	***114***	***31***	***2***	***13***	***1,148***
	Contact Attempted	988	114	31	2	13	1,148
	Subject Unlocatable	(5)	(4)	(2)	(1)	(0)	(12)
	Refused	(82)	(75)	(23)	(0)	(4)	(184)
	Partially Compliant	--	--	(0)	(0)	(0)	(0)
	Fully Compliant	**901**	**35**	**6**	**1**	**9**	**952**

FC = Fully Compliant at Baseline.
NS = New to Study Since Baseline.
PC = Partially Compliant at Baseline.
R = Refusal at Baseline.
UNL= Unlocatable at Baseline.
-- = Undefined Categories.

Table 5-2.
Baseline Compliance and Followup Disposition of Comparisons at the Baseline, 1985, 1987, and 1992 Examination

		Baseline Compliance					
Time Period	**Disposition**	**FC**	**PC**	**R**	**UNL**	**NS**	**Total**
Baseline		***1,224***	***301***	***133***	***9***	***--***	***1,667***
Between Baseline & 1985 Followup	New to Study	--	--	--	--	73	73
	Died	(16)	(9)	(1)	(0)	(0)	(26)
1985 Followup	***Eligible***	***1,208***	***292***	***132***	***9***	***73***	***1,714***
	Contact Attempted	1,208	292	132	9	73	1,714
	Subject Unlocatable	(38)	(26)	(0)	(0)	(1)	(65)
	Refused	(31)	(173)	(87)	(5)	(30)	(326)
	Partially Compliant	--	--	(24)	(0)	(6)	(30)
	Fully Compliant	**1,139**	**93**	**21**	**4**	**36**	**1,293**
1985 Followup	***Eligible***	***1,208***	***292***	***132***	***9***	***73***	***1,714***
Between 1985 & 1987 Followup	New to Study	--	--	--	--	33	33
	Died	(14)	(1)	(1)	(0)	(0)	(16)
1987 Followup	***Eligible***	***1,194***	***291***	***131***	***9***	***106***	***1,731***
	Contact Attempted	1,194	291	131	9	106	1,731
	Subject Unlocatable	(8)	(20)	(9)	(3)	(7)	(47)
	Refused	(73)	(178)	(88)	(3)	(16)	(358)
	Partially Compliant	--	--	(13)	(0)	(14)	(27)
	Fully Compliant	**1,113**	**93**	**21**	**3**	**69**	**1,299**
1987 Followup	***Eligible***	***1,194***	***291***	***131***	***9***	***106***	***1,731***
Between 1987 & 1992 Followup	New to Study	--	--	--	--	82	82
	Died	(37)	(8)	(1)	(0)	(5)	(51)
1992 Followup	***Eligible***	***1,157***	***283***	***130***	***9***	***183***	***1,762***
	Contact Attempted	1,157	283	130	9	183	1,762
	Subject Unlocatable	(9)	(8)	(7)	(3)	(29)	(56)
	No Health Match	--	--	--	--	(11)	(11)
	Refused	(85)	(179)	(95)	(3)	(52)	(414)
	Partially Compliant	--	--	(0)	(0)	(0)	(0)
	Fully Compliant	**1,063**	**96**	**28**	**3**	**91**	**1,281**

FC = Fully Compliant at Baseline.
NS = New to Study Since Baseline.
PC = Partially Compliant at Baseline.
R = Refusal at Baseline.
UNL= Unlocatable at Baseline.
-- = Undefined Categories.

Table 5-3.
Baseline Compliance and Followup Disposition of Original Comparisons at the Baseline, 1985, 1987, and 1992 Examination

		Baseline Compliance					
Time Period	**Disposition**	**FC**	**PC**	**R**	**UNL**	**NS**	**Total**
Baseline		***936***	***216***	***81***	***3***	***--***	***1,236***
Between Baseline & 1985 Followup	New to Study	--	--	--	--	17	17
	Died	(11)	(9)	(1)	(0)	(0)	(21)
1985 Followup	***Eligible***	***925***	***207***	***80***	***3***	***17***	***1,232***
	Contact Attempted	925	207	80	3	17	1,232
	Subject Unlocatable	(28)	(19)	(0)	(0)	(1)	(48)
	Refused	(25)	(127)	(62)	(2)	(3)	(219)
	Partially Compliant	--	--	(8)	(0)	(2)	(10)
	Fully Compliant	**872**	**61**	**10**	**1**	**11**	**955**
1985 Followup	***Eligible***	***925***	***207***	***80***	***3***	***17***	***1,232***
Between 1985 & 1987 Followup	New to Study	--	--	--	--	5	5
	Died	(12)	(1)	(0)	(0)	(0)	(13)
1987 Followup	***Eligible***	***913***	***206***	***80***	***3***	***22***	***1,224***
	Contact Attempted	913	206	80	3	22	1,224
	Subject Unlocatable	(7)	(12)	(9)	(2)	(2)	(32)
	Refused	(51)	(131)	(53)	(1)	(6)	(242)
	Partially Compliant	--	--	(11)	(0)	(0)	(11)
	Fully Compliant	**855**	**63**	**7**	**0**	**14**	**939**
1987 Followup	***Eligible***	***913***	***206***	***80***	***3***	***22***	***1,224***
Between 1987 & 1992 Followup	New to Study	--	--	--	--	4	4
	Died	(25)	(6)	(0)	(0)	(2)	(33)
1992 Followup	***Eligible***	***888***	***200***	***80***	***3***	***24***	***1,195***
	Contact Attempted	888	200	80	3	24	1,195
	Subject Unlocatable	(6)	(4)	(3)	(2)	(2)	(17)
	Refused	(61)	(132)	(64)	(1)	(8)	(266)
	Partially Compliant	--	--	(0)	(0)	(0)	(0)
	Fully Compliant	**821**	**64**	**13**	**0**	**14**	**912**

FC = Fully Compliant at Baseline.
NS = New to Study Since Baseline.
PC = Partially Compliant at Baseline.
R = Refusal at Baseline.
UNL = Unlocatable at Baseline.
-- = Undefined Categories.

Table 5-4.
Baseline Compliance and Followup Disposition of Replacement Comparisons at the Baseline, 1985, 1987, and 1992 Examination

Time Period	Disposition	Baseline Compliance					
		FC	PC	R	UNL	NS	Total
Baseline		***288***	***85***	***52***	***6***	***--***	***431***
Between Baseline & 1985 Followup	New to Study	--	--	--	--	56	56
	Died	(5)	(0)	(0)	(0)	(0)	(5)
1985 Followup	***Eligible***	***283***	***85***	***52***	***6***	***56***	***482***
	Contact Attempted	283	85	52	6	56	482
	Subject Unlocatable	(10)	(7)	(0)	(0)	(0)	(17)
	Refused	(6)	(46)	(25)	(3)	(27)	(107)
	Partially Compliant	--	--	(16)	(0)	(4)	(20)
	Fully Compliant	**267**	**32**	**11**	**3**	**25**	**338**
1985 Followup	***Eligible***	***283***	***85***	***52***	***6***	***56***	***482***
Between 1985 & 1987 Followup	New to Study	--	--	--	--	28	28
	Died	(2)	(0)	(1)	(0)	(0)	(3)
1987 Followup	***Eligible***	***281***	***85***	***51***	***6***	***84***	***507***
	Contact Attempted	281	85	51	6	84	507
	Subject Unlocatable	(1)	(8)	(0)	(1)	(5)	(15)
	Refused	(22)	(47)	(35)	(2)	(10)	(116)
	Partially Compliant	--	--	(2)	(0)	(14)	(16)
	Fully Compliant	**258**	**30**	**14**	**3**	**55**	**360**
1987 Followup	***Eligible***	***281***	***85***	***51***	***6***	***84***	***507***
Between 1987 & 1992 Followup	New to Study	--	--	--	--	78	78
	Died	(12)	(2)	(1)	(0)	(3)	(18)
1992 Followup	***Eligible***	***269***	***83***	***50***	***6***	***159***	***567***
	Contact Attempted	269	83	50	6	159	567
	Subject Unlocatable	(3)	(4)	(4)	(1)	(27)	(39)
	No Health Match	--	--	--	--	(11)	(11)
	Refused	(24)	(47)	(31)	(2)	(44)	(148)
	Partially Compliant	--	--	(0)	(0)	(0)	(0)
	Fully Compliant	**242**	**32**	**15**	**3**	**77**	**369**

FC = Fully Compliant at Baseline.
NS = New to Study Since Baseline.
PC = Partially Compliant at Baseline.
R = Refusal at Baseline.
UNL= Unlocatable at Baseline.
-- = Undefined Categories.

Table 5-5.
New Fully Compliant Participants at the 1992 Followup, by Group and Previous Compliance Status

Previous Compliance			Group		
Baseline	1985	1987	Ranch Hand	Original Comparison	Replacement Comparison
Partial	Refusal	Refusal	1	7	4
Partial	Refusal	Unlocated	0	1	0
Partial	Unlocated	Refusal	0	2	0
Refusal	Refusal	Refusal	2	4	4
Refusal	Partial	Refusal	1	1	2
Refusal	Refusal	Unlocated	0	1	0
Refusal	Refusal	Partial	0	1	1
New 85	Refusal	Refusal	0	0	1
New 85	Unlocated	Unlocated	0	1	0
New 85	Refusal	Partial	0	0	3
New 85	Refusal	Unlocated	0	0	2
	New 87	Refusal	0	1	0
	New 87	Partial	0	0	3
		New 92	0	1	17
		Total	4	20	37

in-home interview did submit to the long telephone interview and were mistakenly classified as PC at Baseline. The long telephone interview is not a surrogate for the in-home interview. Consequently, these two individual's Baseline compliance codes were changed from PC to R. These two individuals additionally were reclassified as partially compliant at the 1985 followup from refusal at the 1985 followup (in the 1987 Followup Report). One of these two individuals subsequently died between the 1985 followup and the 1987 followup. Other changes in the PC and R columns in Table 5-1 are a result of these corrections.

- At the 1985 followup, the number of unlocatable subjects in the Fully Compliant column (FC) at Baseline decreased from 28 (in the 1987 Followup Report) to 27 and the number of refusals increased from 36 (in the 1987 Followup Report) to 37. This was due to the misclassification of one individual.

- Between the 1985 and 1987 followups, the number of deaths in the FC column at Baseline increased from 11 (in the 1987 Followup Report) to 12 because one of the nine individuals previously reported in the 1987 Followup Report as Unlocatable (UNL) during the 1987 followup was deceased.

The following corrections affect the Comparison study compliance reported in Table 5-2.

- The PC column at Baseline decreased from 307 (in the 1987 Followup Report) to 301, and the R column at Baseline increased from 128 (in the 1987 Followup Report) to 133. Five individuals who refused to complete the in-home interview did submit to the long telephone interview and were mistakenly classified as PC at Baseline. The long telephone interview is not a surrogate for the in-home interview. Consequently these five individual's Baseline compliance codes were changed from PC to R. One of these individuals additionally was reclassified as partially compliant at the 1985 followup from refusal at the 1985 followup (in the 1987 Followup Report). In addition, one other individual classified as PC at Baseline in the 1987 Followup Report was determined to be ineligible as a Comparison and was removed from the study. This person had been mistakenly classified as UNL for the 1985 and 1987 followups (in the 1987 Followup Report). Other changes in the PC and R columns in Table 5-2 are a result of these corrections and corrections in Table 5-4 described below.

- At the 1985 followup, the number of unlocatable subjects in the FC column at Baseline decreased from 39 (in the 1987 Followup Report) to 38 and the number of refusals increased from 30 (in the 1987 Followup Report) to 31. This was due to the misclassification of one individual.

- In the New to Study since Baseline (NS) column, the number of participants new to the study between the 1985 and 1987 followup increased from 32 (in the 1987 Followup Report) to 33. This was due to a classification error. One individual should have been reported as a new Original Comparison and was not. This participant is classified as Unlocatable at the 1987 followup in this report. He was mistakenly omitted from the 1987 Followup Report.

- At the 1987 followup, in the NS column, two individuals who were previously classified as "Contact Not Attempted" (in the 1987 Followup Report) were moved to the "Subject Unlocatable" classification. These changes were due to classification errors. In this same column, one individual reported as a refusal (in the 1987 Followup Report) was reclassified as UNL, correcting a classification error.

All the changes in Tables 5-3 and 5-4 are a result of the changes in Table 5-2, with the exception of the corrections described below.

- Both Original Comparison study compliance in Table 5-3 and Replacement Comparison study compliance in Table 5-4 were affected by an error in the reported 1985 followup compliance status of two individuals in the NS column. This error involved the "trading" of one partially compliant Original Comparison misclassified as a Replacement Comparison at the 1985 followup (in the 1987 Followup Report) with one refusal Replacement Comparison misclassified as an Original Comparison at the 1985 followup (in the 1987 Followup Report). Consequently, in the NS column of Table 5-3, the number of refusal Original Comparisons at the 1985 followup decreased from 4 (in the 1987 Followup Report) to 3, and the number of partially compliant Original Comparisons at the 1985 followup increased from 1 (in the 1987 Followup Report) to 2. Additionally, in the NS column of Table 5-4, the number of

refusal Replacement Comparisons at the 1985 followup increased from 26 (in the 1987 Followup Report) to 27, and the number of partially compliant Refusal Comparisons at the 1985 followup decreased from 5 (in the 1987 Followup Report) to 4. The changes made affect Table 5-3 and Table 5-4, but do not affect Table 5-2.

- In the R column at Baseline in Table 5-4, the number of refusal Replacement Comparisons at the 1985 followup decreased from 26 (in the 1987 Followup Report) to 25, and the number of partially compliant Replacement Comparisons at the 1985 followup increased from 15 (in the 1987 Followup Report) to 16 due to the misclassification of one individual. This change additionally affects Table 5-2.

- In the PC column at Baseline in Table 5-4, the number of refusal Replacement Comparisons at the 1987 followup decreased from 48 (in the 1987 Followup Report) to 47, and the number of unlocatable Replacement Comparisons at the 1987 followup increased from 7 (in the 1987 Followup Report) to 8 due to the misclassification of one individual. This change additionally affects Table 5-2.

REFUSING RANCH HANDS VERSUS REFUSING COMPARISONS

Of the 1,148 Ranch Hands and 1,762 Comparisons eligible for the 1992 followup examination, 184 Ranch Hands and 414 Comparisons chose not to attend. Their reasons for refusal are summarized in Table 5-6. Two new refusal categories were added for the 1992 physical examination: "hostile" and "no health-match." Hostile refusals accounted for over 30 percent of both refusing Ranch Hands and refusing Comparisons. Hostile refusals included 162 participants who were abusive at previous examinations. These participants, designated by the Air Force as hostile, were not contacted by schedulers during the 1992 scheduling operation. Five individuals did decide on their own to cooperate with the 1992 followup and contacted the Air Force. Eight of these 162 hostile participants were determined to be deceased and one participant was reclassified as unlocatable. In addition, four of these hostile participants were determined to be refusals for other reasons. Consequently, 144 of the 162 participants initially specified as hostile prior to scheduling remained classified as hostile after the scheduling effort. These 144 participants were included as part of the "Contact Attempted" column, although no actual attempt by schedulers was made to contact these participants at the 1992 followup due to their history of abusiveness at previous examinations. Fifty-three refusing participants were found to be "newly" hostile during the 1992 scheduling process, yielding a total of 197 hostile participants.

The "no health-match" refusal category included participants initially contacted as potential Replacement Comparisons but whose perceived health status did not actually match the health status of the Original Comparison he would have replaced. The 11 "no health-match" potential Replacement Comparisons are included in Tables 5-2 and 5-4. Because they were willing to participate, but were rejected by the Air Force, these 11 potential replacements are not shown in Table 5-6 and were not used in the analysis of refusals that follows.

Table 5-6.
Reason for Refusal, by Group

	Group			
	Ranch Hand		Comparison	
Reason	Number	Percent	Number	Percent
Fear of Physical Exam	0	0.0	3	0.7
Job Commitment	31	16.8	53	12.8
Dissatisfaction with USAF	6	3.3	10	2.4
No Time	13	7.1	50	12.1
Travel Distance, Family	8	4.3	17	4.1
Confidentiality	1	0.5	2	0.5
Health Reasons	19	10.3	21	5.1
Passive Refusal	41	22.3	96	23.2
Dissatisfaction with Baseline	3	1.6	5	1.2
Financial Hardship	2	1.1	2	0.5
Hostile	58	31.5	139	33.6
Other	2	1.1	16	3.9
Total	184		414	

Table 5-7 summarizes reason for refusal versus group adjusted for age and rank. Reason for refusal was collapsed to four categories: logistic (job commitment, no time or interest, travel distance or family constraints, confidentiality, or financial hardship); passive (passive refusal); hostile (hostile refusal); and other (fear of physical examination, dissatisfaction with the U.S. Air Force, health reasons, dissatisfaction with Baseline, or other reason). Age and rank were dichotomized for analysis purposes (born before 1942 and born in or after 1942; officer and enlisted respectively). Due to small cell counts, military occupation could not be accommodated. Forty Blacks (10 Ranch Hands and 30 Comparisons) were deleted due to cell counts too small to support analysis.

A test of association between reason for refusal and group (adjusted for age and rank) was performed and found to be not significant ($p=0.85$). The adjusted association between reason for refusal and age was significant ($p=0.002$), as was the association between reason for refusal and rank ($p=0.005$) for both groups (Ranch Hand, Comparison) combined. There were more hostile officers (42.9%) than enlisted (32.4%) among older participants but the difference is even greater between hostile officers (42.7%) and enlisted (24.7%) in the younger participants.

Of the 598 refusals, reported health status was available for a total of 307 Ranch Hands and Comparisons. Table 5-8 summarizes their responses. Reported health status was obtained by telephone at the time of scheduling. Data were obtained from 95 (51.6%) of 184 refusing Ranch Hands and 212 (51.2%) of 414 refusing Comparisons. Of the 307

Table 5-7.
Reason for Refusal Versus Group, Adjusted for Age and Rank Among Non-Blacks

			Reason for Refusal								
			Logistic		Passive		Hostile		Other		
Birth Year	Rank	Group	n	%	n	%	n	%	n	%	Total
<1942	Officer	RH	12	28.6	7	16.7	18	42.9	5	11.9	42
		C	15	17.9	20	23.8	36	42.9	13	15.5	84
		Total	27	21.4	27	21.4	54	42.9	18	14.3	126
	Enlisted	RH	13	25.5	10	19.6	13	25.5	15	29.4	51
		C	28	29.8	15	16.0	34	36.2	17	18.1	94
		Total	41	28.3	25	17.2	47	32.4	32	22.1	145
≥1942	Officer	RH	7	41.2	3	17.6	5	29.4	2	11.8	17
		C	18	25.0	15	20.8	33	45.8	6	8.3	72
		Total	25	28.1	18	20.2	38	42.7	8	9.0	89
	Enlisted	RH	22	34.4	18	28.1	18	28.1	6	9.4	64
		C	56	41.8	33	24.6	31	23.1	14	10.4	134
		Total	78	39.4	51	25.8	49	24.7	20	10.1	198
		Grand Total	171	30.6	121	21.7	188	33.7	78	14.0	558

RH = Ranch Hand.
C = Comparison.

Table 5-8.
Reported Health Status of Refusals at the 1992 Followup

	Group					
	Ranch Hand		Comparison		Total	
Reported Health Status	Number	Percent	Number	Percent	Number	Percent
Excellent	31	32.6	85	40.1	116	37.8
Good	43	45.3	108	50.9	151	49.2
Fair	16	16.8	13	6.1	29	9.4
Poor	5	5.3	6	2.8	11	3.6
Total	95		212		307	

refusals responding to the health status question, there was a significant association between group and reported health ($p=0.02$). More Ranch Hands reported fair or poor health whereas more Comparisons reported excellent or good health. This trend agrees with results from the 1987 followup but group differences are more pronounced in 1992. A larger percentage of refusing Comparisons (40.1%) reported excellent health than refusing Ranch Hands (32.6%) and a larger percentage of refusing Ranch Hands (16.8%) reported fair health than refusing Comparisons (6.1%).

Ideally, compliance bias between the groups should be assessed by comparing the health of refusing participants to fully compliant participants with adjustment for the matching variables. The only current data available on the refusing participants are responses to the health status question asked during the scheduling procedure. These data are missing almost entirely for hostile refusals. Health status data are available for only 32 hostile refusals. A test of association between reported health status and group adjusted for compliance, age, and rank was performed, and the results appear in Table 5-9. For analysis purposes, reported health status was collapsed to two categories: excellent or good, and fair or poor. The covariates age and rank were dichotomized (born before 1942 and born in or after 1942 and officer and enlisted). Military occupation (flying or ground duty) could not be accommodated due to small cell counts. Blacks ($n=170$) were excluded from the analysis due to small cell counts.

The association between reported health status and group, adjusted for compliance, age, and rank, was significant ($p=0.007$). As seen in Table 5-9, except for the sparse younger officer refusal data, Ranch Hands consistently reported poorer health than Comparisons. Relatively sparse refusal data also may account for the large group differences in reported health status observed for older enlisted refusals. The adjusted association between reported health status and compliance was statistically significant ($p=0.02$). The 1987 analysis suggested that, in general, those who refused to participate reported poorer health more often than did their fully compliant counterparts. For 1992, reporting of poorer health by refusers appears to have held true for older, but not necessarily for younger, participants. Table 5-9 shows that for older officer participants, 91.8 percent of the fully compliant Ranch Hands and 93.3 percent of the fully compliant Comparisons reported excellent or good health, while 84.2 percent of the refusing Ranch Hands and 85.3 percent of the refusing Comparisons reported excellent or good health. A similar pattern holds for older enlisted participants. On the other hand, younger refusals seem to be reporting better health than younger fully compliant participants. It is of interest to note that Ranch Hands reported poorer health more often than Comparisons among both fully compliant and refusing participants. Significant associations also were found between reported health status and both rank ($p<0.001$) and age ($p<0.001$). Table 5-9 shows that officers consistently reported better health than enlisted participants and, as expected, younger participants reported better health than older participants.

REPLACEMENT COMPARISONS VERSUS THE NONCOMPLIANT ORIGINAL COMPARISONS THEY REPLACED

As initiated at the 1985 followup, matching replacements for refusing Original Comparisons on the basis of health status as well as age, race, rank, and occupation was

Table 5-9.
Reported Health Status versus Group, Adjusted for Compliance, Age, and Rank Among Non-Blacks

				Reported Health Status				
				Excellent or Good		Fair or Poor		
Compliance	Birth Year	Rank	Group	n	%	n	%	Total
Fully Compliant	<1942	Officer	RH	259	91.8	23	8.2	282
			C	348	93.3	25	6.7	373
		Enlisted	RH	191	78.0	54	22.0	245
			C	257	83.2	52	16.8	309
	≥1942	Officer	RH	77	96.3	3	3.8	80
			C	121	98.4	2	1.6	123
		Enlisted	RH	248	87.9	34	12.1	282
			C	354	89.8	40	10.2	394
			Total	1,855	88.8	233	11.2	2,088
Refused	<1942	Officer	RH	16	84.2	3	15.8	19
			C	29	85.3	5	14.7	34
		Enlisted	RH	15	55.6	12	44.4	27
			C	45	83.3	9	16.7	54
	≥1942	Officer	RH	7	100.0	0	0.0	7
			C	31	100.0	0	0.0	31
		Enlisted	RH	33	91.7	3	8.3	36
			C	76	96.2	3	3.8	79
			Total	252	87.8	35	12.2	287

maintained at the 1992 followup. The reported health status of new replacements was obtained at the time of telephone scheduling.

At the 1992 followup, an attempt was made to contact a total of 78 potential replacements new to the study since the Baseline (see Table 5-4). Seventeen of the 78 replaced refusing Original Comparisons. The health-matching replacement strategy for the 17 newly matched replacements and their replaced Originals in 1992 is summarized in Table 5-10.

All 17 matched replacements reported excellent or good health. Ten of these replacements were correctly matched to refusing Originals, four with excellent health and six with good health, as required in the Study Protocol. Seven Original Comparisons (labeled "Unknown") either refused to give a self-perception of health or said they did not know how their health compared with that of others. Replacements with excellent or good health were matched to these seven refusing Original Comparisons, as shown in Table 5-10.

Table 5-10.
Reported Health Status of Replaced Originals and Their Matched Replacements at the 1992 Followup

	Original Comparison's Reported Health					
Replacement's Reported Health	**Excellent**	**Good**	**Fair**	**Poor**	**Unknown***	**Total**
Excellent	4	0	0	0	1	5
Good	0	6	0	0	6	12
Fair	0	0	0	0	0	0
Poor	0	0	0	0	0	0
Total	4	6	0	0	7	17

* Subject refused to give perception of health or stated "I don't know."

At the 1992 followup (see Table 5-3), 283 Original Comparisons were noncompliant. The entire matched set of replacement candidates for each noncompliant Original Comparison was reviewed to determine if the appropriate replacement strategy was followed. Results are presented in Table 5-11. Of the 283 noncompliant (refusing or unlocatable) Original Comparisons at the 1992 followup, all but 64 were members of matched sets having at least one other compliant Replacement Comparison. Of the 64, 21 were noncompliant Original Comparisons whose potential replacements were never contacted, and 43 were members of matched sets in which all contacted potential replacements were noncompliant and at least one other potential replacement was not contacted. Exactly how many of the 64 noncompliant Original Comparisons belonged to matched sets containing a health-matched replacement is unknown because current health status could only be obtained from contacted participants.

REPORTED HEALTH IN FULLY COMPLIANT PARTICIPANTS

Partial compliance, which occurred when a participant answered the Baseline questionnaire but had no corresponding physical examination performed, could not be compared with full compliance for 1992 because all questionnaires were given to participants at the site of the physical examination (although, an unusual instance did occur when two Comparisons completed the physical examination but refused the questionnaire). Therefore, Tables 5-12 through 5-14 summarize data on the health status, medication use, and work loss of the 2,233 fully compliant participants at the 1992 followup. Health status and work-loss patterns appear similar to 1987 responses, but nearly half of the fully compliant participants now take medication on a regular basis compared to 25 percent in 1987.

Table 5-12 summarizes the reported health status of participants fully compliant to the 1992 physical examination. Among fully compliant participants, no significant association was found between reported health and group (Ranch Hand, Comparison) ($p=0.24$). A marginally significant association was found between reported use of medication and group ($p=0.08$). As seen in Table 5-13, a greater percentage of Ranch Hands (44.1%) reported medication use than Comparisons (40.4%). Table 5-14 shows how many fully compliant Ranch Hands and Comparisons reported work loss. No significant association was found between work loss and group ($p=0.18$).

Table 5-11.
Matched Set Compliance of 283 Noncompliant Original Comparisons

Matched Set Compliance	Original Comparison's Compliance		
	Refusal	Unlocatable	Total
At Least One Compliant Replacement	207	12	219
All Contacted Replacements Noncompliant and Other Uncontacted Comparisons Remain in the Matched Set	41	2	43
No Comparisons Contacted	18	3	21
Total	266	17	283

Table 5-12.
Reported Health, as Obtained During the Scheduling Procedure, of Fully Compliant Participants at the 1992 Followup

Reported Health	Group					
	Ranch Hand		Comparison			
	Number	Percent	Number	Percent	Total	Percent
Excellent	350	37.0	511	40.2	861	38.8
Good	474	50.2	629	49.4	1,103	49.8
Fair	96	10.2	105	8.3	201	9.1
Poor	25	2.6	27	2.1	52	2.3
Total	945*		1,272**		2,217	

* Seven Ranch Hands did not answer.
** Nine Comparisons did not answer.

Table 5-13.
Reported Medication Use of Fully Compliant Participants at the 1992 Followup

Medication Use	Group					
	Ranch Hand		Comparison			
	Number	Percent	Number	Percent	Total	Percent
Yes	420	44.1	516	40.4	936	42.0
No	532	55.9	762	59.6	1,294	58.0
Total	952		1,278*		2,230	

* Three Comparisons skipped this question.

Table 5-14.
Reported Work Loss of Fully Compliant Participants at the 1992 Followup

	Group					
	Ranch Hand		Comparison			
Work Loss	Number	Percent	Number	Percent	Total	Percent
Yes	136	17.5	163	15.2	299	16.2
No	640	82.5	908	84.8	1,548	83.8
Total	776		1,071		1,847*	

* Does not include 168 retired, 27 unemployed, 189 participants who skipped this question, and 2 participants who completed the physical exam only.

ANALYSIS OF PASSIVE REFUSALS

A potential participant was identified as a passive refusal if he was scheduled for a physical examination but broke the appointment. Passive refusal was the most common type of refusal (second only to hostile attitude) during the 1992 study. Twenty-two percent of the refusing Ranch Hands and 23 percent of refusing Comparisons were passive refusals (see Table 5-6). More than half (54%) of the passive refusals did not give their reported health status during scheduling.

A summary of reported health status for passive refusals can be found in Table 5-15. No significant association between group (Ranch Hand, Original Comparison, Replacement Comparison) and reported health status was found ($p=0.55$). Additionally, health status was collapsed to excellent or good and fair or poor, and group was collapsed to Ranch Hand and Comparison because of sparse data. Analysis of the collapsed table revealed no significant association between group and reported health status ($p=0.56$).

CONCLUSION

These compliance analysis results suggest that Ranch Hands may be experiencing poorer reported health than Comparisons even after accounting for rank, age, and compliance differences. These group differences in self-perception of health are present for both fully compliant participants and refusing participants.

Despite requirements in the Study Protocol, 64 of 283 noncompliant Original Comparisons were not replaced as they should have been by compliant replacements at the 1992 followup. If all 64 noncompliant Original Comparisons had been replaced, the total number of fully compliant study participants (2,233 for the 1992 followup) would have increased by less than 3 percent. It is not known how many of the 64 had potential health-matched replacements in their matched set, but any biasing effect is considered negligible.

Table 5-15.
Reported Health Status of Passive Refusals at the 1992 Followup

	Group							
	Ranch Hand		Original Comparison		Replacement Comparison			
Reported Health	Number	Percent	Number	Percent	Number	Percent	Total	Percent
Excellent	9	45.0	7	33.3	11	50.0	27	42.9
Good	10	50.0	13	61.9	8	36.4	31	49.2
Fair	1	5.0	0	0.0	2	9.1	3	4.8
Poor	0	0.0	1	4.8	1	4.5	2	3.2
Total	20		21		22		63*	

* 74 passive refusals did not answer this question at scheduling.

CHAPTER 5
REFERENCES

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CHAPTER 6

QUALITY CONTROL

During the 1992 Air Force Health Study (AFHS) followup, stringent adherence to quality assurance (QA) was planned for and upheld throughout the study, from project initiation to final product delivery and acceptance by the Air Force. This chapter provides an overview of the specific QA measures developed and used by the project team, specifically in the areas of questionnaire and physical examination quality control (QC), laboratory QC measures, data management QC, statistical QC, and administrative QA.

QUESTIONNAIRE QUALITY CONTROL

The National Opinion Research Center (NORC) used both onsite and home office procedures to produce a comprehensive, high-quality data set. All AFHS questionnaires were pretested to evaluate completion time and participant acceptability before they were used during the 1992 followup. Onsite QC procedures included observing and rating interviewers, and reviewing every questionnaire twice at the completion of the interview (once by the interviewer who administered the questionnaire and then again by NORC's onsite supervisor or editor). Science Applications International Corporation (SAIC) conducted a review of 10 percent of the questionnaires for management acceptance throughout the program. SAIC reviewed 100 percent of the questionnaires during the first 4 weeks of the physical examination process. The Air Force also continuously conducted QA observations of all onsite activities.

QC of data processing included the following:

- Manual editing of each questionnaire
- 100-percent blind verification of data entry by a second key entry operator
- Computerized data cleaning to identify values out of range, inconsistent responses, and logic and arithmetic errors
- Review of response frequencies
- Review of the actual questionnaires to reconcile or correct detected errors.

NORC recruited and trained 11 interviewers according to the procedures described in Chapter 3. A minimum number of interviewers was selected to reduce variability between interviewing techniques. Additionally, the interviewers were blind to the participants' exposure status to avoid bias. Interviewers were required to ask questions exactly as written, and in the order in which they appeared. No personal interpretation was allowed.

NORC's onsite supervisor closely monitored both the staff of interviewers and the onsite editor. The supervisor reported to NORC's Project Manager at least weekly, and she

was in turn evaluated by the Project Manager at the beginning of the study and during quarterly site visits.

Interviewers were closely observed in training to ensure that they were able to administer the questionnaire and record responses smoothly and correctly. During the study, the onsite supervisor checked interviewers for accuracy in following questionnaire skip patterns, circling the correct codes, and controlling the interview, including voice quality, reading, and use of associated forms and documents. The supervisor observed at least one interview per interviewer per quarter, and gave immediate retraining if she observed any errors.

Either the supervisor or NORC's onsite editor reviewed and edited each questionnaire immediately following each interview, and reported any errors to the supervisor, who retrained interviewers during daily contacts. Generalizations from individual interviews were used to train the entire group of interviewers. Whenever possible, missing information was retrieved from participants before they left the examination site. If errors were discovered when participants were no longer onsite, information was retrieved from them by telephone.

Once participant questionnaires were received by NORC's home office for data processing, they were reviewed for completeness by a coding supervisor and staff. The coding staff resolved inconsistencies in the questionnaires and prepared the forms for data entry. This included coding of open-ended responses, such as in the category "occupation." Ten percent of open-ended items for each batch of questionnaires were recoded. When a batch failed the 10-percent recode, the entire batch was recoded and the coding staff was retrained.

Key entry of data was 100-percent blind, verified by a second key entry operator. Interval Questionnaire data were passed through a computer program that checked for out-of-range data, inter-item inconsistencies, and logic and arithmetic errors. When discrepancies were detected, the questionnaires were reviewed and the errors corrected. Response frequencies also were reviewed, and any anomalies or errors previously undetected were corrected by reviewing the questionnaires. The process continued until no errors were found. All corrections were documented and entered into the data base, but no changes were made to the original data recorded in the questionnaires.

Baseline Questionnaire data was subject to reviews of response frequencies and cross-tabulations of related variables. Again, corrections were documented and entered into the data base, but the original data recorded in the questionnaires were not altered.

Diet Assessment forms were coded, read into electronic form, and cleaned by the subcontractor, Willett Associates. NORC performed a 10-percent check of the data delivered by Willett, consisting of an item-by-item comparison of answers recorded on the hard copy and those contained in the data base. Diet Assessment forms were checked in batches. No batches failed the QA check in the 1992 study. If any batch had failed the QA step, that batch would have been returned to the subcontractor for recoding, re-entry and recleaning. NORC performed a final recoding of Diet Assessment data to make missing values codes consistent with the rest of the Interval Questionnaire.

PHYSICAL EXAMINATION QUALITY CONTROL

QA was emphasized in administering the physical examination, as this data source provided a large part of the medical information for clinical and epidemiologic analyses.

Initial concern for a high-quality physical examination was addressed by a stringent Scripps Clinic and Research Foundation (SCRF) selection process for all personnel who were to interact directly with the participants. Each staff member was hand-selected for the AFHS on the basis of expertise, experience, and a commitment to remain with the study throughout the examination cycle. Furthermore, the Air Force reviewed the credentials of all key staff members and approved their participation in the study.

A complete pretest physical examination, interview, psychological test, and laboratory workup was done for 10 volunteers several weeks before the scheduled start of the study. The dermatologists received refresher training to enhance their skill in diagnosing chloracne, internists were provided with a review of techniques for detecting specific heart sounds, and diagnosticians were reminded to review Baseline, 1985, and 1987 examination data as they formulated all diagnoses. Furthermore, all aspects of patient contact were reviewed: the initial inbriefing of the participants, the logistics of transportation and patient flow within the clinic, and the final outbriefing by the diagnostician.

During the examinations, refinements continued whenever operational problems were detected by the SCRF staff and the Air Force onsite monitor, or when participants identified areas requiring improvement. Both of these types of information were addressed during the weekly clinical QA meeting of key SCRF staff. Written critique forms submitted by all participants also were reviewed in detail at the SCRF weekly meetings, providing additional insight to both temporary shortcomings of the entire logistic process and the numerous strong points of the programs.

Following examination of each participant group, all physical examination forms were reviewed by the SCRF staff for omissions, incomplete examinations, and inconsistencies. The examiners or technicians quickly were contacted to correct the data. Special effort was made to complete this review while the participants were at the examination site. In all cases of data correction, a complete audit trail was maintained. All mark-sense physical examination forms were read by an optical scanner as an ongoing QA of form completion. (This subject is discussed in more detail in the Data Management Quality Control section of this chapter.)

Compliance with all aspects of the physical examination process was monitored daily by the Air Force onsite monitor and the SCRF administrative team. Additional periodic inspections were conducted by the SCRF Chief of Medicine and the SAIC Project Manager. All such clinical reviews were done unobtrusively and with the full consent of the participant; suggestions or corrections to the examination procedure were always discussed privately with the attending physician. These inspections emphasized aspects of clinical techniques, sequence, and completeness of the clinical data with respect to the examination forms, and the blindness of the examinations. Of particular note were the detailed daily log entries of the five Air Force monitors. These entries ensured continuity of knowledge (the

monitors rotated approximately every 2 weeks) by documenting examination procedural changes and recording events requiring followup by either the Air Force or SAIC.

Establishing a rapport with each study participant was a primary goal of all the organizations involved in this study. Although "rapport building" may not be a traditional QA parameter in most research studies, it is paramount in the AFHS because maintaining the satisfaction of participants encourages them to continue in the study, thus helping to avoid a significant reduction in future statistical power or introducing bias, or both. Therefore, every staff member, from the initial telephone recruiter to the nurse coordinator and the Project Manager, emphasized courtesy, empathy, assistance, and personalized treatment of each participant. Based on the evaluation forms, 73.5 percent of the participants evaluated their experience in the 1992 followup as excellent, and 22 percent classified it as good. Only 3.9 percent of the participants rated the experience as satisfactory, and only 0.7 percent felt that it was unsatisfactory.

LABORATORY QUALITY CONTROL

Before the study began, specific QC laboratory procedures were designed, developed, and implemented to rapidly detect problems related to test and assay performance, validity of reagents, analysis of data, and reporting of results. All laboratory assays for the study were performed with state-of-the-art laboratory equipment and techniques. Laboratory facilities all had the equivalent of National Institutes of Health (NIH) Biosafety Level 2 approval ratings and were certified by the College of American Pathology.

Quality Control Procedures for the Clinical Laboratory

The following list outlines the tests that were performed and the methods and equipment used:

- Hematology assays were performed on Coulter S-Plus® equipment.
- Sedimentation-rate determinations were performed using the large-tube Westergren method.
- Biochemical assays were performed using Baxter/Dade Paramax® Automated Chemical Analyzer.
- Radioimmunoassays were performed with standard test kits.
- Electrophoresis and occult blood tests were performed manually.
- Hepatitis B tests were performed using Abbott Diagnostic® kits.
- Monospecific antibodies were used for immunologlobulin assays using the Beckman Array Protein System®.
- Blood-cell counts were performed with standard microscopy.

- All urinalyses were performed using Clinitek®, a reflectance spectrometry urinalysis.

- All other assays were done using industry-standard equipment and techniques.

All laboratory operations were controlled with the use of an integrated medical laboratory management information system that incorporated direct device-to-data base interfaces for automated testing equipment. Data entry for manual tests was performed by the laboratory technologists. An automated audit trail and a set of comments for technologist remarks were kept for each test so that any QC results could be retraced.

Procedural QC included using the same instrument and reagents from the same lot numbers whenever possible throughout the study. If single lots were unavailable, an overlap analysis of both lots was used. Strict standards of calibration for all automated laboratory equipment were maintained at all times.

Trilevel or bilevel controls were used as the primary means for monitoring the quality of all tests. On every group of participant samples, one control (low, medium, or high) was run at the start, after every 9th sample, and at the end of each test run. Each trilevel control was used before repeating it in the run, when more than 18 experimental samples were analyzed. In addition, split aliquots were made from every 10th participant sample and were analyzed separately to measure test reproducibility. In radiommunoassays, all three control levels were run initially to validate the standard curve generated.

All QC data were analyzed and summarized in formal QC reports generated monthly. QC data were subjected to independent statistical analysis by the Air Force to produce and analyze time-dependent trends. For all equipment malfunctions or other exceptions, a formal QC exception report was prepared by the responsible individual and forwarded to the project management team.

An additional measure of QC used during the study was the cumulative sum (CUSUM) tests run with trilevel controls (1). In particular, the fast initial response (FIR) CUSUM QC technique was used in detecting long-term subtle drift that could have substantial adverse analytical consequences (2). FIR is a special case of the CUSUM QC scheme that increases the overall effectiveness of the QC procedure. Unlike QC procedures using standard control charts, which compare each observation to designated limits, these tests utilize the CUSUM of deviations from a target value.

CUSUM statistics were accumulated for each of the trilevels to quickly detect instrument calibration problems as identified by excessive drift. If an out-of-control situation was indicated, the graph showed when the change first occurred. When the CUSUM indicated an out-of-control situation, all adjacent patient samples were reanalyzed after the equipment was thoroughly checked and fresh controls were run. Coefficient of variation (CV) requirements were established for each test prior to the beginning of the physical examination process.

FIR CUSUM generally has been applied to QC in industry, particularly in high-volume, high-precision applications. It is believed that FIR CUSUM generally has not been applied in a biomedical setting, but it has proved to be effective in the AFHS.

As the examination portion of this study ended, laboratory outliers were analyzed for logical validity by an independent clinician. All out-of-range test results were examined and scored as clinically explainable, clinically possible, or clinically unexplained. No clinical laboratory data were excluded because all potential out-of-range results were found to be clinically explainable or clinically possible.

Quality Control Procedures for the Immunology Laboratory

The QC procedures for the cellular immunology section of the AFHS were structured to rapidly detect any problems in four major test parameters: assay performance, reagent validity, data analysis, and results reporting. The cellular immunology laboratory supervisor monitored compliance daily. Key aspects of the program included instrument and equipment calibration and maintenance, assay controls, accuracy and precision determination, and system failure checks.

The following QC measures were adhered to in all cellular immunology assays:

- Testing of a blood sample from a normal, healthy control individual with each group of AFHS patient samples.
- Duplicate testing of one random participant sample in each assay.
- Quadruplicate testing of each participant sample for each variable in each of the functional assays (e.g., phytohemagglutinin [PHA] stimulation, natural killer cell (NKC), and mixed lymphocyte culture).
- Parallel testing and monitoring reactivity of various lots of reagents when appropriate.
- Verification of participant and specimen identification by at least two individuals before final reporting to the data base.
- Note codes attached to any data point with a detected deviation due to procedural setup error, assay malfunction, equipment malfunction, or assay technical error.
- Note codes attached to any data point outside the range of expected values as identified by the cellular immunology laboratory supervisor.
- Review of all final assay reports by the cellular immunology laboratory supervisor prior to entry into the data base.

QC for each functional assay (including PHA, NKC, and mixed lymphocyte culture), consisted of monitoring assay controls, duplicate sample reproducibility, and trends in

reagent reactivity. Assay precision was determined by calculating the CV of the quadruplicates for each variable tested. Also, a mean value of the CV for each assay was calculated. Individual CVs of 15 percent or less were the target values for the stimulated samples in the mitogen and NKC assays. The Student's t-test was applied to duplicates to determine if there was a significant difference in sampling for the functional assays. Critical t-values at the 0.05 significance level were used to determine if duplicate sample results varied significantly. Positive and negative values were assigned, arbitrarily subtracting the second duplicate value from the first, to determine if there was a systematic bias in one direction. Grubbs' statistical test (3) was used to identify any statistically significant outlier. This test was applied only to samples whose CVs were greater than 20 percent at a p-value of 0.01. The PHA stimulation effect was followed by daily evaluation of the radioactive counts in counts per minute. When counts fell below expected values, suggesting that reagent deterioration had occurred, new aliquots were used.

QC measures for the cell-surfaced marker assays included calculation of (CD4 + CD8)/ CD3 (formerly $[T_4 + T_8]/T_{11}$) cell ratios, evaluation of flow cytometer computer outputs (cytograms and histograms), and duplicate sample testing. The cellular ratios should approximate the value 1.0 for a normal population. Validity of cytogram and histogram distributions generated by the flow cytometer was confirmed by the cellular immunology laboratory supervisor for each sample analyzed. The proportional difference between duplicate samples was calculated and monitored for significant differences.

DATA MANAGEMENT QUALITY CONTROL

Overview of Quality Control Procedures

The QC program for the data management activity consisted of multiple checks at all steps of the examination, data collection, and data processing cycle. Data QC procedures for data collection, conversion, and integration were developed before the clinical examinations began. Pretesting of all forms was conducted 4 weeks before the examinations actually began. Additionally, during the first 2 months of the clinical examinations, all data collection activities were intensely scrutinized to detect and correct procedural deficiencies. QC activities also included the following:

- Automated QC techniques applied to laboratory data
- Clinical evaluations of all laboratory outliers
- Review of all physical examination findings by one of two diagnosticians who was not involved in the conduct of the physical examinations
- Automated and manual data quality checking of hard copy against transcribed computer files for all questionnaire, physical examination, and medical coding data streams.

Five interwoven layers of QC were instituted to ensure data integrity. Efforts focused on data processing system design, design and administration of all exams or questionnaires, data completeness checks, data validation, and QC of medical records coding.

Data Processing System Design

Standards were established for data element formats (character or numeric), data element naming conventions, data element text labels, numeric codes for qualitative responses and results, QC range checks for continuous data elements, and QC validity checks for categorical data. A data dictionary provided detailed information on each data element.

A systems integration approach was applied to the design and implementation of data collection procedures so that data emanating from study sources (physical examination, questionnaire, laboratory) were consistent in file format and structure. This approach was necessary to ensure that all data could be integrated into a single data base management system for analysis. Figure 6-1 provides an overview of the QC activities used in the data management process.

Forms and questionnaires were carefully designed to ensure that all required data elements would be collected in accordance with the Study Protocol and in a standardized format. The design of these instruments was such that they reflected the order in which the examination itself would be administered and provided for the sequential recoding of information to streamline remaining data management activities.

Completed clinical examination forms and questionnaires were converted from hard copy to machine-readable images using customized data-entry systems or state-of-the-art optical mark reading equipment. Verification procedures were performed to ensure that a uniquely identified participant record existed within each data file, and that the appropriate number of responses for each applicable field was provided. Data files were then verified against original data sheets and corrected as necessary.

Data files were then subjected to validity checks. Any potentially conflicting results, as well as any data values falling at the extremes of expected ranges, were manually reviewed. Extreme values were reverified against the original raw data copies and either corrected or documented as valid results. Potentially conflicting results were returned to the examiners for review. These results were then documented as having been correctly recorded, corrected, or flagged for exclusion from analysis because of unresolvable examiner errors or omissions. This process was continued until all results were properly documented.

Once the edits were completed and the data reverified, the "cleaned" files or tapes were transferred to the data analysis center for final inspection and integration into the study data base. For this QC measure, each data file was loaded into a SAS® data set, and descriptive analyses were run. The validation, correction, transmission, and analysis QC procedures were repeated as necessary to ensure that all extreme or suspicious values had been validated.

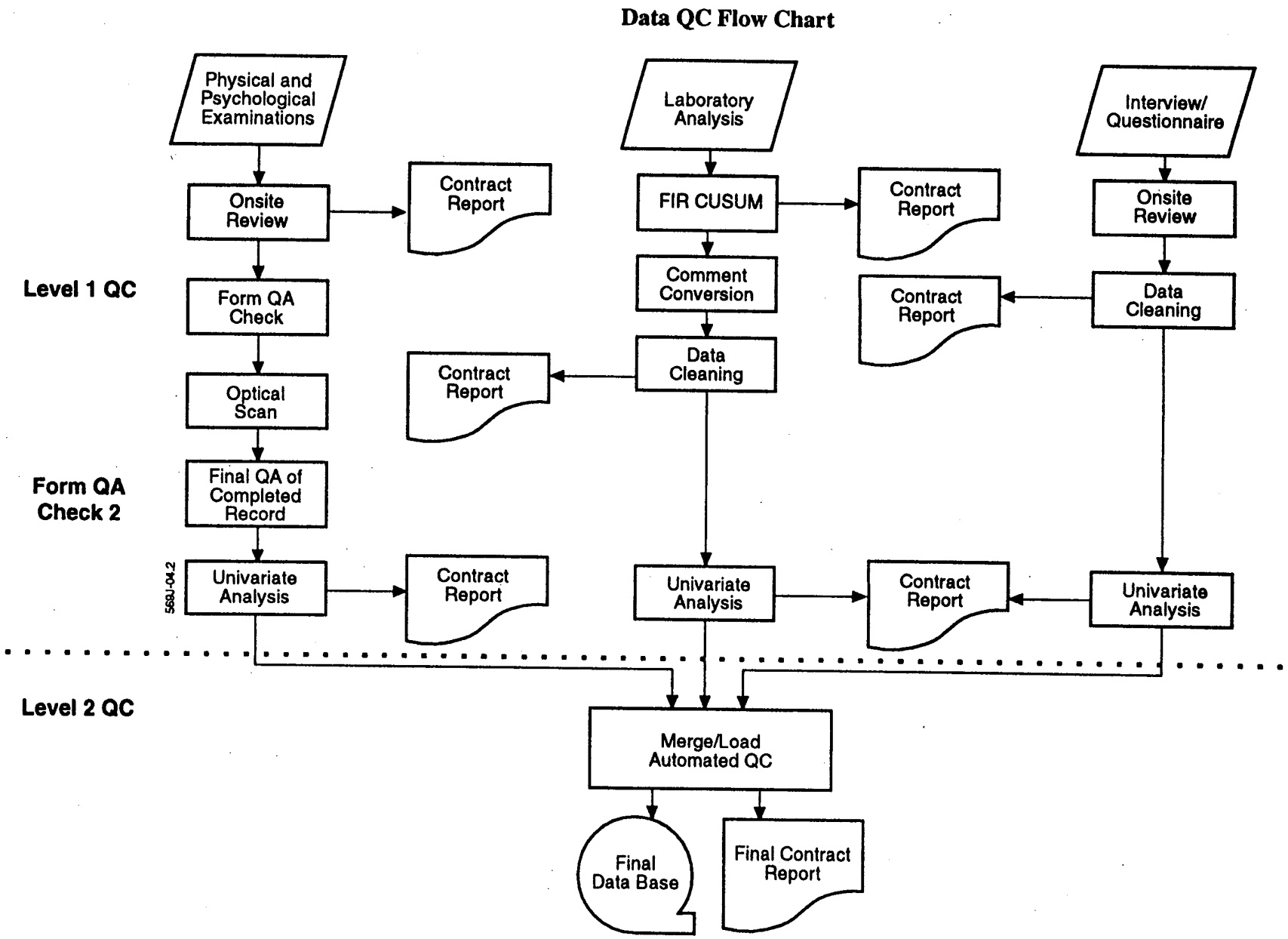

Figure 6-1.
Two Levels of Quality Control Applied to All Collected Data Prior to Statistical Analysis

Design and Administration of Physical and Psychological Examination Forms

As mentioned previously, the examination forms were designed to solicit all required data such that recording time was minimized, comprehension was enhanced, and data input could occur with a minimum of transcription errors. Optical mark recognition (OMR) technologies were selected to eliminate the risk of transcription errors and were applied to all psychological tests. Customized mark-sense forms also were developed and OMR technology was used to achieve these same objectives for segments of the physical examination and the self-administered questionnaires. The use of mark-sense forms allowed the creation of computerized data files directly from the raw data recorded on these forms.

QC procedures for all data collection instruments began with a review of each form as it was completed. A mark-sense reader was used at SCRF to scan for completeness and to conduct some broad-based logic checks. Any forms containing missing, incomplete, or contradictory examination results were returned to the examining physician for completion before the participants left the site. Any questionable results or "hard-to-diagnose" conditions (such as heart sounds or peripheral pulses) were verified by the diagnostician at the outbriefing. In addition, any differences in interpretation between examiners were identified, and adjustments in recording protocols and programmed data extraction were made as necessary. All examination forms were signed by the examining physician, and the examiner identification number was coded in the data base. A final level of QC audit was accomplished by Air Force statisticians, who conducted a detailed screening of the data and checked for errors.

Data Completeness Checks

Customized programming of the OMR allowed for the identification of those forms (and their corresponding data records) with missing responses, as well as those with multiple responses to questions that required a single response. The OMR scanner was programmed to reject forms that failed completeness and multiple response checks and generate control code for each rejected form. The control code identified the location of all verification checks failed for a given form.

When a raw data form was rejected, the reason for the rejection was determined and the exact data element corrected by comparing the rejected raw data form to the values recorded in the data record created by the scanner. A customized set of rejection and resolution codes was developed for the study to describe all the reasons for a form's rejection and any subsequent reasons for changing a data value. Various codes identified values recovered from light marks, missing marks explained by examiner comments, and missing comment flags resolved by the presence or absence of text in the comment areas. These codes ensured data completeness by accounting for all questionable or missing responses.

Some of the rejected forms did not contain actual data errors, but rather, anomalies created in using mark-sense cards for data collection. For example, the scanner incorrectly counted incompletely erased responses, and missed responses marked with too little carbon or graphite. Also, examiners tended to mark responses clearly for abnormal findings and to mark responses lightly or to bypass responses for expected or desired findings. Failure of

the form to provide the correct number of expected responses always resulted in rejection. These errors were resolved, as were the anticipated, more traditional errors.

The rejection code, data location code, resolution code, data inspector's initials, and correct data value were posted directly on a participant's data record. This procedure not only effectively maintained a comprehensive audit trail of all record manipulations, but also provided a mechanism for measuring the frequency of specific errors.

Statistics were compiled on out-of-range results and data omissions that had been accepted in the previous QC audits. The results were monitored to detect trends, possible bias situations, and other data quality problems. This information was reviewed and relayed to examiners and internal auditors to assist in preventing or correcting chronic, but avoidable, problems. Refresher training was provided to examining physicians to avoid data omissions. Physicians were consulted to recover missing data, and out-of-range results were reviewed for logical validity by an independent clinician.

Data Validation

Data files were examined in a series of verification and validation procedures developed to check the results within each participant's record for logical consistency and abnormal findings. Any records noted to have ambiguous findings, incongruent observations, extreme results, errors, or omissions were listed and submitted for review to a physician.

Again, clinical judgments were made by the auditing physician in assigning a validation code for each extreme or questionable data result. The validation codes allowed the physicians to indicate that data were deciphered from examiner comments or from related findings from another specialty area, or were accurately recorded and logically consistent with other findings for the participant. Data items that could not be definitively validated or recovered through clinical judgment and consultation with the original examiner were assigned codes noting missing or invalid data values. Some reasons for unavailable data included the following:

- Participant refusal
- Incomplete, confusing, ambiguous, or unclassifiable information
- Contaminated samples
- Unscorable psychological examinations
- Use of data from previous Air Force studies, at which the 1992 participant was not present
- Exemption from testing (e.g., exemption from delayed skin testing to prevent confounding of immunology panel results).

These unrecoverable data were excluded from subsequent analysis. The number of values not available for analyses is presented in the clinical chapters by variable.

Medical Records Coding Quality Control

SAIC forwarded completed questionnaires and physical examination records to the Air Force at Brooks Air Force Base, Texas, for diagnostic coding and verification of all subjectively reported conditions. The Air Force used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for morbidity coding; the Systematized Nomenclature of Medicine for anatomic site coding; and the American Hospital Formulary Service for medication coding. Two coders independently processed each questionnaire and physical examination. Both codings were then subjected to a 100-percent QA and QC review, during which every posted code was checked against medical records. A third coder adjudicated any discrepancies.

After QA and QC review and/or adjudication, information from the coding sheets was placed into the AFHS data base using 100-percent, double-blind data entry and verification. Any discrepancies were reviewed, corrected, and again subjected to double-blind data entry and verification. After coding and data entry, the Air Force batched the questionnaires and forwarded them to NORC in Chicago, Illinois, for data processing. The Air Force then obtained the NORC questionnaire data tape, matched this information to the Air Force data file, and resolved any differences. A single, final combined data base was produced by NORC, and a copy sent to the Air Force.

Processing of Questionnaire Data

All questionnaires completed at the examination site were edited twice: first by the interviewer who administered the questionnaire, and then by the site supervisor or editor. These reviews were conducted prior to each participant's departure from the examination site, so that any missing information could be retrieved from the participant onsite. Completed questionnaires, with the exception of the Diet Assessment Questionnaire from the Interval interview, were sent to the Air Force for medical coding. Diet Assessment Questionnaires were sent directly from the examination site to the NORC Chicago office.

After completion of the medical coding, questionnaires were sent to the NORC Chicago office for data processing. Upon receipt, questionnaires were logged into the receipt control system. Diet Assessment Questionnaires were sent to the subcontractor, Willett Associates, for coding and data entry. The rest of the questionnaires were processed by NORC in Chicago.

To process the questionnaires, NORC first coded responses to open-ended questions and key entered the data into a data base. Data entry was 100-percent verified by a second key entry operator. Then, an editing program was executed that checked for valid value ranges, inter-item consistency, and correct logic, dates, and arithmetic. The editing program produced an error sheet for each questionnaire in which a discrepancy was identified. Questionnaires were reviewed to resolve discrepancies on a case-by-case basis. No changes

were ever made to the hard copy data; corrections were entered only into the data base and the editing program was re-run. This process was repeated until no errors were detected.

STATISTICAL ANALYSIS QUALITY CONTROL

Specific QC measures were developed for the statistical analysis task efforts, such as construction of data bases for the statistical analysis of each clinical chapter, the statistical analysis itself, and the preparation of the clinical chapters.

Each specialized statistical data base was constructed by defining and locating every variable within the many subparts of the composite followup data base. Although the data had been subjected to QC procedures during collection and were frozen prior to starting the statistical analysis, statistical checks for outliers and other improbable values were conducted; anomalies identified by the statisticians were discussed with those responsible for the data collection (i.e., NORC, SCRF, or the Air Force).

QA largely depended on regular communication and general agreement among statisticians. Several meetings and consultations between the Air Force team and SAIC statisticians were held in conjunction with the development of the data analysis plan. Additionally, frequent telephone conversations took place during the course of the physical exam. During the analysis, there were frequent telephone conversations and any problems identified in the statistical analysis were resolved by team discussion. The software was checked by comparing results from analyses on the same variable by different programs. The statisticians frequently checked to determine that the number of observations used in an analysis was correct, and peer review ensured that the program code was appropriate for the chosen procedure. The analyses were conducted in accordance with the data analysis plan, which was reviewed extensively. Throughout the study, the Air Force and SAIC maintained duplicate data bases. Upon completion of the analyses, SAIC delivered all analysis software and SAS® data sets for each clinical area to the Air Force for final review and archiving.

All tables and statistical results were checked against the computer output from which they were derived, and all statistical statements in the texts were checked for consistency with the results given in the tables. In addition, drafts of each chapter in this report were reviewed by the Air Force and SAIC investigators and the SAIC Quality Review Committee (QRC).

Data Base Modifications

After the statistical analyses were underway, errors were discovered in the data base. One participant was coded in the data base as Black, when he was actually non-Black. After the data base had been created, one additional Ranch Hand was found to have a history of hepatitis C. Also, due to discrepancies in the heights coded in the data base, body fat measurements were incorrect for 17 participants.

The non-Black participant who was coded as Black in the data base was a 50-year-old Comparison in the enlisted flyer cohort with a current serum dioxin value less than 10 ppt. Because he is a Comparison, he was only included in the Model 1 and Model 3 analyses (see

Chapter 7, Statistical Methods). Race was used as a candidate covariate in the analyses of all clinical chapters; therefore, this Comparison was erroneously used as a Black, rather than as a non-Black participant in the Model 1 and Model 3 analyses of all clinical chapters. In the Neoplasia Assessment, this participant was excluded from the analyses of melanoma because he was erroneously coded as Black. However, additional analyses of melanoma were performed with the participant properly coded as non-Black and the conclusions from the analyses did not change in response to this misclassification.

The data base was corrected to account for the Ranch Hand that was found to have a history of hepatitis C after the data base had been created. However, statistical analyses in the Gastrointestinal Assessment that excluded participants with a presence of hepatitis C antibodies were underway prior to discovery of this misclassification. This Ranch Hand did not have a dioxin measurement and therefore only the results of Model 1 were affected. The corrected data base was used for the statistical analyses of the dependent variable "Antibodies for Hepatitis C."

Body fat measurements in the original data base contained inconsistencies due to variations in participants' heights across examination cycles. Body fat was calculated according to the formula:

$$\text{Body fat (in percent)} = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2} \times 1.264 - 13.305.$$

For 85 participants, recorded heights fluctuated by more than 5 centimeters across the time of duty in Southeast Asia (SEA) and 1982, 1985, 1987, and 1992 examination records. Discrepancies in recorded heights between the 1992 physical examination form and the 1992 pulmonary examination form were identified for 17 of these participants. Heights recorded in the data base for these 17 participants were replaced with the reported heights from the pulmonary form because these heights were closer to reported heights from previous cycles. However, the data base was corrected after statistical analyses of Model 1 were started for the four clinical areas in which body fat was used as a candidate covariate (General Health Assessment, Cardiovascular Assessment, Endocrine Assessment, and Pulmonary Assessment). Therefore, the revised body fat measurements were used only in the analyses of Models 2 through 6 in these four clinical chapters; Model 1 analyses used the original body fat measurements. In future cycles, additional QC procedures will be implemented to ensure consistent height measurements across and within the examination cycles.

Statistical Longitudinal Analysis Implications Due to a Change in Laboratory Equipment

Some of the chemical determinations analyzed in this study were performed at the 1982 Baseline examination with a Dupont® Automated Chemical Analyzer and at the 1992 followup examination with a Baxter/Dade Paramax® Automated Chemical Analyzer. This change was dictated by new technology and an increase in efficiency with high precision and reliability. However, because longitudinal analyses require contrasts of changes from 1982 to 1992, a concern was raised that the change in equipment might bias the outcome of the longitudinal statistical analyses.

For the eight chemical determinations to be investigated in the statistical longitudinal analysis that were measured with the Dupont® equipment at the Baseline examination and the Baxter/Dade Paramax® equipment at the 1992 followup examination, a comparison of the two instruments was conducted. The eight chemical determinations of interest were aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose, and serum creatinine. For each of the eight chemical determinations, the machines were compared on each of 30 split tri-level control samples (10 samples each at low, medium, and high levels) and the results were plotted (Dupont® versus Baxter/Dade Paramax® determination) and statistically assessed for linearity. All analyses exhibited a high degree of linearity (4). Because these chemical determinations were longitudinally analyzed with linear models, these results suggest that the change in instrumentation was not a source of bias.

ADMINISTRATIVE QUALITY ASSURANCE

In recognition of the magnitude, complexity, and importance of the AFHS, the QRC was established by SAIC at the initiation of the 1985 followup and continued through the 1987 and 1992 followup studies for the purpose of providing general oversight to the AFHS program and advice on the appropriateness of program management and QC actions. The QRC was composed of SAIC senior corporate personnel. These independent reviewers remained separate from the project management staff. The QRC met periodically to review recent study progress and any issues that either had an impact on study quality or were perceived as a potential problem. Members of the QRC also conducted first-hand evaluations of ongoing program operations.

CHAPTER 6
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CHAPTER 7

STATISTICAL METHODS

INTRODUCTION

This chapter summarizes the statistical methods used in this report to investigate relationships between the health status of the 2,233 participants attending the Air Force Health Study (AFHS) 1992 followup examination and their corresponding group (Ranch Hand or Comparison) or serum dioxin estimates and measurements. Group contrast models are similar to analyses performed for the 1982 Baseline and 1985 and 1987 followup examinations (1,2,3). Models relating health to dioxin estimates and measurements are based on analyses performed for the Serum Dioxin Analysis Report for the 1987 Followup (4).

The statistical methods presented in this chapter encompass six different forms of hypotheses or models applied to more than 300 study endpoints across clinical areas. Each of these models inherently specifies the study cohort or subset of participants to be included in the respective analyses together with the dioxin exposure or proxy estimates to be used in the analysis. The first model specifies contrasts between Ranch Hands and Comparisons using group as a proxy for exposure, and it does not incorporate serum dioxin measurements. The remaining five models all incorporate serum dioxin measurements. A summary description of each of the six models is provided in the section "Models and Assumptions."

Each model and exposure estimate combination is implemented for study variables and type of analysis (unadjusted, adjusted, or longitudinal). The implementation is carried out with specific statistical procedures (e.g., analysis of variance or logistic regression) depending on the analysis being conducted as presented in the section "Factors Determining Statistical Analysis Method." The relationship between the factors and statistical procedures is presented in the "Analysis Methodologies" section. That presentation is followed by a discussion of Interpretive Considerations and a review of conventions for display of analysis results in the "Explanation of Tables" section.

MODELS AND ASSUMPTIONS

The statistical analyses in this report are based primarily on six models, each using a different estimate of exposure. The first model used group and military occupation (officer, enlisted flyer, and enlisted groundcrew) to assess health effects and dose-response relationships related to exposure. Serum dioxin measurements are not used in this model. The other five models account for dioxin effects either through estimated initial dioxin levels for Ranch Hands or using current or recent serum dioxin levels for Ranch Hands and Comparisons to assess health effects and dose-response relationships related to exposure. Analyses based on these models were carried out both unadjusted and adjusted for covariates.

Model 1: Group and Occupation as Estimates of Exposure

This section describes models that use the group (Ranch Hand, Comparison) of a participant to assess the relationship between health status and dioxin exposure. Statistical analyses of these models are termed "Model 1" in the assessment of the clinical areas. Analyses of this type are straightforward, easy to interpret, and well-established in epidemiological studies. In this model, exposure was defined as "yes" for Ranch Hands and "no" for Comparisons without regard to the magnitude of the exposure. As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast. These three contrasts compared Ranch Hands and Comparisons within each occupational category (officers, enlisted flyers, and enlisted groundcrew). As discovered in the analyses performed for the Serum Dioxin Analysis Report for the 1987 Followup, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers and then officers. While using occupation as a surrogate for exposure may be somewhat imprecise, it provides an estimate of exposure that cannot possibly be influenced by a health condition. Occupation as a surrogate for exposure is not subject to the possible biases based on health conditions that can occur with serum dioxin estimates. However, an implicit assumption underlying this model is that Comparisons were not exposed and Ranch Hands were exposed.

Table 7-1 shows these models, the assumptions, advantages, and disadvantages for a continuously distributed health variable y. The model presented in Table 7-1 is unadjusted for any covariates—adjusted models are a straightforward extension.

Models 2 through 6: Serum Dioxin as an Estimate of Exposure

Current dioxin levels in 1987 were determined by the Centers for Disease Control (CDC) from serum samples taken from approximately 2,000 Ranch Hands and Comparisons. Additional serum samples were taken from selected Ranch Hands and Comparisons at the 1992 followup to provide further insight on current dioxin levels and the elimination of dioxin from the body.

Further investigation of the mechanics of dioxin elimination are currently under study by the Air Force at this time. Based on samples collected at the pilot study, 1987 followup, and 1992 followup, issues such as half-life estimation and first-order pharmacokinetic assumptions are being further investigated.

Prior Knowledge Regarding Dioxin

This section presents analytic strategies based on assumptions and models conceived in 1988 and after the publication of the Ranch Hand dioxin pilot study and half-life substudy. At that time, available data showed that dioxin elimination appeared to follow first-order mechanisms. This observation was based on measurements subsequent to the ingestion of dioxin by an individual (5). Data on 36 Ranch Hand veterans with dioxin measured in blood drawn in 1982 and in 1987 produced a median half-life estimate of 7.1 years (6), and this median was used in all calculations involving half-life in this report.

Table 7-1.
Model 1: Assessing Health versus Group Status in Ranch Hands and Comparisons: Assumptions, Advantages, and Disadvantages

Model 1: $y = \mu + G_i + e$ **(All Ranch Hands and Comparisons)**
$y = \mu + G_i + O_j + (GO)_{ij} + e$ **(Ranch Hands and Comparisons by occupation)**

where,

- y = health variable
- G_i = effect due to group status (i = 1,2 - Comparisons, Ranch Hands)
- O_j = effect due to occupation (j = 1,2,3 - Officers, Enlisted Flyers, Enlisted Groundcrew)
- GO_{ij} = interaction between group status and occupation (i = 1,2, j= 1,2,3); used to examine Ranch Hand and Comparison differences for each occupation
- e = zero mean error.

Assumptions: Comparisons were unexposed and Ranch Hands were exposed.

For the purposes of investigating dose-response effects, enlisted groundcrew were more heavily exposed than enlisted flyers, and enlisted flyers were more heavily exposed than officers.

The error variance does not change with group status or occupation.

Advantages: Easily interpretable.

Occupation is an estimate of exposure that cannot possibly be influenced by a health condition, whereas the serum dioxin estimate can be influenced by a health condition.

Disadvantages: Results will be biased toward the null hypothesis of no dioxin effect if unexposed Ranch Hands are misclassified (i.e., remain in the analysis as exposed Ranch Hands). It is not possible to fully distinguish unexposed Ranch Hands from exposed Ranch Hands.

The term "elimination" denotes the overall removal of dioxin from the body. Some analyses in this report assume that the amount of dioxin in the body (C) decays exponentially with time according to the model $C = I \bullet \exp(-rt)$, where I is the initial level, $r = \log(2)/h$ is the decay rate, h is the half-life, and t is the length of time between the participant's time of duty in Southeast Asia (SEA) and the blood draw for dioxin performed at the pilot study in April 1987, the blood draw for dioxin performed at the 1987 physical examination, or the blood draw for dioxin performed at the 1992 physical examination. If a participant had measurements at more than one of these points in time, the measurement closest to the time of duty in SEA was used. This exponential decay law is termed "first-order elimination" in this report.

The first-order elimination assumption is not equivalent to assuming a one compartment model for dioxin distribution within the body. While a multicompartment model incorporating body composition and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) binding to tissue receptors would provide a detailed description of dioxin concentrations in

different compartments, published multicompartment models for TCDD distribution within the body predict first-order elimination of TCDD, overwhelmingly due to fecal excretion (7).

The lipid-weight concentration of TCDD, expressed in parts per trillion (ppt) (8,9), is a derived quantity calculated from the formula ppt = ppq•102.6/W, where ppt is the lipid-weight concentration, ppq (parts per quadrillion) is the actual whole weight of dioxin in the sample in femtograms, 102.6 corrects for the average density of serum, and W is the total lipid weight of the sample (7).

The relationship between the serum lipid-weight concentration of dioxin and lipid-weight concentrations in adipose tissue is a subject of continuing research. The correlation between the serum lipid-weight concentration and adipose tissue lipid-weight concentration of dioxin has been observed by Patterson et al. to be 0.98 in 50 persons from Missouri (10). Using the same data, Patterson et al. calculated the partitioning ratio of dioxin between adipose tissue and serum on a lipid-weight basis as 1.09 (95% C.I.=[0.97, 1.21]). On the basis of these data, a one-to-one partitioning ratio of dioxin between lipids in adipose tissue and the lipids in serum cannot be excluded. Measurements of dioxin in adipose tissue generally have been accepted as representing the body burden concentration of dioxin. The high correlation between serum dioxin levels and adipose tissue dioxin levels in the Patterson et al. study suggests that serum dioxin is also a valid measurement of dioxin body burden.

Fundamental Limitations of the Serum Dioxin Data

There are two evident limitations to the available data:

- While Ranch Hand data and ingestion data do not appear to violate a first-order elimination assumption, no serially repeated dioxin assay results taken over many years and with which to evaluate directly the adequacy of the first-order elimination model in humans are available yet.

- It is not known whether Ranch Hands with body burdens of dioxin at or below 10 ppt were exposed, and their body burdens had decayed to these levels since their time of duty in SEA, or whether they were not exposed at all during their time of duty in SEA.

Model 2: Health versus Initial Dioxin in Ranch Hands

The relationship between an estimated initial dioxin exposure and health was assessed within Ranch Hands using the model described in Table 7-2. Statistical analyses of these models are termed "Model 2" in the assessment of the clinical areas. In this model, an initial dioxin exposure was estimated for a Ranch Hand from a current or recent lipid-weight dioxin measure, the length of time between the time of duty in SEA and the date of the blood draw for dioxin, and an estimated half-life of 7.1 years. From exploratory studies conducted by the Air Force, body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin appear to be related to the half-life of a participant. These body fat variables were included in this model as explanatory, or independent, variables and were not removed during stepwise procedures,

Table 7-2.
Model 2: Assessing Health versus Initial Dioxin in Ranch Hands: Assumptions, Advantages, and Disadvantages

Model 2: $y = b_0 + b_1\log_2(I) + b_2BFTR + b_3BFCH + e$

where,

- y = health variable
- I = extrapolated initial dose, assuming first-order elimination, $I = 4+(C-4) \bullet \exp(\log(2) \bullet t/h)$, where 4 ppt is considered the median background level of lipid-adjusted current dioxin
- t = length of time between the time of duty in SEA and the date of the blood draw for dioxin in 1987 or 1992
- C = lipid-adjusted current dioxin, determined in 1987 or 1992
- h = dioxin half-life in Ranch Hands assuming first-order elimination (7.1 years assumed for analysis)
- BFTR = body fat at the participant's time of duty in SEA, calculated from the formula shown below.
- BFCH = change in body fat between the time of the participant's duty in SEA and the date of the blood draw for dioxin in 1987 or 1992, calculated from the formula shown below
- e = zero mean error.

Body fat will be calculated from a metric body mass index (11); the formula is

$$\textit{Body Fat (in percent)} = \frac{\textit{Weight (kg)}}{[\textit{Height (m)}]^2} \bullet 1.264 - 13.305.$$

Assumptions: Ranch Hands received a single dioxin dose in Vietnam and background exposure thereafter.

Ranch Hands experienced first-order dioxin elimination.

The error variance does not change with health status or initial dioxin dose.

Advantages: Easily interpretable.

Most efficient if first-order elimination and half-life are valid and y is linearly related to $\log_2(I)$.

Disadvantages: Will be biased if first-order elimination or constant half-life assumption is not valid.

which are explained subsequently. Table 7-2 also includes assumptions, advantages, and disadvantages for a continuously distributed health variable y. The model presented in Table 7-2 is unadjusted for any additional risk factors, but extension to an adjusted model is straightforward.

In Table 7-2, the phrase, "single dioxin dose," is a simplification of the process by which Ranch Hands accumulated dioxin during their time of duty in SEA. This process, which undoubtedly varied from individual to individual, is unknown. However, the time of duty in SEA for an individual Ranch Hand generally was short (1 to 3 years) relative to the time elapsed since his duty in SEA. Hence, additional knowledge regarding the accumulation of dioxin during an individual Ranch Hand's time of duty in SEA, were it to become available, likely would not change conclusions drawn from any of the statistical analyses.

Analyses were carried out on Ranch Hands who had lipid-adjusted current dioxin levels greater than 10 ppt at either the 1987 or 1992 physical examination. The value 10 ppt corresponds to the approximate 98th percentile of the Comparison lipid-adjusted current dioxin distribution. Based on this Comparison dioxin distribution, it is believed that participants with greater than 10 ppt lipid-adjusted current dioxin were definitely exposed. It is not known whether Ranch Hands with dioxin burdens at or below 10 ppt were exposed and their body burdens had decayed to these levels since their time of duty in SEA, or whether they were not exposed at all during their time of duty in SEA. Current dioxin levels less than 10 ppt are subsequently called "background" levels. No additional data or other information exist to determine whether any of the Ranch Hands with background levels (≤ 10 ppt) of current dioxin received a dose above background levels in SEA.

Model 3: Health versus Dioxin in Ranch Hands and Comparisons

An assessment of the health consequences of dioxin above background levels was carried out with a model that was applied to both Ranch Hand and Comparison data. This model assesses health versus dioxin body burden categorized into four levels. The four levels of categorized dioxin are given below:

- Comparisons—Comparisons with up to 10 ppt current lipid-adjusted dioxin
- Background—Ranch Hands with up to 10 ppt current lipid-adjusted dioxin
- Low, High—Ranch Hands with more than 10 ppt current lipid-adjusted dioxin.

Statistical analyses of these models are termed "Model 3" in the assessment of the clinical areas. The low and high Ranch Hand categories, of approximately equal size, were determined by the median estimated initial dioxin level of the Ranch Hands with more than 10 ppt current dioxin (i.e., the sample used in Model 2). In this model, an initial dioxin exposure was estimated for a Ranch Hand from a current or recent lipid-weight dioxin measure, the length of time between the time of duty in SEA and the date of the blood draw for dioxin, and an estimated half-life of 7.1 years. From exploratory studies conducted by the Air Force, body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin appear to be related to the dioxin half-life of a participant. These body fat variables were included in this model as independent variables that were not removed during stepwise procedures, which are explained subsequently. Using these body fat measures in Model 3 for all Comparisons and Ranch Hands with dioxin measurements allows body fat to act as a potential risk factor as well as an adjusting variable to explain half-life differences.

For a continuously distributed health variable y, for example, the mean values of y within the unknown, low, high, and low plus high categories combined were contrasted with the mean values of y within the background category. Relative frequencies were contrasted for discrete health variables. Table 7-3 shows this model, the assumptions, advantages, and disadvantages for the unadjusted analysis of a continuous variable—extension to an adjusted model is straightforward.

Table 7-3.
Model 3: Assessing Health versus Categorized Dioxin in Ranch Hands and Comparisons

Model 3: $y = b_0 + b_1I_1 + b_2I_2 + b_3I_3 + b_4I_4 + b_5BFTR + b_6BFCH + e,$

where

- y = health variable
- I_1 = indicator variable for current dioxin; $I_1 = 1$ if participant is a Comparison, $I_1 = 0$ if participant is not a Comparison
- I_2 = indicator variable for current dioxin; $I_2 = 1$ if participant is in background category, $I_2 = 0$ if participant is not in background category
- I_3 = indicator variable for current dioxin; $I_3 = 1$ if participant is in low category, $I_3 = 0$ if participant is not in low category
- I_4 = indicator variable for current dioxin; $I_4 = 1$ if participant is in high category, $I_4 = 0$ if participant is not in high category
- BFTR = body fat at the participant's time of duty in SEA, calculated from the formula shown below
- BFCH = change in body fat between the participant's time of duty in SEA and the date of the blood draw for dioxin in 1987 or 1992, calculated from the formula shown below
- e = zero mean error.

Body fat will be calculated from a metric body mass index (11); the formula is

$$\textit{Body Fat (in percent)} = \frac{\textit{Weight (kg)}}{[\textit{Height (m)}]^2} \cdot 1.264 - 13.305.$$

Assumptions: Dioxin body burden has accumulated with time.

The error variance does not change with categorized current dioxin body burden.

Advantages: Requires no assumption regarding the time course of dioxin accumulation or elimination.

Initial dioxin is probably a better measure for determining low and high exposure than current dioxin.

Less dependent on the accuracy of the estimation algorithm for determining initial dioxin than Model 2.

Disadvantages: Makes no use of prior belief that Ranch Hands received an unusually large dioxin dose in Vietnam; all Ranch Hands with high dioxin levels are treated similarly.

"Background" Ranch Hand category is probably a mixture of exposed and unexposed Ranch Hands. Analysis is biased toward the null hypothesis of no dioxin effect.

"Low" and "high" Ranch Hand categories are based on initial dioxin model, which is based on valid half-life and first-order dioxin elimination. Bias is possible if model is incorrect. Also, a conditional null hypothesis is tested using these categories ("Is there a dioxin effect, given a specified level of exposure?").

Models 4, 5, and 6: Health versus Current Dioxin in Ranch Hands

The relationship between current dioxin, as determined for most Ranch Hands at the 1987 followup, and health was assessed using the models described in Table 7-4. This table also describes the assumptions, advantages, and disadvantages for the unadjusted analysis of a continuously distributed health variable y.

Ranch Hands with a dioxin measurement may have had their blood drawn at the pilot study in April 1987, at the 1987 physical examination, or at the 1992 physical examination. If an individual has measurements at more than one of these points in time, the measurement closest to the time of duty in SEA was used. If only a 1992 serum dioxin measurement was available, the level was extrapolated to the date of the 1987 physical examination. The model

$$C_{1987} = 4+(C_{1992}-4)\bullet\exp(rt)$$

was used for extrapolation of lipid-adjusted current dioxin to 1987 levels (C_{1987}), and

$$C_{1987} = 24+(C_{1992}-24)\bullet\exp(rt)$$

was used for extrapolation of whole-weight current dioxin to 1987 levels (C_{1987}), where C_{1992} is the current dioxin level (lipid-adjusted or whole-weight) in 1992, 4 ppt is considered the median background level for lipid-adjusted current dioxin, 24 ppq is considered the median background level for whole-weight current dioxin, $r = \log(2)/h$ is the decay rate, h is the half-life (7.1 years), and t is the length of time between the physical examination in 1987 and the physical examination in 1992. This model was only used if the lipid-adjusted current dioxin level in 1992 was greater than 10 ppt; otherwise the 1992 measurement was used.

Three models were analyzed with current dioxin used as the estimate of exposure. Statistical analyses of these models are termed "Model 4," "Model 5," and "Model 6" in the assessment of the clinical areas. There is scientific debate as to the appropriate current dioxin measure. For the Serum Dioxin Analysis Report for the 1987 Followup, a lipid-weight current dioxin measure was used. As described above, the lipid-weight current dioxin measure (ppt) is related to the whole-weight dioxin measure (ppq) from the formula $ppt=ppq\bullet 102.6/W$, where ppt is the lipid-weight concentration, ppq is the actual whole weight of dioxin in the sample in femtograms, 102.6 corrects for the average density of serum, and W is the total lipid weight of the sample. Other researchers advocate the use of the whole-weight current dioxin measure.

The models are similar in form to Model 2 ($y = b_0 + b_1\log_2(I) + e$, see Table 7.2), except that a current dioxin measure was used instead of an initial dioxin estimate. Model 4 used the logarithm (base 2) of lipid-weight current dioxin. Model 5 used the logarithm (base 2) of whole-weight current dioxin. Model 6 used the logarithm (base 2) of whole-weight current dioxin, with the logarithm (base 2) of the total lipid weight of the sample ($\log_2[W]$) as an independent variable that was not removed during stepwise procedures, which are explained subsequently.

Table 7-4.
Models 4, 5, and 6: Assessing Health versus Current Dioxin in Ranch Hands: Assumptions, Advantages, and Disadvantages

Model 4: $y = b_0 + b_1\log_2(ppt) + e$
Model 5: $y = b_0 + b_1\log_2(ppq) + e$
Model 6: $y = b_0 + b_1\log_2(ppq) + b_2\log_2(W) + e$

where

y = health variable
ppt = lipid-weight current dioxin = ppq•102.6/W,
ppq = whole-weight of dioxin in the sample in femtograms (102.6 corrects for the average density of serum)
W = total lipid weight of the sample
e = zero mean error.

Assumptions: Ranch Hands received a single dioxin dose in Vietnam and background exposure thereafter.

The error variance does not change with health status or current dioxin.

Advantages: Using current dioxin has less inherent variation than initial dioxin, which is extrapolated by a first-order elimination model across a 15- to 25-year time period.

Disadvantages: Current dioxin may not be a good surrogate for exposure if elimination rate differs for individuals.

Individuals with measurements in 1992 only will be extrapolated to 1987, and variation will be increased with estimation using a first-order elimination model.

FACTORS DETERMINING STATISTICAL ANALYSIS METHOD

For a specified questionnaire-based or clinical measurement determined from the physical or laboratory examination, the selection of an analytical method depends on each of the following:

- Dependent Variable Form: Continuous or discrete
- Exposure Estimate and Analysis Cohort:
  - Model 1: Group—All Ranch Hands and Comparisons
  - Model 2: Initial dioxin—Ranch Hands greater than 10 ppt of current lipid-weight dioxin
  - Model 3: Categorized dioxin—Comparisons with 10 ppt lipid-weight dioxin or less and all Ranch Hands with a dioxin measurement
  - Models 4, 5, & 6: Current dioxin—All Ranch Hands with a dioxin measurement
- Analysis Type: Unadjusted, adjusted, or longitudinal.

Appendix Table D-1 specifies 22 separate analysis situations based on dependent variable form, exposure estimate, analysis cohort, and analysis type. For each of the 22 situations, the statistical method is specified. For example, linear regression models are used for adjusted analyses of initial dioxin for continuous dependent variables.

ANALYSIS METHODOLOGIES

Methods for Analyzing Continuous and Discrete Variables

Similar to the analyses conducted in previous AFHS reports, health endpoints, or dependent variables, were treated as either continuous or discrete. For unadjusted analyses of Model 1, t-tests were used for continuous dependent variables and chi-square tests were used for discrete dichotomous variables to test for differences between Ranch Hands and Comparisons.

For other analyses of continuous dependent variables, the general linear model approach was used for applying such techniques as simple and multiple linear regression, analysis of variance, analysis of covariance, repeated measures analysis, and failure time analysis. This approach permitted model fitting of the dependent variable as a function of group or dioxin, relevant covariates, group-by-covariate or dioxin-by-covariate interactions, and interactions between covariates. Continuous dependent variables were examined to ensure that assumptions underlying appropriate statistical methods were met. Transformations were used to enhance normality for specific continuous health variables. A general method for determining a transformation can be found in an article by Box and Cox (12), and this method was used as a guide in determining the appropriate transformation. A further discussion of general linear models, as well as other methods used for the statistical analysis in this report, is found in Table 7-5.

For these continuous analyses, the SAS® procedure GLM (13) was used. When a "best" model was fitted, tests of significance for a group or dioxin effect were made. Associations with a p-value less than or equal to 0.05 were described as significant, and associations with a p-value greater than 0.05 but less than or equal to 0.10 were described as marginally significant. If there was a significant interaction between group or dioxin and any covariate, the effect of group or dioxin on the dependent variable was assessed using stratification by different levels of the covariate(s) involved in the interaction.

The SAS® procedures LIFEREG and LIFETEST (13) were used for the time to diabetes onset variable in the endocrine clinical assessment. This variable consisted of censored and noncensored data, and statistical methods used to analyze measures of this type implement a technique known as "failure time" analysis. A further discussion of failure time analysis is found in Table 7-5.

Discrete dependent variables were analyzed by methods parallel to those used for continuous variables. For dichotomous discrete dependent variables, logistic regression was performed using BMDP®-LR (14). For dependent variables with more than two categories, polychotomous logistic regression was performed using BMDP®-PR (14). Parameter estimation and model selection for polychotomous logistic regression and ordinary logistic

Table 7-5.
Summary of Statistical Procedures

Chi-square Contingency Table Test

The chi-square test of independence (15) is calculated for a contingency table by the following formula:

$$\chi^2 = \sum \frac{(f_O - f_E)^2}{f_E}$$

where the sum is taken over all cells of the contingency table and

f_o = observed frequency in a cell
f_e = expected frequency under the hypothesis of independence.

Large values indicate deviations from the null hypothesis and are tested for significance by comparing the calculated χ^2 to the tables of the chi-square distribution.

For 2x2 tables, the chi-square statistic above will be adjusted for the continuity of the χ^2 distribution. This test statistic yields p-values approximately equal to Fisher's exact test (16) for a two-sided alternative and is as follows:

$$\chi^2 = \sum \frac{\max\left(0, \left(|f_O - f_E| - \frac{1}{2}\right)\right)^2}{f_E}$$

Correlation Coefficient (Pearson's Product-Moment)

The population correlation ρ (17) measures the strength of the linear relationship between two random variables X and Y. A commonly used sample-based estimate of this correlation coefficient is

$$\rho = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{[\sum (x_i - \bar{x})^2 (y_i - \bar{y})^2]}}$$

where the sum is taken over all (x,y) pairs in the sample. A student's t-test based on this estimator is used to test for a significant correlation between the two random variables of interest. For the sample size of 2,233 in this study, a sample correlation coefficient of 0.0415 is sufficient to attain a statistically significant correlation at a 5-percent level for a two-sided hypothesis test, assuming normality of X and Y.

Table 7-5. (Continued)
Summary of Statistical Procedures

Failure Time Analysis

The failure time (or survival time) model (18) permits a dependent variable with censored observations to be modeled in a general linear models framework. For example, if the time to diabetes onset is defined as a "failure," the time for participants that have not "failed" is right censored. The failure time model is

$$y = X\beta + \sigma\epsilon$$

where,

- y = vector of responses (e.g., time to diabetes onset), usually the logarithm of the failure times
- X = matrix of covariates, or risk factors (e.g., group status and age)
- β = vector of unknown regression parameters
- σ = unknown scale parameter
- ϵ = vector of errors assumed to come from a known distribution.

For a model with a dependent variable containing right censored data, the log likelihood function is a combination of a probability density function for noncensored values and a survival distribution function for right-censored values. The model parameters can be estimated by maximum likelihood in the SAS® LIFEREG procedure, using a Newton-Raphson algorithm, where the distribution of the random error term can be specified. The distributional assumptions of the error term can be tested by examining plots of the Kaplan-Meier survival functions using the SAS® LIFETEST procedure.

The LIFEREG procedure will provide estimates, standard errors, and p-values associated with a chi-square test on each parameter (i.e., risk factor) in the model. These are used to test the significance of the group or dioxin term in the unadjusted and adjusted models, and to step out the nonsignificant covariate terms. In this procedure, percentile estimates also can be produced for each group or each dioxin category in the unadjusted model. The percentile estimates are used to determine parameter estimates from the Weibull distribution. The Weibull distribution parameter estimates are then used in an iterative nonlinear estimation procedure (SAS® PROC NLIN) to produce estimated means from a censored Weibull distribution. The loss function that is minimized in the estimation procedure is

$$Loss = -\log[x \bullet (\frac{\beta}{\theta^{\beta}} \bullet y^{\beta-1} \bullet e^{-(\frac{y}{\theta})^{\beta}}) + (1-x) \bullet (1-e^{-(\frac{y}{\theta})^{\beta}})],$$

where, $x=1$ if diabetic
$x=0$ if not diabetic

and y=time to onset of diabetes.

Table 7-5. (Continued)
Summary of Statistical Procedures

Fisher's Exact Test

Fisher's exact test (15) is a randomization test of the hypothesis of independence for a 2 x 2 contingency table. This technique was used for small samples and sparse cells. This is a permutation test based on the exact probability of observing the particular set of frequencies, or of one more extreme.

General Linear Models Analysis

The form of the general linear model (17) for two independent variables is

$$Y_i = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \epsilon_i$$

where,

Y	=	dependent variable (continuous)
α	=	level of Y at $X_1 = 0$ and $X_2 = 0$ (i.e., the intercept)
X_1, X_2	=	measured value of the first and second independent variables respectively, which may be continuous or discrete (e.g., group status and age)
β_1, β_2	=	coefficient indicating linear association between Y and X_1, Y and X_2 respectively; each coefficient reflects the effect on the model of the corresponding independent variable adjusted for the effect of the other independent variable
β_{12}	=	coefficient reflecting the linear interaction of X_1 and X_2, adjusted for linear main effects
ϵ_i	=	error term.

This model assumes that the error terms are independent and normally distributed with a mean of 0 and a constant variance. Extension to more than two independent variables and interaction terms is immediate. Simple linear regression, multiple linear regression, analysis of variance, analysis of covariance, and repeated measures analysis of variance are all examples of general linear models analysis.

Log-linear Analysis

Log-linear analysis (15) is a statistical technique for analyzing cross classified data or contingency tables. A saturated log-linear model for a three-way table, for example, is

$$\ln (Z_{ijk}) = U_0 + U_{1(i)} + U_{2(j)} + U_{3(k)} + U_{12(ij)} + U_{23(jk)} + U_{13(ik)} + U_{123(ijk)}$$

where,

Z_{ijk}	= expected cell count
$U_{1(i)}$	= specific one-factor effect
$U_{12(ij)}$	= specific two factor interaction
$U_{123(ijk)}$	= three-factor interaction.

The simplest models are obtained by including only the significant U-terms. Adjusted relative risks are derived from the estimated U-terms from a fitted model.

Table 7-5. (Continued)
Summary of Statistical Procedures

Logistic Regression Analysis

The logistic regression model (19) enables a dichotomous dependent variable to be modeled in a regression framework with continuous and/or discrete independent variables. For two risk factors, such as dioxin and age, the logistic regression model would be

$$\text{logit } P_i = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \epsilon_i$$

where,

P_i	=	probability of disease for an individual with risk factors X_1 and X_2
logit P_i	=	ln $(P_i/(1-P_i))$ (i.e., the log odds for disease)
X_1	=	first risk factor (e.g., dioxin)
X_2	=	second risk factor (e.g., age).

The parameters are interpreted as follows:

α	=	log odds for the disease when $X_1 = 0$ and $X_2 = 0$
β_1	=	coefficient indicating the dioxin effect adjusted for age
β_2	=	coefficient indicating the age effect adjusted for dioxin
β_{12}	=	coefficient indicating the interaction between dioxin and age, adjusted for linear main effects
ϵ_i	=	error term.

In the absence of an interaction ($\beta_{12} = 0$) for a dichotomous measure (e.g., Comparisons, Ranch Hands), $\exp(\beta_1)$ reflects the adjusted odds ratio for individuals in group 1 ($X_1 = 1$) relative to group 0 ($X_1 = 0$). If the probability of disease is small, the odds ratio will be approximately equal to the relative risk. In the absence of an interaction for a continuous risk factor (e.g., initial dioxin in its continuous form), $\exp(\beta_1)$ reflects the adjusted odds ratio for a unit increase in the risk factor. If the risk factor is expressed in logarithmic (base 2) form, $\exp(\beta_1)$ reflects the adjusted odds ratio for a twofold increase in the risk factor. Throughout this report, the adjusted odds ratios will be referred to as adjusted relative risks. Correspondingly, in the absence of covariates (i.e., unadjusted analysis), the odds ratios will be referred to as estimated relative risks.

This technique also will be used for longitudinal analyses of dichotomous dependent variables to examine changes in health status between 1982 (or 1985) and 1992 in relation to the dioxin measures.

Two-Sample t-Test

A statistical test for determining whether or not it is reasonable to conclude that two population means are unequal utilizes the t-distribution (17). Tests can be performed when population variances are equal or unequal; however, different t-distributions are used.

Table 7-5. (Continued)
Summary of Statistical Procedures

Polychotomous Logistic Regression Analysis

Polychotomous logistic regression (19,20) allows a categorical dependent variable with more than two outcomes to be modeled in a regression environment with continuous and discrete independent variables. For polychotomous logistic regression, the model equation depends upon the scale of the dependent variable. This discussion will focus on nominal scaled dependent variables.

Suppose Y is a nominal scaled dependent variable with three outcomes labeled 0, 1, or 2 (normal, low, or high). Polychotomous logistic regression models two logit functions, one for Y = 1 versus Y = 0 and the other for Y = 2 versus Y = 0. The zero outcome for Y is called the reference category. To model Y with two covariates such as group status and age, the polychotomous regression model would be

$$\text{logit } P_1 = \alpha_1 + \beta_{1(1)}X_1 + \beta_{1(2)}X_2 + \beta_{1(12)}X_1X_2 + \epsilon_1$$

$$\text{logit } P_2 = \alpha_2 + \beta_{2(1)}X_1 + \beta_{2(2)}X_2 + \beta_{2(12)}X_1X_2 + \epsilon_2$$

where,

P_i = probability that Y = i (outcome i) with covariates X_1 and X_2, i = 0, 1, 2
logit P_i = ln (P_i/P_0) (i.e., the log odds of outcome i versus outcome 0, i = 1, 2)
X_1 = first effect (e.g., group status)
X_2 = second effect (e.g., age).

The parameters are interpreted as follows:

α_i = log odds of outcome i versus outcome 0 when $X_1 = 0$ and $X_2 = 0$, i = 1, 2
$\beta_{i(1)}$ = coefficient indicating the group status effect on the logit P_i, adjusted for age, i = 1, 2
$\beta_{i(2)}$ = coefficient indicating the age effect on the logit P_i, adjusted for group status, i = 1, 2
$\beta_{i(12)}$ = coefficient representing the interaction effect of group status and age on the logit P_i, adjusted for the main effects, i = 1, 2
ϵ_i = error term for logit P_i, i = 1, 2.

This model assumes independent multinomial sampling.

Because the interpretation of each logistic modeling function is similar, consider the logit P_1 and suppose X_1 is a binary covariate ($X_1 = 1$ for Ranch Hands or $X_1 = 0$ for Comparisons). In the absence of interaction ($\beta_{1(12)} = 0$), $\exp(\beta_{1(1)})$ equals the adjusted odds ratio of low versus normal for Ranch Hands ($X_1 = 1$) compared to Comparisons ($X_1 = 0$). If the probability of being low is small compared to being normal for both the Ranch Hand and Comparison groups, the odds ratio of low versus normal will be approximately equal to the relative risk of being low between the two groups. If X_1 is a continuous covariate that does not interact with X_2, $\exp(\beta_{1(1)})$ represents the adjusted log odds ratio of outcome 1 versus outcome 0 for a unit increase in X_1.

regression are very similar. Both forms of regression use the maximum likelihood principle to obtain parameter estimates. For a model with k parameters for two equations, 2k parameters need to be estimated, k for each logit function. If ordinary logistic regression is applied twice, (for example, once for abnormal low versus normal and then for abnormal high versus normal) 2k parameters also will need to be estimated. However, ordinary logistic regression maximizes two likelihood equations, each with k parameters, while polychotomous logistic regression estimates all 2k parameters simultaneously with one likelihood equation. To select a final model, polychotomous logistic regression utilizes a stepwise regression procedure similar to the stepwise procedure used in BMDP®-LR. Polychotomous linear regression also can be used for dependent variables that have more than three levels and require more than two contrasts with a normal category. A further discussion of logistic regression and polychotomous logistic regression is found in Table 7-5.

The abnormal and normal categorizations for many of the discrete analyses were defined by categorizing laboratory and physical examination measures according to laboratory and clinic reference values. Cutpoints for the dependent variables sedimentation rate, cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and free testosterone were age-dependent. Consequently, normal and abnormal levels were constructed according to a participant's laboratory value and age at the physical examination. Additionally, cutpoints for serum insulin, serum glucagon, serum proinsulin, and serum C peptide were dependent on whether the participant was fasting. Normal and abnormal levels for these variables were constructed according to a participant's laboratory value and fasting status at the physical examination.

Modeling Strategy

In each clinical category, many covariates were considered for inclusion in the statistical models relating specific health endpoints and group or dioxin. The large number of covariates, consequent interaction terms, and resulting difficulties of interpretation obligate the adoption of a strategy for identifying a moderately simple model using a stepwise strategy, as outlined below. Interpretation of possible relationships were then made in the context of this simpler model.

In general, based on one of the adjusted analysis models described in Appendix Table D-1, a starting model for continuous variables was constructed containing two-factor interactions. First, screening was performed at the 0.15 significance level to eliminate unnecessary two-factor interactions. A hierarchical stepwise deletion strategy then was applied at the 0.15 significance level on the set of main effect covariates (to address possible confounding effects between the covariates and group or dioxin) and at the 0.05 significance level for interactions.

The modeling strategy was refined slightly for adjusted statistical analyses of discrete dependent variables. In particular, the starting model included all main effects and excluded all interactions. Main effects were stepped out of the model if the associated p-value was greater than 0.15 and interactions were entered into the model if the associated p-value was less than or equal to 0.05. The alternative strategy was used to avoid overspecification of the model and minimize collinearity among terms that could lead to imprecise parameter and

standard error estimates, especially where a large number of covariates or sparse number of abnormalities were encountered.

In general, the only effects not subject to the deletion strategy were the group or dioxin variables of interest (that is, group, initial dioxin, or current dioxin). For specific clinical areas, certain covariates were entered into the model and were not subject to the deletion strategy. In particular, caloric intake was retained in one set of analyses for body fat in the General Health Assessment (Chapter 9). For the analysis of diabetic participants in the Endocrine Assessment (Chapter 18), diabetic severity was retained in the model and was not subject to the deletion strategy. Age was retained in all final models of verified medical records variables in the Neurology Assessment and the Gastrointestinal Assessment (Chapters 11 and 13 respectively).

As described above, body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin were included in Models 2 and 3 and were not removed during stepwise procedures. Also, in Model 6, the logarithm (base 2) of the total lipid weight of the sample ($\log_2[W]$) was not subject to the deletion strategy.

With the objective of producing the simplest model, other lower-order effects were retained in the model only if they were involved in significant higher-order interactions. Significant two-factor interactions between covariates were retained in the model. If necessary, the modeling strategy for the adjusted analyses of dependent variables in certain clinical areas was modified because of the large number of covariates and sparse number of abnormalities, which could cause problems in the model estimation. As appropriate, pairwise covariate interactions were not investigated. If estimation problems were still encountered, stepwise procedures began with main effects only models. Also, preliminary investigation of dependent variable-covariate associations was conducted to possibly reduce the number of candidate covariates in the adjusted analyses of some clinical areas (for example, investigations of the lifetime alcohol history and current alcohol use covariates were conducted for the Cardiovascular Assessment, and the lifetime alcohol history covariate was retained for use in adjusted analyses—see Chapter 15).

In the analysis of a particular health variable, when no group or dioxin-by-covariate interactions were significant at the 0.05 level, adjusted means (21) and slopes or adjusted relative risks were presented. If the interaction was significant at the 0.05 level, the behavior of the group or dioxin variable was explored for different levels (categories) of the covariate to identify subpopulations for which a relationship might exist or where the relationship differs between subpopulations. Further, if any group or dioxin-by-covariate interaction was significant at a level between 0.01 and 0.05, the adjusted means and slopes or adjusted relative risks also were presented, after dropping the interaction term from the model. Also, at the discretion of the analyst, adjusted results may be presented after dropping the interaction term from the model if a group-by-covariate interaction or a dioxin-by-covariate interaction was significant at a level less than or equal to 0.01.

In many instances the clinical importance of a statistically significant group-by-covariate or dioxin-by-covariate interaction is unknown or uncertain. The clinical relevance of a

statistically significant interaction is strengthened if the same interaction persisted among related endpoints. Due to the large number of these types of interactions examined for approximately 330 variables, it is recognized that some of the group-by-covariate or dioxin-by-covariate interactions judged significant at the 0.05 level were spurious; that is, chance occurrences not of biological or clinical relevance. This issue was considered when these significant interactions were interpreted. It is important that the size of the p-value associated with each of these interactions is weighed carefully; for this reason, if the p-value for a group-by-covariate or dioxin-by-covariate interaction was between 0.01 and 0.05, the adjusted means or relative risks (omitting the interaction) were reported.

For all models that included a group-by-covariate or dioxin-by-covariate interaction in the final adjusted model, the stratified results display adjusted means, adjusted slopes, or relative risks, confidence intervals, and associated p-values determined from a model that included the interaction term. On occasions where cell sizes were small, statistics were generated from separate models for each covariate stratum. In general, results based on an analysis stratified by the covariate(s) involved in a group-by-covariate interaction or a dioxin-by-covariate interaction are not discussed in the text of a chapter. Usually only the results based on analyses performed after the deletion of an interaction are discussed in the text of a chapter. Exceptions to this strategy include interactions judged to be clinically relevant and situations where no additional analyses were performed omitting the interaction ($p \leq 0.01$ for the group-by-covariate or dioxin-by-covariate interaction).

Specialized Analyses

Military occupation was used in specialized analyses of Model 1. In particular, occupation and a group-by-occupation interaction was investigated in the context of the final model for Model 1 analyses. A final model was developed for each dependent variable, with group contained in the final model. As an additional analysis, if occupation and the group-by-occupation interaction were not in the final model, then they were added to this model. Summary statistics and results for the group variable were reported, and statistics and results on the group variable were presented for each occupational stratum.

For all clinical areas, with the exception of neoplasia, additional analyses were performed when occupation was retained in the final model for the five models involving dioxin. Dioxin exposure and occupation are related due to the military occupational duties performed by the participants. With the exception of neoplasia, occupation also is considered to be a risk factor in assessing the health of the participants. Analyses were consequently performed with occupation in the final model when it was significant, and again with occupation removed from the model. The results of analyses without occupation in the final adjusted model are only discussed in the text if the level of significance (significant, marginally significant, nonsignificant) differs from the original final adjusted model.

For the Neurology, Cardiovascular, Renal, Endocrine, and Pulmonary clinical assessments, additional analyses were performed when certain covariates were retained in the final model for the five models involving dioxin. These data showed significant associations with dioxin for the 1992 followup data, and included diabetic class (Neurology, Cardiovascular, Renal, and Endocrine Assessments), percent body fat (Cardiovascular,

Endocrine, and Pulmonary Assessments), total cholesterol (Cardiovascular and Endocrine Assessments) and HDL cholesterol (Cardiovascular and Endocrine Assessments). These covariates are well-known risk factors and should be introduced into adjusted models; however, these covariates may have been affected by dioxin exposure. Adjustment for these covariates has the potential to "over-adjust" the model for the effects of dioxin exposure. Due to the association between these covariates and dioxin, both the statistical and clinical interpretations of other health variables can be affected. When these analyses were found to be significantly associated with a dependent variable and retained in the final model, the dioxin effect was evaluated in the context of two models. In particular, analyses were performed with and without these covariates in the model to investigate whether conclusions regarding the association between the health endpoint and dioxin differ. The results of the analyses without these covariates in the final adjusted model are only discussed in the text if the level of significance (significant, marginally significant, nonsignificant) differs from the original final adjusted model.

Longitudinal Analyses

Selected longitudinal analyses were performed investigating changes in health status between 1982 and 1992 for Models 1, 2, and 3 as a function of dioxin exposure. Models 4, 5, and 6 were not examined in longitudinal analyses because current dioxin, the estimate of exposure in these models, changes over time and is not available for all participants in 1982 or 1992. All three models were adjusted for age in 1992. Age is a well-known risk factor for nearly all clinical areas, and although Ranch Hands and Comparisons were matched on age, the estimates of dioxin exposure in Models 2 and 3 were not.

In the longitudinal analysis of discrete variables, only those participants whose health was classified as normal in 1982 were included in the analysis of the participants' health at the 1992 examination. Participants classified as "abnormal" in 1982 were excluded because the focus of the analysis was to investigate the temporal effects of dioxin exposure between 1982 and 1992. Participants classified as "abnormal" in 1982 were already abnormal before this period; consequently, only participants classified as "normal" at the 1982 examination were considered to be at risk when the effects of dioxin over time are explored. The rate of abnormalities under this restriction approximates the cumulative incidence rate between 1982 and 1992.

The dependent variable in this type of analysis was the health of participants at the 1992 examination whose health was normal in 1982. The independent variables were the appropriate exposure estimate and age in 1982. The analyses of Models 2 and 3 also were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin. Tabular displays of the longitudinal analyses results of discrete dependent variables include summary statistics for 1982 and 1992, as well as 1985 and 1987 summaries if available. The results of the statistical analyses restricted to those participants who were normal in 1982 also are provided.

In the longitudinal analyses of continuous variables, a general linear model approach, as explained in Table 7-5, was used. The dependent variable was the difference between the

1992 measurement and the 1982 measurement. This difference, measuring the change in the endpoint over this period of time, was modeled as a function of the estimate of exposure (group or dioxin), the participant's age in 1982, and the 1982 measurement of the continuous dependent variable. The analyses of Models 2 and 3 also were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin. Use of the health endpoint measurement from 1982 has the following three purposes:

- A linear relationship between measurements of the dependent variable in 1982 and 1992 due to a difference in measuring devices will be accounted for by using the 1982 measurement as an independent variable. For many of the laboratory measurements in 1982, 1985, and 1987 the Dupont Automated Chemical Analyzer® (ACA) was used. The Baxter/Dade Paramax® was used extensively in the 1992 laboratory analyses.

- The difference between two values taken over a period of time is generally correlated with the first measurement (22).

- The relationship between the difference of the 1992 and 1982 measurements and the estimate of exposure may be confounded with the 1982 measurement, especially if the endpoint and the estimate of exposure are related.

Tabular displays of the results of longitudinal analyses of continuous dependent variables include summary statistics for 1982 and 1992, as well as 1985 and 1987 summaries if available. Results of the statistical analyses relating the difference in the 1992 and 1982 measurements to the estimate of exposure also are provided.

For some variables, 1985 clinical measurements were substituted for 1982 measurements because the variable was not analyzed at the 1982 examination or was inherently different from the 1992 variable due to differing analytical methods. For example, to enhance comparability, the longitudinal analyses for the Neurological Assessment were based on changes between 1985 and 1992 because Scripps Clinic and Research Foundation (SCRF) conducted both of these examinations, whereas the Kelsey-Seybold Clinic conducted the 1982 examinations.

INTERPRETIVE CONSIDERATIONS

Several specific issues to be considered when interpreting the results found in this report are discussed in this section. The issues discussed here include adjusted analyses, multiple testing, trends in the results of endpoints within a clinical area, the proportion of variation explained by the model (R^2), interpretation of continuous and discrete analyses of a health endpoint, and the ability to detect a significant difference based on the data at hand (power of the analyses). Additional interpretive considerations can be found in Chapter 1, Introduction.

Adjustments for Covariates and Interactions

In contrasts between all Ranch Hands and all Comparisons (Model 1) the matching variables age, race, and occupation were effectively eliminated as confounders. The current dioxin and initial dioxin analyses within Ranch Hands (Models 2, 4, 5, and 6) and the categorized current dioxin analyses within Ranch Hands and Comparisons (Model 3) did not benefit from the matched design. For example, military occupation is a strong confounder because it is highly correlated with current dioxin levels in Ranch Hands and is related to some health variables through socioeconomic differences between officers and enlisted personnel. Education is highly associated with military occupation and certain psychometric results. Consequently, with the exception of a few analyses where the prevalence or history of abnormal results is sparse, all health endpoints were analyzed with and without adjustment for clinically relevant covariates.

In addition, some covariates (e.g., percent body fat) may themselves be associated with dioxin exposure and may be related to the dependent health variable through their relationship with dioxin. In this situation, analyses of covariance adjusted for such a covariate are not valid, because the assumed independence of the "treatment" (current or initial dioxin) and the covariate is not met (23). There is no recourse but to analyze the data with and without adjustment for the covariate (see Specialized Analyses section above); both analyses potentially are biased. Unadjusted analyses must be viewed with caution and circumspection and, because some covariates may act in an intervening manner relating the "treatment" to the dependent variable, some adjusted analyses of covariance are themselves subject to bias. Bias introduced by intervening covariates is unavoidable in an observational study.

The adjusted models assessed the statistical significance of interactions between group or dioxin and the covariates to determine whether the relationship between group or dioxin and the health endpoint differed across levels of the covariate. Many times, the clinical importance of a statistically significant group-by-covariate or dioxin-by-covariate interaction is unknown or uncertain. The clinical relevance of a statistically significant interaction would be strengthened if the same interaction persisted among related endpoints. Due to the large number of group-by-covariate or dioxin-by-covariate interactions that were examined for approximately 300 variables, some of the interactions found significant at the 0.05 level might be spurious (i.e., chance occurrences not of biological or clinical relevance). This issue should be considered when significant group-by-covariate or dioxin-by-covariate interactions are interpreted. It also is important that the size of the p-value associated with each interaction be weighed carefully. For this reason, models without the dioxin-by-covariate interaction were implemented to address the possibility that some interactions may arise from multiple testing (see Modeling Strategy section above and Multiple Testing section below). Also, implementing models without the group-by-covariate or dioxin-by-covariate interactions allows the reader to examine results for all participants combined, whereas the interaction analyses explore the different relationships between dioxin and the dependent variable, depending on the subgroups of participants examined.

Multiple Testing

Numerous dependent variables were considered because of the lack of a predefined medical endpoint. Each dependent variable was analyzed in many different ways to accommodate covariate information and different statistical models. Under the hypothesis of no relationship between physical health and dioxin, approximately 5 percent of the many statistical tests (group or dioxin effects and group-by-covariate or dioxin-by-covariate interactions) in this report would be expected to detect an association between group or dioxin and health (p-values ≤ 0.05). Observing significant results due to multiple testing, even when there is no relationship between dioxin and health, is known as the multiple-testing artifact and is common in all large studies. Unfortunately, there is no statistical procedure to distinguish between those statistically significant results that arise due to the multiple testing artifact and those that may be due to an actual dioxin effect. Instead, in order to weigh and interpret the findings, the authors have considered the strength of the association, consistency, dose-response patterns, and biologic plausibility.

Trends

Assessing consistent and meaningful trends is essential when interpreting any comprehensive study with multiple endpoints, clinical areas, and covariates; however, caution must be used. Increased numbers of abnormalities or mean values with increased dioxin levels across medically related variables within a clinical area might indicate a group or dioxin effect. However, there may be a moderate-to-strong correlation between these endpoints, where a change in one variable leads directly to a change in the other. Hence, the strength of the trends also must be considered when assessing the suspected association.

Interpretation of the Coefficient of Determination

The coefficient of determination (R^2) measures the proportionate reduction of the total variation in a continuously distributed health variable (y) associated with the set of independent variables in a linear regression. A large value of R^2 does not necessarily imply that the fitted model is a useful one. Large values of R^2 would occur, for example, if y is regressed on an independent variable with only a few observed values. On the other hand, very small values of R^2 are generally seen in observational studies because little or no control has been applied in the assignment of the values of the "treatment" (dioxin) or the conditions under which the "treatment" has been applied. In this study, the dioxin measurements were taken many years after exposure and are themselves subject to some measurement error. Thus, in most analyses in this report, the values of R^2 are small.

Clinical Interpretation of Discrete versus Continuous Data

Small but significant mean differences in a continuously measured health variable (e.g., systolic blood pressure) between exposed and unexposed groups when there are no corresponding differences in the percentage of abnormal tests are difficult to assess in any study. In this study, significant mean differences are sometimes observed without a corresponding group difference in the proportion outside the normal range. Such contrasting situations may be interpreted as spurious outcomes of no clinical consequence, or as a

subclinical dioxin effect. Significant trends in the mean with increasing levels of dioxin are interpreted as a dioxin-related effect if a corresponding trend is seen in the proportion above or below the normal range or if the trend is consistent with other findings.

Power

Conducting a statistical test using a type I error, also called an alpha or significance level, of 0.05 means that, on the average in 5 cases out of 100, a false conclusion would be made that an association (group or dioxin effect) exists when, in reality, there is no association. The other possible inference error, a type II error, is the failure to detect an association when one actually exists. The power of a statistical test is 1 minus the probability of a type II error. The power of the test is the probability that the test will reject the hypothesis of no group or dioxin effect when an effect does in fact exist.

The fixed size of the Ranch Hand cohort limits the ability of this study to detect some group or dioxin associations if they exist. This limitation is most obvious for specific types of cancer, such as soft tissue sarcoma and non-Hodgkin's lymphoma. These conditions are so uncommon that fewer than two cases are expected in this study, indicating that there is virtually no statistical power to detect low-to-moderate associations between dioxin and cancer. In an attempt to overcome the lack of power to detect group differences for specific types of systemic cancer, for example, all types of systemic cancer were combined into a single variable. It is still possible, however, that an increased risk could exist for a particularly rare type of cancer, allowing that increased risk to be missed in this study.

Table 7-6 and Appendix Tables D-2 through D-5 contain the approximate power at a significance level of 0.05 to detect specified relative risks for a given prevalence rate of a discrete dependent variable. Table 7-6 presents power calculations for Model 1 (group), and Appendix Tables D-2 through D-5 presents power calculations for Model 2 (initial dioxin), Model 3 (categorized dioxin—low plus high Ranch Hand versus Comparison contrast), Model 4 (lipid-adjusted current dioxin), and Models 5 and 6 (whole-weight current dioxin). Power calculations were performed using the logarithm (base 2) of dioxin in Models 2, 4, 5, and 6, and consequently, the relative risk is for a twofold increase in dioxin. The power of a test for a discrete variable depends on the significance level, actual relative risk, prevalence of the condition, and the Ranch Hand and Comparison sample sizes (for Models 1 and 3) or the distribution of the dioxin data (for Models 2, 4, 5, and 6).

As an example, using age-adjusted incidence rates for all U.S. males (based on data from the Surveillance Epidemiology and End Results program of the National Cancer Institute), prevalence rates for all cancers, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma (STS) were estimated as 0.07, 0.002, and 0.001 respectively. Thus, Table 7-6 shows at least a power of approximately 0.65 to detect a relative risk of 1.5 given an estimated prevalence of 0.07 for all cancers. For the estimated prevalences of NHL and STS, the power to detect a relative risk of 2.0 would be less than 0.20.

Table 7-7 and Appendix Tables D-6 through D-9 provide the same information as Table 7-6 and Appendix Table D-2 through D-5 at a significance level of 0.05 for continuous dependent variables in terms of coefficients of variation (100 times the standard deviation of

Table 7-6.
Approximate Power to Detect a Group Effect at a 5 Percent Level of Significance (Discrete Dependent Variable)

Prevalence of Condition	Relative Risk						
	1.10	1.20	1.30	1.40	1.50	1.75	2.00
0.005	0.05	0.06	0.07	0.09	0.10	0.16	0.21
0.01	0.06	0.07	0.09	0.13	0.16	0.26	0.38
0.02	0.06	0.09	0.14	0.20	0.27	0.46	0.64
0.03	0.07	0.11	0.19	0.28	0.38	0.62	0.80
0.04	0.07	0.13	0.23	0.35	0.4	0.74	0.90
0.05	0.08	0.16	0.27	0.41	0.56	0.83	0.95
0.10	0.10	0.25	0.46	0.67	0.82	0.98	1.00
0.15	0.13	0.34	0.60	0.81	0.93	1.00	1.00
0.20	0.15	0.40	0.70	0.89	0.97	1.00	1.00

the dependent variable divided by the mean of the dependent variable) and the proportion mean changes. Table 7-7 presents power calculations for Model 1 (group) and Appendix Tables D-6 through D-9 presents power calculations for Model 2 (initial dioxin), Model 3 (categorized dioxin—low plus high Ranch Hand versus Comparison contrast), Model 4 (lipid-adjusted current dioxin), and Models 5 and 6 (whole-weight current dioxin). Power calculations were performed using the logarithm (base 2) of dioxin in Models 2, 4, 5, and 6, and consequently the relative risk is for a twofold increase in dioxin. The power of a test for a continuous variable depends on the significance level, actual difference in the true dependent variable means or slope of the dioxin coefficient, variation in the dependent variable data, sample size, and the distribution of the dioxin data, if dioxin is the exposure estimate.

The proportion mean change in Table 7-7 and Appendix Table D-7 is defined as the difference in the true Ranch Hand and Comparison means, relative to the combined average of the two groups, assuming no transformation of the dependent variable. The proportion mean change in Appendix Tables D-6, D-8, and D-9 is defined as the change in the expected value (mean) of the dependent variable for a twofold increase in initial dioxin, relative to the dependent variable mean. The proportion mean change in Appendix Tables D-6, D-8, and D-9 corresponds mathematically to the slope corresponding to initial or current dioxin divided by the dependent variable mean, assuming no transformation of the dependent variable. Analogous quantities can be derived based on transformed statistics. As an example, serum insulin (on the natural logarithm scale) for all participants has a coefficient of variation of approximately 22 percent. With this coefficient of variation, for the 952 Ranch Hands and 1,281 Comparisons in Model 1, the power is slightly greater than 0.80 for detecting a 13 percent increase in the mean serum insulin of Ranch Hands relative to the mean serum insulin level of Comparisons (mean change = 0.03).

Table 7-7.
Approximate Power to Detect a Group Effect at a 5 Percent Level of Significance (Continuous Dependent Variable)

	Coefficient of Variation ($100\sigma/\mu$)				
Mean Change	5	10	25	50	75
0.005	0.65	0.22	0.08	0.06	0.05
0.01	1.00	0.65	0.15	0.08	0.06
0.02	1.00	1.00	0.46	0.15	0.10
0.03	1.00	1.00	0.80	0.29	0.15
0.04	1.00	1.00	0.96	0.46	0.24
0.05	1.00	1.00	1.00	0.65	0.34
0.10	1.00	1.00	1.00	1.00	0.88

In summary, this study has good power to detect relative risks of 2.0 or more with respect to diseases, such as heart disease and basal cell carcinoma, occurring at histories of at least 5 percent in unexposed populations. In addition, the study size is sufficient to detect small mean shifts in the continuously distributed variables. The detection of significant mean shifts without a corresponding indication of increased Ranch Hand abnormalities or disease may be an artifact of multiple testing, could represent a subclinical effect, or could be of little or no medical importance.

EXPLANATION OF TABLES

This section explains the contents of the tables used to report the results of the analyses for continuous and discrete dependent variables (two levels and more than two levels). Selected tables from the Gastrointestinal Assessment (Chapter 13) will be referenced throughout this discussion. The contents of each summary table depend on the form of the health status endpoint (i.e., whether the dependent variable under analysis is a continuous or discrete variable). Generally, the results of the various analyses will be summarized in subpanels within each table as specified in Table 7-8. The subpanel specifications may be slightly different when adjusted analyses are not performed. This section also provides an explanation of the information contained in these tables.

Continuous Variables

Table 13-12 presents an example of the results of analysis when the dependent variable is continuous. Subpanels (a) and (b) show the results of unadjusted and adjusted analyses that compare the means of a dependent variable between Ranch Hands and Comparisons. Contrasts between Ranch Hands and Comparisons also are presented within each occupational category (i.e., officer, enlisted flyer, and enlisted groundcrew).

Table 7-8.
Location of Table Results from Different Analysis Models

Models	Subpanel in Table	Exposure Estimate	Type of Analysis
1	a	Group[a]	Unadjusted
1	b	Group[a]	Adjusted
2	c	Initial Dioxin[b]	Unadjusted
2	d	Initial Dioxin[b]	Adjusted
3	e	Categorized Dioxin[a]	Unadjusted
3	f	Categorized Dioxin[a]	Adjusted
4,5,6	g	Current Dioxin[b]	Unadjusted
4,5,6	h	Current Dioxin[b]	Adjusted

[a]Ranch Hands and Comparisons.
[b]Ranch Hands only.

For the unadjusted analysis, continuous dependent variable samples sizes (n) and means are presented for all occupational categories combined and separately for each occupational category. If the dependent variable was transformed for the analysis, the means of the transformed values are converted to the original scale and the column heading is footnoted. For each contrast of Ranch Hands versus Comparisons, the difference of means on the original scale and the associated 95 percent confidence interval are reported. Confidence intervals are determined from analysis of variance models for all occupational categories combined and for each occupational category, assuming equal variances in each group (i.e., Ranch Hands, Comparisons). If the analyses were performed on a transformed scale, 95 percent confidence intervals on the differences of means are not presented and the column is footnoted. A p-value also is reported to determine whether a difference in means on the scale used for analysis for a specified contrast is different from zero. The p-values are determined from t-tests for all occupational categories combined and within each occupational category, assuming equal variances in each group, unless the test for equal variances is rejected and the significance (≤ 0.05, > 0.05) of the t-test is dependent upon the equality of the variances.

For an adjusted analysis, the table is modified to include sample sizes, adjusted means, differences of adjusted means on the original scale and the associated 95 percent confidence interval (if the analysis was performed on the original scale), and any covariates and interactions retained in the final adjusted model along with their associated p-values. Sample sizes for corresponding panels of unadjusted and adjusted analyses may differ because of missing covariate information. Confidence intervals and p-values for each occupational category are determined from the group-by-occupation interaction in the final adjusted model using analysis of covariance techniques. Covariates with p-values less than or equal to 0.15 and interactions with p-values less than or equal to 0.05 retained in the final model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanel (c) of Table 13-12, for example, reports summary statistics assessing the association between the continuous dependent variable and initial dioxin without adjusting for covariate information. Sample sizes and means of the dependent variable (transformed to the original units, if necessary) are presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. The low, medium, and high categories are based on categorizing all Ranch Hands with initial dioxin estimates into three approximately equally-sized categories, based on their initial dioxin estimate. Means of the dependent variable adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin also are presented for the low, medium, and high categories of initial dioxin. Based on the linear regression analysis, adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, the coefficient of determination (R^2), the estimated slope, and its associated standard error are reported. If the dependent variable was transformed for the regression analysis, the means, slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value associated with testing whether the estimated slope is equal to zero also is presented.

Based on analyses that incorporate covariate and interaction information, subpanel (d) reports summary statistics assessing the association between the continuous dependent variable and initial dioxin. Similar to the unadjusted analyses, sample sizes and adjusted means of the dependent variable (transformed to the original units, if necessary) are presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. Sample sizes for corresponding panels of unadjusted and adjusted analyses may differ because of missing covariate information. Based on the multiple linear regression of the dependent variable on $\log_2$ (initial dioxin), including percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariate and interaction effects, the coefficient of determination (R^2), the adjusted slope for $\log_2$ (initial dioxin) and its associated standard error are reported. If the dependent variable was transformed for the regression analysis, the adjusted means, adjusted slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value for testing whether the adjusted slope is equal to zero also is presented. Covariates with p-values less than or equal to 0.15 and interactions with p-values less than or equal to 0.05 retained in the final model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanels (e) and (f) of Table 13-12, for example, show the results of unadjusted and adjusted analyses that compare the means of a continuous dependent variable for Ranch Hands having background, low, high, and low plus high dioxin levels with Comparisons having background current dioxin levels. The note at the bottom of the table defines the dioxin categories. The low and high Ranch Hand categories are based on categorizing all Ranch Hands with lipid-adjusted current dioxin estimates greater than 10 ppt into two approximately equal-sized categories, based on their initial dioxin estimate. The low plus high Ranch Hand category is a combination of the low and high categories. For the unadjusted analysis, sample sizes and dependent variable means are presented for each category. If the dependent variable was transformed for the analysis, the means of the

transformed values are converted to the original scale and the column heading is footnoted. Means of the dependent variable adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin also are presented for each dioxin category. The mean for the low plus high category is a weighted average of the low Ranch Hand and high Ranch Hand category means, based on the low and high Ranch Hand category sample sizes. For each individual contrast of the Ranch Hand category versus the Comparison category, the difference of means on the original scale and the associated 95 percent confidence interval are reported. If the analyses were performed on a transformed scale, the 95 percent confidence intervals on the differences of means are not presented and the column is footnoted. A p-value also is reported to determine whether a difference in means for a specified contrast is different from zero. The p-value is based on the difference of means on the scale used for analysis. Adjusted means, confidence intervals, and p-values for each contrast are determined from an analysis of variance model with covariate adjustments for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

For an adjusted analysis, the table is modified to include adjusted means (adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates and interactions retained in the final model), differences in adjusted means on the original scale, 95 percent confidence intervals on the differences in adjusted means (if the analysis was performed on the original scale), and any covariates and interactions retained in the adjusted model along with their associated p-values. Covariates with p-values less than or equal to 0.15 and interactions with p-values less than or equal to 0.05 retained in the final model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanel (g) of Table 13-12, for example, reports summary statistics from three models (Models 4, 5, and 6) assessing the association between the continuous dependent variable and current dioxin without adjusting for covariate information. A lipid-adjusted current dioxin measurement is used for Model 4, and a whole-weight current dioxin measurement is used in Models 5 and 6. The linear regression model in Model 6 additionally adjusts for $\log_2$ (total lipids). Means of the dependent variable (transformed to the original units, if necessary) are presented for low, medium, and high categories of current dioxin. Dependent variable means for Model 6 are adjusted for $\log_2$ (total lipids). Samples sizes are presented immediately below the mean in each level of current dioxin for each model. The numerical values defining the low, medium, and high categories of current dioxin are specified in a table footnote. The low, medium, and high categories are based on categorizing all Ranch Hands with current dioxin levels into three approximately equal-sized categories, based on their current dioxin measurement. Based on a linear regression of the dependent variable on $\log_2$ (current dioxin + 1), the coefficient of determination (R^2), the estimated slope, and its associated standard error are reported for each model. A value of 1 was added to each measurement because of the presence of current dioxin measurements of 0 ppt or ppq. If the dependent variable was transformed for the regression analysis, the means, slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value

associated with testing whether the estimated slope is equal to zero also is presented for each model.

Based on analyses that incorporate covariate and interaction information, subpanel (h) reports summary statistics assessing the association between the continuous dependent variable and current dioxin for Models 4, 5, and 6. Similar to the unadjusted analyses, sample sizes and adjusted means of the dependent variable (transformed to the original units, if necessary) are presented for low, medium, and high categories of current dioxin. The numerical values defining these categories are specified in a table footnote. Sample sizes for corresponding panels of unadjusted and adjusted analyses may differ because of missing covariate information. Based on the multiple linear regression of the dependent variable on $\log_2$ (current dioxin + 1), including covariates and interactions (and $\log_2$ [total lipids] for Model 6), the coefficient of determination (R^2), the adjusted slope for $\log_2$ (current dioxin + 1) and its associated standard error are reported for each model. If the dependent variable was transformed for the regression analysis, the adjusted means, adjusted slope, and standard error are footnoted and the transformation is identified in the footnote. The p-value for testing whether the adjusted slope is equal to zero also is presented for each model. Covariates with p-values less than or equal to 0.15 and interactions with p-values less than or equal to 0.05 retained in the multiple regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values, for each model.

For each of the six adjusted models, if the final model contains a significant group-by-covariate or dioxin-by-covariate interaction with an associated p-value less than or equal to 0.01, then the adjusted means, difference of means, 95 percent confidence interval, and p-value or adjusted slope, standard error, and p-value may not be reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model are, however, reported in a covariate remarks section. For some clinical assessments, an analyst may exercise discretion and report the adjusted means, difference of means, 95 percent confidence interval, and p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results are reported along with two asterisks (**) and are explained by a table footnote. If the final model contains a significant group-by-covariate or dioxin-by-covariate interaction with an associated p-value between 0.01 and 0.05, then the adjusted means, difference of adjusted means, 95 percent confidence interval, and p-value or the adjusted slope, standard error, and p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case (i.e., $p \leq 0.01$ or $0.01 < p \leq 0.05$), stratified analyses are undertaken and the results are reported in an associated appendix for each individual clinical area. The specific appendix table that presents the stratified analyses is referenced in a table footnote.

Discrete Variables

Discrete Variable With Two Categories

Table 13-3 presents an example of the results of analysis when the dependent variable is discrete and dichotomous in form. Subpanels (a) and (b) display the results of unadjusted and adjusted analyses that compare Ranch Hands and Comparisons on the relative frequency for a specified discrete dependent variable (e.g., percent of participants with an abnormal condition). Contrasts between Ranch Hands and Comparisons also are presented within each occupational category (i.e., officer, enlisted flyer, and enlisted groundcrew). For the unadjusted analysis, a sample size and relative frequency is presented for each group within each occupational category. For the contrasts of Ranch Hands versus Comparisons, estimated relative risks, associated 95 percent confidence intervals for the relative risks, and p-values associated with testing whether the risks equal 1.0 are presented. The normal distribution is used to calculate an approximate 95 percent confidence interval, and the continuity adjusted chi-square test is used to determine the corresponding p-value.

For an adjusted analysis, the table presents adjusted relative risks, 95 percent confidence intervals on the relative risks, and covariates and interactions retained in the adjusted model along with their associated p-values. Adjusted relative risks, confidence intervals, and p-values are determined from a multiple logistic regression model using the BMDP®-LR procedure, which utilizes the normal distribution for determining an approximate 95 percent confidence interval and the chi-square distribution based on a likelihood ratio statistic (17) for determining the p-value. Results from each occupational category are determined from the group-by-occupation interaction that is forced into the final model. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple logistic regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanel (c) of Table 13-3, for example, reports summary statistics assessing the association between the dependent variable and initial dioxin without adjusting for covariate information. Sample sizes are presented for low, medium, and high categories of initial dioxin. The numerical values defining these categories are specified in a table footnote. The percentage of Ranch Hands with the specified dichotomous characteristic (as cited in the column heading) is calculated from the data and presented for the low, medium, and high initial dioxin categories. Based on the logistic regression model adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, an estimated relative risk and its associated 95 percent confidence interval are reported. The p-value associated with testing whether the relative risk is equal to 1.0 also is presented. The normal distribution is used to determine an approximate 95 percent confidence interval, and the chi-square distribution based on a likelihood ratio statistic is used for determining the p-value. The summary statistics are reported for initial dioxin divided into three categories, whereas the relative risk, confidence interval, and p-value are based on $\log_2$ (initial dioxin) in its continuous form.

Subpanel (d) reports summary statistics assessing the association between the discrete dependent variable and initial dioxin, adjusted for percent body fat at the time of duty in

SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariate and interaction information. The aggregate sample size (n) is presented for a multiple logistic regression of the discrete dependent variable on $\log_2$ (initial dioxin) including covariates and interactions in the adjusted model. Based on a multiple logistic regression model, the adjusted relative risk for $\log_2$ (initial dioxin) and its associated 95 percent confidence interval are reported. The p-value for testing whether the relative risk is equal to 1.0 also is presented. The normal distribution is used to determine an approximate 95 percent confidence interval, and the chi-square distribution based on a likelihood ratio statistic is used for determining the p-value. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanels (e) and (f) of Table 13-3, for example, show the results of unadjusted and adjusted analyses that contrast Ranch Hands having background, low, high, and low plus high dioxin levels with Comparisons having background current dioxin levels based on the relative frequency for a specified discrete dependent variable (e.g., percent of participants in a dioxin category with an abnormal condition). The note at the bottom of the table defines the dioxin categories. The low and high Ranch Hand categories are based on categorizing all Ranch Hands with lipid-adjusted current dioxin estimates greater than 10 ppt into two approximately equal-sized categories, based on their initial dioxin estimate. The low plus high Ranch Hand category is a combination of the low and high Ranch Hand categories.

For the unadjusted analysis, a relative frequency and sample size is presented for each current dioxin category. For the individual contrasts of the Ranch Hand categories versus Comparisons, estimated relative risks, associated 95 percent confidence intervals for the relative risks, and p-values associated with testing whether the risks equal 1.0 are presented. The relative risks, confidence intervals, and p-values are determined from a logistic regression model, adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin. The low plus high Ranch Hand versus Comparison contrast is based on a separate logistic regression model in which the low and high Ranch Hand categories are combined. The normal distribution is used to determine an approximate 95 percent confidence interval, and the chi-square distribution based on a likelihood ratio statistic is used for determining the p-value.

For an adjusted analysis, subpanel (f) of the table presents adjusted relative risks, associated 95 percent confidence intervals for the relative risks, and p-values associated with testing whether the risks equal 1.0 for the individual contrasts of the Ranch Hand categories versus Comparisons. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

Subpanels (g) and (h) of Table 13-3, for example, present summary statistics from three models assessing the association between the dependent variable and current dioxin. The current dioxin measurement in Model 4 is lipid-adjusted current dioxin. In Models 5 and 6,

the dioxin measurement is whole-weight current dioxin, where Model 6 also is adjusted for total lipids.

For the unadjusted analyses, the percentage of Ranch Hands with the specified dichotomous characteristic (as cited in the column heading) and sample sizes are presented for low, medium, and high categories of current dioxin for each of the three models. The low, medium, and high categories are based on categorizing all Ranch Hands with current dioxin levels into three approximately equal-sized categories, based on their current dioxin measurement. The numerical values defining these categories are specified in a table footnote. Based on each logistic regression model, an estimated relative risk and its associated 95 percent confidence interval are reported. The p-value associated with testing whether the relative risk is equal to 1.0 also is presented. The normal distribution is used to determine an approximate 95 percent confidence interval, and the chi-square distribution based on a likelihood ratio statistic is used for determining the p-value. The summary statistics are reported for initial dioxin divided into three categories, whereas the relative risk, confidence interval, and p-value are based on $\log_2$ (current dioxin + 1) in its continuous form.

Incorporating covariate and interaction information, subpanel (h) reports summary statistics assessing the association between the discrete dependent variable and current dioxin for each of the three models. The aggregate sample size (n) is presented for a multiple logistic regression of the discrete dependent variable on $\log_2$ (current dioxin + 1) including covariates and interactions in the final adjusted model. Based on the multiple logistic regression models, the adjusted relative risk for $\log_2$ (current dioxin + 1) and its associated 95 percent confidence interval are reported. The p-value for testing whether the relative risk is equal to 1.0 also is presented for each model. The normal distribution is used to determine an approximate 95 percent confidence interval, and the chi-square distribution based on a likelihood ratio statistic is used for determining the p-value. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the multiple regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

In each of the six adjusted models, if the multiple logistic regression model contains a significant group-by-covariate or dioxin-by-covariate interaction with an associated p-value less than or equal to 0.01, then the adjusted relative risk, 95 percent confidence interval, and associated p-value may not be reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained in the model are, however, reported in a covariate remarks section. For some clinical assessments, an analyst may exercise discretion and report an adjusted relative risk, 95 percent confidence interval, and an associated p-value from a model that excludes the interaction having a p-value less than 0.01. When these discretionary followup analyses are performed, the results are reported along with two asterisks (**) and are explained by a table footnote. If the multiple logistic regression model contains a significant group-by-covariate or dioxin-by-covariate interaction with a p-value between 0.01 and 0.05, then the adjusted relative risk, 95 percent confidence interval, and associated p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case (i.e., $p \leq 0.01$ or

$0.01 < p \leq 0.05$), stratified analyses are undertaken and the results are reported in an associated appendix for each individual clinical area. The specific appendix table that presents the stratified analyses is referenced in a table footnote.

Discrete Variable With More Than Two Categories

Polychotomous regression techniques were used to analyze discrete dependent variables having more than two levels (e.g., abnormal low, normal, abnormal high—see Table 13-48). Results are presented in a similar fashion to discrete variables with only two categories, except that percentages are presented for all levels of the dependent variable, including normal, and relative risks, confidence intervals, and p-values are presented for each contrast with the normal level of the dependent variable (e.g., abnormal low versus normal and abnormal high versus normal).

Subpanels (a) and (b) of Table 13-48, for example, display the results of unadjusted and adjusted analyses that compare Ranch Hands and Comparisons on the relative frequencies of each abnormal level for a specified discrete dependent variable (e.g., percent of participants with an abnormally high condition versus those with a normal condition and percent of participants with an abnormally low condition versus those with a normal condition). Contrasts between Ranch Hands and Comparisons also are presented within each occupational category (i.e., officer, enlisted flyer, and enlisted groundcrew). For the unadjusted analysis, a sample size is presented for each group within each occupational category. Relative frequencies are presented for each level of the dependent variable for each group within each occupational category. Therefore, for each group within each occupational category, the relative frequencies sum to 100 percent across the dependent variable categories. For the contrasts of Ranch Hands versus Comparisons, estimated relative risks, associated 95 percent confidence intervals for the relative risks, and p-values associated with testing whether the risks equal 1.0 are determined from the BMDP®-PR procedure and presented for each contrast against the normal level of the dependent variable (e.g., abnormal low versus normal and abnormal high versus normal).

For an adjusted analysis, the table presents adjusted relative risks, 95 percent confidence intervals on the relative risks, and covariates and interactions retained in the adjusted model along with their associated p-values. Covariates (p-values less than or equal to 0.15) and interactions (p-values less than or equal to 0.05) retained in the polychotomous regression model after implementing the modeling strategy are presented in a covariate remarks section, along with the associated p-values.

For the unadjusted and adjusted analyses relating discrete dependent variables having more than two categories to initial dioxin, subpanels (c) and (d) of Table 13-48, for example, present sample sizes, relative frequencies, relative risks, 95 percent confidence intervals for the relative risks, and associated p-values. For the adjusted analysis, any covariates and interactions retained in the model along with their associated p-values also are presented. One difference between the table presentations for dichotomous dependent variables and discrete dependent variables with more than two levels is that relative frequencies of Ranch Hands belonging to each of the dependent variable categories are summarized with respect to each initial dioxin category (i.e., low, medium, and high initial dioxin). Therefore, for each

initial dioxin level, the relative frequencies sum to 100 percent across the dependent variable categories. Also, associations with initial dioxin are presented for each abnormal level of the dependent variable (e.g., abnormal low vs. normal and abnormal high vs. normal).

Subpanels (e) and (f) of Table 13-48, for example, present unadjusted and adjusted analyses of categorized dioxin versus a discrete dependent variable having more than two categories. Results are presented in a similar fashion to the group analysis (Model 1) except that contrasts involve the four Ranch Hand categories (background, low, high, and low plus high) versus Comparisons and contrasts are not performed for each occupation. For the unadjusted analysis, a sample size is presented for each dioxin category. The low plus high Ranch Hand category is a combination of the low and high Ranch Hand categories. Relative frequencies are presented for each level of the dependent variable for each dioxin category. Therefore, for each dioxin category, the relative frequencies sum to 100 percent across the dependent variable levels. For each contrast of a Ranch Hand category versus the Comparison group, estimated relative risks, associated 95 percent confidence intervals for the relative risks, and p-values associated with testing whether the risks equal 1.0 are presented for each contrast against the normal level of the dependent variable (e.g., abnormal low versus normal and abnormal high versus normal). The low plus high Ranch Hand versus Comparison contrast is based on a separate polychotomous logistic regression model in which the low and high Ranch Hand categories are combined. For an adjusted analysis, the table presents adjusted relative risks, 95 percent confidence intervals on the relative risks, and p-values for each contrast of Ranch Hands versus Comparisons under each abnormal level of the dependent variable. Covariates and interactions retained in the adjusted polychotomous model, along with their associated p-values, also are presented.

Similar to the polychotomous regression analysis using initial dioxin, unadjusted and adjusted analyses of discrete dependent variables with more than two categories were performed using current dioxin in Models 4, 5, and 6. Summaries of the analyses are given in subpanels (g) and (h) (see Table 13-48 for an example). The current dioxin measurement in Model 4 is lipid-adjusted current dioxin. In Models 5 and 6, the dioxin measurement is whole-weight current dioxin, where Model 6 also is adjusted for total lipids. For the unadjusted analysis, sample sizes are presented for each current dioxin level within each of the three models. Relative frequencies (within each current dioxin level) are presented for each dependent variable category. Estimated relative risks, 95 percent confidence intervals on the relative risks, and associated contrast p-values are reported for each abnormal level of the dependent variable (e.g., abnormal low vs. normal and abnormal high vs. normal) for all three models. Adjusted analysis results, including adjusted relative risks, 95 percent confidence intervals on the relative risks, and associated p-values for the abnormal dependent variable categories are presented on the following page of the table. Covariates and interactions retained in the adjusted polychotomous model, along with the associated p-values, also are presented for each of the three adjusted models.

In each of the six adjusted models, if the polychotomous regression model contains a significant group-by-covariate or dioxin-by-covariate interaction with an associated p-value less than or equal to 0.01, then the adjusted relative risk, 95 percent confidence interval, and associated p-value may not be reported. The entries for these statistics are reported as four asterisks (****) and are identified by a table footnote. Covariates and interactions retained

in the model are, however, reported under a covariate remarks section. If the polychotomous regression model contains a significant group-by-covariate or dioxin-by-covariate interaction with a p-value between 0.01 and 0.05, or when an analyst deems it appropriate to present results from a model with a group-by-covariate interaction having a p-value less than 0.01, then the adjusted relative risk, 95 percent confidence interval, and associated p-value are reported from a model that excludes that interaction. The entries for these statistics are reported along with two asterisks (**) accompanied by a table footnote. In either case (i.e., $p \leq 0.01$ or $0.01 < p \leq 0.05$), stratified analyses are undertaken and the results are reported in an associated appendix for each individual clinical area. The specific appendix table that presents the stratified analyses is referenced in a table footnote.

GRAPHICS

The analytic activities for the analyses were supplemented by data plots. These graphics were produced using the S-PLUS® graphics procedure (24).

As part of the analyses of current dioxin, bivariate scatterplots were produced describing the relationship between selected dependent variables and the logarithm (base 2) of lipid-adjusted current dioxin + 1. Both the dependent variable and current dioxin are displayed in continuous form. The dependent variable transformation used in the analysis also has been used in the scatterplots. Participants excluded from the analysis are not displayed on these scatterplots, and consequently the graphical displays parallel the Model 4 analyses. These scatterplots are presented in Appendix Q-2.

CHAPTER 7
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CHAPTER 8

COVARIATE ASSOCIATIONS WITH ESTIMATES OF DIOXIN EXPOSURE

INTRODUCTION

The associations between the covariates used throughout this report and five estimates of dioxin exposure are evaluated in this chapter. The purpose of studying these associations is to determine if these covariates, which have been determined to be risk factors for one or more particular clinical areas, are associated with an estimate of dioxin exposure, and, therefore, could potentially be confounding variables in subsequent statistical analyses in this report. These covariates and estimates of dioxin exposure are used extensively in the statistical analyses in Chapters 9 through 20, which comprise the clinical portions of the report. The results in this chapter, however, should not be interpreted as indicating causal relationships between dioxin exposure and covariate levels (e.g., diabetes) because these analyses are not adjusted for known and suspected confounders.

Model 1 refers to the relationship of an individual covariate with group (Ranch Hand or Comparison). Model 2 refers to the relationship between an individual covariate and an extrapolated initial dioxin measure for Ranch Hands. The estimate of dioxin exposure in Model 3 dichotomizes the Ranch Hands in Model 2 based on their initial dioxin measures; these two categories of Ranch Hands are referred to as the "low Ranch Hand" category and the "high Ranch Hand" category. Ranch Hands and Comparisons with current lipid-adjusted serum dioxin levels at or below 10 ppt also are used to create a total of four categories. Ranch Hands with current lipid-adjusted serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. The relationship between a covariate and the four categories of Ranch Hands and Comparisons is examined.

Models 4, 5, and 6 refer to the relationship between a covariate and 1987 (current) dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a measured 1987 dioxin level, a 1992 measurement was used when available. The 1992 level was extrapolated to the 1987 level using a first-order pharmacokinetics model (additional details are given in Chapter 2, Dioxin Assay and Chapter 7, Statistical Methods). The measure of dioxin in Model 4 is lipid-adjusted, whereas the measure of dioxin (the same for both) in Models 5 and 6 is whole-weight adjusted. Model 6 differs from Model 5 in that a statistical adjustment for total lipids is included in the Model 6 analysis in subsequent chapters. Details on dioxin and the models are found in Chapters 2 and 7 respectively.

The summary statistics listed in the tables in this chapter are either percentages, correlations (r), or means ($\bar{x}$). If a covariate is discrete in Models 1 and 3, the percentage of participants (Ranch Hands and Comparisons for Model 1 and Comparisons and background, low, and high Ranch Hands for Model 3) in each of the covariate categories is shown. If a covariate is continuous, the mean of the covariate is given for each exposure category.

Because the measure of dioxin is in a continuous form for Model 2, 3, 5, and 6 analyses, if a covariate is continuous, a correlation coefficient between initial dioxin and the

covariate is provided. If a covariate is discrete, dioxin means for each of the covariate categories are displayed. Consistent with the methodology used in each of the clinical chapters (Chapters 9 through 20), these means are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2 (X+1)$) scale for current dioxin in Models 4, 5, and 6.

The p-values used in these tables measure the association of the relationship with a covariate. A smaller p-value corresponds to a greater degree of association. The p-value referred to for Model 1 refers to the strength of the association between a covariate and group, and the p-value for Model 2 refers to the strength of the association between a covariate and initial dioxin in Ranch Hands. The Model 3 p-value describes the strength of association between a covariate and categorized dioxin, as described above. The p-values for Models 4, 5, and 6 quantify the strength of the association between a covariate and current dioxin, whether it be lipid-adjusted in Model 4 or whole-weight adjusted in Models 5 and 6.

MATCHING DEMOGRAPHIC VARIABLES (AGE, RACE, AND MILITARY OCCUPATION)

The variables age, race, and military occupation were used in the design of the Air Force Health Study (AFHS) to match Ranch Hand participants with Comparisons and thus reduce the association between these variables and group status. However, it was not possible to eliminate the association of these variables with serum dioxin in Models 2 through 6 through the study design. Results of tests of association between age, race, and occupation and the five estimates of dioxin exposure are given in Table 8-1.

Examining the association between age, in both its continuous and discrete forms, and dioxin revealed highly significant relationships in the analyses of Models 2 through 6 ($p<0.001$ for each model, both continuous and discrete). In the Model 3 analysis, the mean ages in the Comparison, background Ranch Hand, low Ranch Hand, and high Ranch Hand categories are 53.8, 54.8, 55.3, and 51.2 years respectively. Older Ranch Hands tended to have lower dioxin levels in analyses of Models 2, 4, 5 and 6. In the Model 3 analysis, a significant difference in the percentage of younger participants (born in or after 1942) was seen among Comparisons (42.7%), background Ranch Hands (34.2%), low Ranch Hands (32.7%), and high Ranch Hands (59.2%). The relationship between age and dioxin in Models 2 through 6 is most likely due to the relationship between dioxin and military occupation, as discussed below (Ranch Hand enlisted groundcrew, the occupational category with the greatest risk of exposure, tended to be younger than Ranch Hand officers and enlisted flyers).

Similar to the correlation between age and dioxin, a highly significant association was found between military occupation and dioxin in analyses using Models 2, 3, 4, 5, and 6 ($p<0.001$ for each model). In Models 2, 4, 5, and 6, the mean dioxin levels were lowest among officers, followed by enlisted flyers and enlisted groundcrew. In the Model 3 analysis, a significant difference between the percentage of officers, enlisted flyers, and enlisted groundcrew was seen among Comparisons (38.5%, 16.3%, and 45.3%), background Ranch Hands (63.1%, 10.7%, and 26.2%), low Ranch Hands (39.6%, 21.2%, and 39.2%), and high Ranch Hands (3.5%, 21.2%, and 75.4%).

Table 8-1.
Associations Between Matching Demographic Variables (Age, Race, and Military Occupation) and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Age (years) (Continuous)	--	n=952 $\bar{x}$=53.8	n=1,281 $\bar{x}$=53.6	n=520 r=-0.264
		p=0.533		p<0.001
Age (Discrete)		n=952	n=1,281	
	Born ≥ 1942	41.6%	43.7%	$\bar{x}$=220.94 (n=239)
	Born < 1942	58.4%	56.3%	$\bar{x}$=130.78 (n=281)
		p=0.338		p<0.001
Race		n=952	n=1,281	
	Black	5.9%	5.9%	$\bar{x}$=126.21 (n=36)
	Non-Black	94.1%	94.1%	$\bar{x}$=169.88 (n=484)
		p=0.999		p=0.062
Occupation		n=952	n=1,281	
	Officer	38.6%	39.2%	$\bar{x}$=77.18 (n=112)
	Enlisted Flyer	17.0%	15.8%	$\bar{x}$=156.01 (n=110)
	Enlisted Groundcrew	44.4%	45.0%	$\bar{x}$=227.51 (n=298)
		p=0.760		p<0.001

Table 8-1. (Continued)
Associations Between Matching Demographic Variables (Age, Race, and Military Occupation) and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Age (years) (Continuous)	--	n=1,063 $\bar{x}$=53.8	n=374 $\bar{x}$=54.8	n=260 $\bar{x}$=55.3	n=260 $\bar{x}$=51.2
			p<0.001		
Age (Discrete)		n=1,063	n=374	n=260	n=260
	Born ≥ 1942	42.7%	34.2%	32.7%	59.2%
	Born < 1942	57.3%	65.8%	67.3%	40.8%
			p<0.001		
Race		n=1,063	n=374	n=260	n=260
	Black	5.2%	4.0%	8.9%	5.0%
	Non-Black	94.8%	96.0%	91.2%	95.0%
			p=0.054		
Occupation		n=1,063	n=374	n=260	n=260
	Officer	38.5%	63.1%	39.6%	3.5%
	Enlisted Flyer	16.3%	10.7%	21.2%	21.2%
	Enlisted Groundcrew	45.3%	26.2%	39.2%	75.4%
			p<0.001		

Table 8-1. (Continued)
Associations Between Matching Demographic Variables (Age, Race, and Military Occupation) and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Age (years) (Continuous)	--	n=894 r=-0.214 p<0.001	n=894 r=-0.186 p<0.001
Age (Discrete)	Born ≥ 1942 Born < 1942	$\bar{x}$=19.63 (n=367) $\bar{x}$=11.74 (n=527) p<0.001	$\bar{x}$=111.05 (n=367) $\bar{x}$=68.01 (n=527) p<0.001
Race	Black Non-Black	$\bar{x}$=14.71 (n=51) $\bar{x}$=14.52 (n=843) p=0.934	$\bar{x}$=79.98 (n=51) $\bar{x}$=83.40 (n=843) p=0.808
Occupation	Officer Enlisted Flyer Enlisted Groundcrew	$\bar{x}$=7.47 (n=348) $\bar{x}$=17.24 (n=150) $\bar{x}$=23.91 (n=396) p<0.001	$\bar{x}$=42.14 (n=348) $\bar{x}$=100.73 (n=150) $\bar{x}$=140.07 (n=396) p<0.001

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

No significant ($p \leq 0.05$) associations were observed between race and the five estimates of dioxin exposure.

TIME OF DUTY IN SOUTHEAST ASIA CHARACTERISTICS

Results of tests of association between variables related to the participants' time of duty in Southeast Asia (SEA) and the estimates of dioxin exposure are presented in Table 8-2. Model 1 analysis showed a highly significant association between the number of days in combat and group ($p<0.001$). The mean number of days in combat for the Ranch Hands was 452.5 days and 210.3 days for the Comparisons. The Model 3 analysis revealed a significant relationship between categorized dioxin and the number of days in combat ($p<0.001$), due to the inherent difference between Ranch Hands and Comparisons. The mean number of days in combat in the Comparison, background Ranch Hand, low Ranch Hand, and high Ranch Hand categories are 203.9, 445.9, 454.0, and 458.7 days respectively.

Stratifying the number of days a participant spent in combat into fewer than or equal to 360 days and more than 360 days revealed significant relationships with group in Model 1 ($p<0.001$) and dioxin in Model 3 ($p<0.001$), Model 4 ($p=0.001$), and Models 5 and 6 ($p=0.002$). A significant difference between the percentage of participants who were in combat fewer than 360 days was seen between Ranch Hands (14.0%) and Comparisons (76.7%). In Model 3, a significant difference between the percentage of participants who were in combat less than 360 days was seen among Comparisons (77.4%), background Ranch Hands (18.2%), low Ranch Hands (11.2%), and high Ranch Hands (10.4%). The mean current dioxin levels in Models 4, 5, and 6 were higher for participants who were in combat more than 360 days. However, the association with initial dioxin in Model 2 was not statistically significant, which may be due to the restricted sample size of participants with greater than 10 ppt lipid-adjusted current dioxin, and thus, decreased statistical power.

No significant ($p \leq 0.05$) associations were observed between the occurrence of acne in reference to duty in SEA (Pre- & Post-SEA, Post-SEA) or presence of pre-SEA acne (yes, no) and the five estimates of dioxin exposure.

ALCOHOL CONSUMPTION

Results of tests of association between alcohol consumption and the estimates of dioxin exposure are shown in Table 8-3. Statistically significant associations were found between current wine use in its continuous form and dioxin for Model 1 ($p=0.025$), Model 3 ($p=0.001$), Model 4 ($p=0.002$), and Models 5 and 6 ($p=0.001$). The mean current wine use was 0.13 drinks per day for Ranch Hands and 0.10 drinks per day for Comparisons. In Model 3, the mean drinks of wine per day in the Comparison, background Ranch Hands, low Ranch Hands, and high Ranch Hands categories are 0.10, 0.17, 0.14, and 0.07 respectively. The drinks of wine per day increased as the current dioxin levels decreased in Model 4 and Models 5 and 6. This association may be due to occupation, because officers are more likely to drink wine than are enlisted personnel ($p<0.001$).

Table 8-2.
Associations Between Time of Duty in Southeast Asia Characteristics and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Combat Service (number of days) (Continuous)	--	n=952 $\bar{x}$=452.5	n=1,281 $\bar{x}$=210.3	n=520 r=0.071
		p<0.001		p=0.108
Combat Service (number of days) (Discrete)		n=952	n=1,281	
	0-360 days	14.0%	76.7%	$\bar{x}$=160.26 (n=56)
	>360 days	86.0%	23.3%	$\bar{x}$=167.18 (n=464)
		p<0.001		p=0.746
Time Reference of Acne to Southeast Asia		n=826	n=1,083	
	Pre & Post	89.2%	88.2%	$\bar{x}$=180.83 (n=47)
	Post	10.8%	11.8%	$\bar{x}$=163.17 (n=401)
		p=0.523		p=0.472
Presence of Pre-SEA Acne		n=952	n=1,281	
	Yes	90.2%	89.7%	$\bar{x}$=180.62 (n=50)
	No	9.8%	10.3%	$\bar{x}$=164.98 (n=470)
		p=0.730		p=0.509

Table 8-2. (Continued)
Associations Between Time of Duty in Southeast Asia Characteristics and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Combat Service (number of days) (Continuous)	--	n=1,063 $\bar{x}$=203.9	n=374 $\bar{x}$=445.9	n=260 $\bar{x}$=454.0	n=260 $\bar{x}$=458.7
			p<0.001		
Combat Service (number of days) (Discrete)		n=1,063	n=374	n=260	n=260
	0-360 days	77.4%	18.2%	11.2%	10.4%
	>360 days	22.6%	81.8%	88.8%	89.6%
			p<0.001		
Time Reference of Acne to Southeast Asia		n=911	n=329	n=227	n=221
	Pre & Post	12.4%	10.9%	9.3%	11.8%
	Post	87.6%	89.1%	90.7%	88.2%
			p=0.585		
Presence of Pre-SEA Acne		n=1,063	n=374	n=260	n=260
	No	89.0%	90.1%	91.2%	89.6%
	Yes	11.0%	9.9%	8.8%	10.4%
			p=0.755		

Table 8-2. (Continued)
Associations Between Time of Duty in Southeast Asia Characteristics and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Combat Service (number of days) (Continuous)	--	n=894 r=0.069 p=0.042	n=894 r=0.064 p=0.056
Combat Service (number of days) (Discrete)	0-360 Days >360 Days	$\bar{x}$=10.61 (n=124) $\bar{x}$=15.28 (n=770) p=0.001	$\bar{x}$=60.74 (n=124) $\bar{x}$=87.52 (n=770) p=0.002
Time Reference of Acne to SEA	Pre & Post Post	$\bar{x}$=14.46 (n=83) $\bar{x}$=14.39 (n=694) p=0.970	$\bar{x}$=80.62 (n=83) $\bar{x}$=82.80 (n=694) p=0.847
Presence of Pre-SEA Acne	No Yes	$\bar{x}$=14.52 (n=807) $\bar{x}$=14.64 (n=87) p=0.946	$\bar{x}$=83.3 (n=807) $\bar{x}$=81.9 (n=87) p=0.899

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

Table 8-3.
Associations Between Alcohol Consumption and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Current Alcohol Use (drinks/day) (Continuous)	--	n=942 $\bar{x}$=0.73	n=1,263 $\bar{x}$=0.75	n=513 r=-0.034
		p=0.738		p=0.445
Current Alcohol Use (drinks/day) (Discrete)		n=942	n=1,263	
	0-1	78.5%	79.7%	$\bar{x}$=172.24 (n=407)
	>1-4	19.5%	17.2%	$\bar{x}$=144.56 (n=98)
	>4	2.0%	3.2%	$\bar{x}$=153.15 (n=8)
		p=0.110		p=0.234
Lifetime Alcohol History (drink-years) (Continuous)	--	n=930 $\bar{x}$=33.91	n=1,260 $\bar{x}$=32.71	n=507 r=0.042
		p=0.573		p=0.341
Lifetime Alcohol History (drink-years) (Discrete)		n=930	n=1,260	
	0	6.8%	5.6%	$\bar{x}$=217.27 (n=39)
	>0-40	68.0%	68.3%	$\bar{x}$=162.11 (n=335)
	>40	25.3%	26.1%	$\bar{x}$=162.56 (n=133)
		p=0.525		p=0.166
Current Wine Use (drinks/day) (Continuous)	--	n=941 $\bar{x}$=0.13	n=1,263 $\bar{x}$=0.10	n=513 r=-0.071
		p=0.025		p=0.108
Current Wine Use (drinks/day) (Discrete)		n=941	n=1,263	
	0	46.0%	42.4%	$\bar{x}$=193.19 (n=254)
	>0	54.0%	57.6%	$\bar{x}$=143.51 (n=259)
		p=0.096		p<0.001
Lifetime Wine History (wine-years) (Continuous)	--	n=933 $\bar{x}$=2.92	n=1,260 $\bar{x}$=2.50	n=509 r=-0.165
		p=0.235		p<0.001
Lifetime Wine History (wine-years) (Discrete)		n=933	n=1,260	
	0	33.8%	29.0%	$\bar{x}$=206.21 (n=186)
	>0	66.2%	71.0%	$\bar{x}$=147.27 (n=323)
		p=0.019		p<0.001

Table 8-3. (Continued)
Associations Between Alcohol Consumption and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Current Alcohol Use (drinks/day) (Continuous)	--	n=1,047 $\bar{x}$=0.77	n=372 $\bar{x}$=0.75	n=257 $\bar{x}$=0.71	n=256 $\bar{x}$=0.68
			p=0.759		
Current Alcohol Use (drinks/day) (Discrete)		n=1,047	n=372	n=257	n=256
	0-1	79.4%	77.2%	76.7%	82.0%
	>1-4	17.2%	20.4%	22.2%	16.0%
	>4	3.4%	2.4%	1.2%	2.0%
			p=0.124		
Lifetime Alcohol History (drink-years) (Continuous)	--	n=1,045 $\bar{x}$=33.66	n=367 $\bar{x}$=31.61	n=254 $\bar{x}$=33.08	n=253 $\bar{x}$=35.88
			p=0.768		
Lifetime Alcohol History (drink-years) (Discrete)		n=1,045	n=367	n=254	n=253
	0	5.2%	5.4%	5.9%	9.5%
	>0-40	67.9%	71.1%	66.9%	65.2%
	>40	26.9%	23.4%	27.2%	25.3%
			p=0.180		
Current Wine Use (drinks/day) (Continuous)	--	n=1,047 $\bar{x}$=0.10	n=371 $\bar{x}$=0.17	n=257 $\bar{x}$=0.14	n=256 $\bar{x}$=0.07
			p=0.001		
Current Wine Use (drinks/day) (Discrete)		n=1,047	n=371	n=257	n=256
	0	41.7%	40.7%	45.1%	53.9%
	>0	58.3%	59.3%	54.9%	46.1%
			p=0.003		
Lifetime Wine History (drink-years) (Continuous)	--	n=1,045 $\bar{x}$=2.60	n=368 $\bar{x}$=3.69	n=254 $\bar{x}$=3.62	n=255 $\bar{x}$=1.31
			p=0.003		
Lifetime Wine History (wine-years) (Discrete)		n=1,045	n=368	n=254	n=255
	0	28.1%	29.9%	32.7%	40.4%
	>0	71.9%	70.1%	67.3%	59.6%
			p=0.002		

Table 8-3. (Continued)
Associations Between Alcohol Consumption and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Current Alcohol Use (drinks/day) (Continuous)	--	n=885 r=-0.021 p=0.534	n=885 r=-0.007 p=0.842
Current Alcohol Use (drinks/day) (Discrete)	0-1 >1-4 >4	$\bar{x}$=14.84 (n=694) $\bar{x}$=13.38 (n=174) $\bar{x}$=11.71 (n=17) p=0.381	$\bar{x}$=84.44 (n=694) $\bar{x}$=78.49 (n=174) $\bar{x}$=69.49 (n=17) p=0.639
Lifetime Alcohol History (drink-years) (Continuous)	--	n=874 r=0.032 p=0.348	n=874 r=0.031 p=0.362
Lifetime Alcohol History (drink-years) (Discrete)	0 >0-40 >40	$\bar{x}$=18.40 (n=59) $\bar{x}$=13.98 (n=596) $\bar{x}$=14.75 (n=219) p=0.166	$\bar{x}$=102.17 (n=59) $\bar{x}$=80.32 (n=596) $\bar{x}$=84.41 (n=219) p=0.324
Current Wine Use (drinks/day) (Continuous)	--	n=884 r=-0.105 p=0.002	n=884 r=-0.114 p=0.001
Current Wine Use (drinks/day) (Discrete)	0 >0	$\bar{x}$=16.72 (n=405) $\bar{x}$=12.82 (n=479) p<0.001	$\bar{x}$=95.98 (n=405) $\bar{x}$=73.34 (n=479) p=0.001
Lifetime Wine Use (wine-years) (Continuous)	--	n=877 r=-0.102 p=0.003	n=877 r=-0.110 p=0.001
Lifetime Wine Use (wine-years) (Discrete)	0 >0	$\bar{x}$=17.23 (n=296) $\bar{x}$=13.25 (n=581) p=0.001	$\bar{x}$=98.03 (n=296) $\bar{x}$=76.12 (n=581) p=0.003

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

The examination of current wine use, when stratified into categories of those who do not currently drink wine and those who currently drink wine, showed a significant association with dioxin in Model 2 ($p<0.001$), Model 3 ($p=0.003$), Model 4 ($p<0.001$), and Models 5 and 6 ($p=0.001$). In Model 3, a significant difference between the percentage of participants who do not drink wine was seen among Comparisons (41.7%), background Ranch Hands (40.7%), low Ranch Hands (45.1%), and high Ranch Hands (53.9%). In Models 2, 4, 5, and 6, the mean dioxin levels are higher for participants who do not currently drink wine.

Lifetime wine history in its continuous form showed significant inverse associations with dioxin in Model 2 ($p<0.001$), Model 3 ($p=0.003$), Model 4 ($p=0.003$), and Models 5 and 6 ($p=0.001$). The mean wine-years in the Comparison, background Ranch Hands, low Ranch Hands, and high Ranch Hands categories for Model 3 are 2.60, 3.69, 3.62, and 1.31 respectively. In Models 2, 4, 5, and 6, wine consumption increased as dioxin levels decreased.

Stratifying participants into those who have never consumed wine and those who have showed a significant relationship between lifetime wine history and group in Model 1 analysis ($p=0.019$). A significant difference between the percentage of participants who have never had wine was seen between Ranch Hands (33.8%) and Comparisons (29.0%). Additionally, significant relationships between lifetime wine history and dioxin were revealed in analyses of Model 2 ($p<0.001$), Model 3 ($p=0.002$), Model 4 ($p=0.001$), and Models 5 and 6 ($p=0.003$). In Models 2, 4, 5, and 6, the mean dioxin levels were lower for those participants who had consumed wine in the past than for those who had not. In the Model 3 analysis, a significant difference between the percentage of participants who have never had wine was seen among Comparisons (28.1%), background Ranch Hands (29.9%), low Ranch Hands (32.7%), and high Ranch Hands (40.4%).

No significant ($p \leq 0.05$) associations were observed between alcohol (beer, wine, and liquor combined) consumption and the five estimates of dioxin exposure.

CIGARETTE SMOKING HISTORY

No significant ($p \leq 0.05$) associations were observed between either current or lifetime cigarette smoking and the five estimates of dioxin exposure. Results of tests of association between cigarette smoking and the estimates of dioxin exposure are given in Table 8-4.

EXPOSURE TO CARCINOGENS

Results of tests of association between reported exposure to asbestos, ionizing radiation, industrial chemicals, herbicides, insecticides, and degreasing chemicals and the estimates of dioxin exposure are presented in Table 8-5. These variables were constructed based on responses given by participants and were intended to capture post-SEA exposures to these suspected carcinogens.

Table 8-4.
Associations Between Cigarette Smoking and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Current Cigarette Smoking (cigarettes/day) (Continuous)	--	n=952 $\bar{x}$=6.07	n=1,279 $\bar{x}$=5.42	n=520 r=0.050
		p=0.205		p=0.258
Current Cigarette Smoking (cigarettes/day) (Discrete)		n=952	n=1,279	
	0-Never Smoked	27.0%	27.8%	$\bar{x}$=174.72 (n=139)
	0-Former Smoker	46.0%	48.4%	$\bar{x}$=154.06 (n=239)
	0-20	16.7%	14.9%	$\bar{x}$=181.29 (n=88)
	>20	10.3%	8.9%	$\bar{x}$=179.75 (n=54)
		p=0.399		p=0.362
Lifetime Cigarette Smoking History (pack-years) (Continuous)	--	n=951 $\bar{x}$=14.78	n=1,279 $\bar{x}$=14.19	n=520 r=-0.058
		p=0.476		p=0.185
Lifetime Cigarette Smoking History (pack-years) (Discrete)		n=951	n=1,279	
	0	27.0%	27.8%	$\bar{x}$=174.72 (n=139)
	>0-10	31.3%	30.0%	$\bar{x}$=182.38 (n=162)
	>10	41.6%	42.2%	$\bar{x}$=150.79 (n=219)
		p=0.796		p=0.105

Table 8-4. (Continued)
Associations Between Cigarette Smoking and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Current Cigarette Smoking (cigarettes/day) (Continuous)	--	n=1,061 $\bar{x}$=5.44	n=374 $\bar{x}$=6.18	n=260 $\bar{x}$=5.13	n=260 $\bar{x}$=6.62
			p=0.373		
Current Cigarette Smoking (cigarettes/day) (Discrete)		n=1,061	n=374	n=260	n=260
	0-Never Smoked	26.6%	29.1%	27.7%	25.8%
	0-Former Smoker	50.0%	45.5%	48.5%	43.5%
	0-20	14.3%	15.8%	15.0%	18.8%
	>20	9.1%	9.6%	8.8%	11.9%
			p=0.526		
Lifetime Cigarette Smoking History (pack-years) (Continuous)	--	n=1,061 $\bar{x}$=14.31	n=373 $\bar{x}$=14.48	n=260 $\bar{x}$=15.84	n=260 $\bar{x}$=13.96
			p=0.674		
Lifetime Cigarette Smoking History (pack-years) (Discrete)		n=1,061	n=373	n=260	n=260
	0	26.6%	29.2%	27.7%	25.8%
	>0-10	30.5%	29.2%	26.5%	35.8%
	>10	42.9%	41.6%	45.8%	38.5%
			p=0.359		

Table 8-4. (Continued)
Associations Between Cigarette Smoking and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Current Cigarette Smoking (cigarettes/ day) (Continuous)	--	n=894 r=-0.015 p=0.665	n=894 r=-0.011 p=0.744
Current Cigarette Smoking (cigarettes/ day) (Discrete)	0-Never Smoked 0-Former Smoker >0-20 >20	$\bar{x}$=15.00 (n=248) $\bar{x}$=14.08 (n=409) $\bar{x}$=15.03 (n=147) $\bar{x}$=14.52 (n=90) p=0.873	$\bar{x}$=83.15 (n=248) $\bar{x}$=81.89 (n=409) $\bar{x}$=86.49 (n=147) $\bar{x}$=84.10 (n=90) p=0.972
Lifetime Cigarette Smoking History (pack-years) (Continuous)	--	n=893 r=-0.051 p=0.129	n=893 r=-0.041 p=0.226
Lifetime Cigarette Smoking History (pack-years) (Discrete)	0 >0-10 >10	$\bar{x}$=15.00 (n=248) $\bar{x}$=15.47 (n=271) $\bar{x}$=13.62 (n=374) p=0.293	$\bar{x}$=83.15 (n=248) $\bar{x}$=87.46 (n=271) $\bar{x}$=80.41 (n=374) p=0.677

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

Table 8-5.
Associations Between Exposure to Carcinogens and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1 Ranch Hand	Model 1 Comparison	Model 2 Initial Dioxin (ppt)
Asbestos Exposure		n=952	n=1,281	
	No	73.6%	71.5%	$\bar{x}$=164.33 (n=379)
	Yes	26.4%	28.5%	$\bar{x}$=172.19 (n=141)
			p=0.287	p=0.607
Ionizing Radiation Exposure		n=952	n=1,281	
	No	78.7%	73.1%	$\bar{x}$=172.43 (n=408)
	Yes	21.3%	26.9%	$\bar{x}$=146.25 (n=112)
			p=0.003	p=0.094
Industrial Chemical Exposure		n=952	n=1,281	
	No	42.0%	40.7%	$\bar{x}$=142.86 (n=187)
	Yes	58.0%	59.3%	$\bar{x}$=181.32 (n=333)
			p=0.577	p=0.005
Herbicide Exposure		n=952	n=1,281	
	No	5.1%	61.7%	$\bar{x}$=191.21 (n=21)
	Yes	94.9%	38.3%	$\bar{x}$=165.45 (n=499)
			p<0.001	p=0.481
Insecticide Exposure		n=952	n=1,281	
	No	23.6%	37.3%	$\bar{x}$=190.80 (n=119)
	Yes	76.4%	62.7%	$\bar{x}$=159.81 (n=401)
			p<0.001	p=0.065
Degreasing Chemical Exposure		n=952	n=1,281	
	No	37.0%	36.9%	$\bar{x}$=133.37 (n=148)
	Yes	63.0%	63.1%	$\bar{x}$=181.75 (n=372)
			p=0.999	p=0.001

Table 8-5. (Continued)
Associations Between Exposure to Carcinogens and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Asbestos Exposure		n=1,063	n=374	n=260	n=260
	No	71.8%	73.8%	73.1%	72.7%
	Yes	28.2%	26.2%	26.9%	27.3%
			p=0.887		
Ionizing Radiation Exposure		n=1,063	n=374	n=260	n=260
	No	72.7%	78.3%	74.6%	82.3%
	Yes	27.3%	21.7%	25.4%	17.7%
			p=0.006		
Industrial Chemical Exposure		n=1,063	n=374	n=260	n=260
	No	40.5%	51.3%	41.2%	30.8%
	Yes	59.5%	48.7%	58.8%	69.2%
			p<0.001		
Herbicide Exposure		n=1,063	n=374	n=260	n=260
	No	61.8%	6.1%	3.5%	4.6%
	Yes	38.2%	93.9%	96.5%	95.4%
			p<0.001		
Insecticide Exposure		n=1,063	n=374	n=260	n=260
	No	37.3%	24.6%	19.6%	26.2%
	Yes	62.7%	75.4%	80.4%	73.8%
			p<0.001		
Degreasing Chemical Exposure		n=1,063	n=374	n=260	n=260
	No	35.3%	48.7%	36.9%	20.0%
	Yes	64.7%	51.3%	63.1%	80.0%
			p<0.001		

Table 8-5. (Continued)
Associations Between Exposure to Carcinogens and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Asbestos Exposure	No	$\bar{x}$=14.28 (n=655)	$\bar{x}$=82.09 (n=655)
	Yes	$\bar{x}$=15.26 (n=239)	$\bar{x}$=86.31 (n=239)
		p=0.416	p=0.578
Ionizing Radiation Exposure	No	$\bar{x}$=14.99 (n=701)	$\bar{x}$=86.87 (n=701)
	Yes	$\bar{x}$=12.96 (n=193)	$\bar{x}$=71.13 (n=193)
		p=0.098	p=0.039
Industrial Chemical Exposure	No	$\bar{x}$=11.65 (n=379)	$\bar{x}$=66.13 (n=379)
	Yes	$\bar{x}$=17.06 (n=515)	$\bar{x}$=98.48 (n=515)
		p<0.001	p<0.001
Herbicide Exposure	No	$\bar{x}$=11.78 (n=44)	$\bar{x}$=66.29 (n=44)
	Yes	$\bar{x}$=14.69 (n=850)	$\bar{x}$=84.19 (n=850)
		p=0.191	p=0.196
Insecticide Exposure	No	$\bar{x}$=14.94 (n=211)	$\bar{x}$=85.58 (n=211)
	Yes	$\bar{x}$=14.41 (n=683)	$\bar{x}$=82.48 (n=683)
		p=0.668	p=0.695
Degreasing Chemical Exposure	No	$\bar{x}$=10.37 (n=330)	$\bar{x}$=57.80 (n=330)
	Yes	$\bar{x}$=17.64 (n=564)	$\bar{x}$=102.88 (n=564)
		p<0.001	p<0.001

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

The Model 1 analysis showed a highly significant association between group and exposure to ionizing radiation ($p=0.003$). A significant difference between the percentage of participants who have never been exposed to ionizing radiation was seen between Ranch Hands (78.7%) and Comparisons (73.1%). In Model 3, a significant difference in the percentage of participants who have never been exposed to ionizing radiation was seen among Comparisons (72.7%), background Ranch Hands (78.3%), low Ranch Hands (74.6%), and high Ranch Hands (82.3%) ($p=0.006$). A significant association existed for Models 5 and 6 between current dioxin and exposure to ionizing radiation ($p=0.039$). The mean current whole-weight dioxin level was greater for those who had never been exposed to ionizing radiation than for those who were exposed.

The association between industrial chemical exposure and dioxin was highly significant in the analysis of Models 2 through 6 ($p=0.005$ for Model 2 and $p<0.001$ for Models 3 through 6). Participants who were exposed to industrial chemicals had higher mean dioxin levels in Models 2, 4, 5, and 6 than those participants who were not exposed. In Model 3, a significant difference in the percentage of participants who were not exposed to industrial chemicals was seen among Comparisons (40.5%), background Ranch Hands (51.3%), low Ranch Hands (41.2%), and high Ranch Hands (30.8%).

As expected, a highly significant association between group and reported exposure to herbicides was revealed in Model 1 ($p<0.001$). A significant difference between the percentage of participants who have never been exposed to herbicides was seen between Ranch Hands (5.1%) and Comparisons (61.7%). A highly significant association between categorized dioxin and exposure to herbicides also was revealed in Model 3 ($p<0.001$), due to the inherent difference between Ranch Hands and Comparisons. A significant difference between the percentage of participants not exposed to herbicides was seen among Comparisons (61.8%), background Ranch Hands (6.1%), low Ranch Hands (3.5%), and high Ranch Hands (4.6%).

Highly significant associations were shown between insecticide exposure and group in Model 1 ($p<0.001$), as well as between insecticide exposure and categorized dioxin in Model 3 ($p<0.001$). In Model 1, 23.6 percent of Ranch Hands and 37.3 percent of Comparisons were never exposed to insecticides. In Model 3, the percentage of participants not exposed to insecticides was 37.3 among Comparisons, 24.6 among background Ranch Hands, 19.6 among low Ranch Hands, and 26.2 among high Ranch Hands.

The association between reported degreasing chemical exposure and dioxin was highly significant in the analysis of Models 2 through 6 ($p\leq0.001$ for each model). The mean dioxin level increased with exposure to degreasing chemicals in Models 2, 4, 5, and 6. In Model 3, a significant difference between the percentage of participants who have not been exposed to degreasing chemicals was seen among Comparisons (35.3%), background Ranch Hands (48.7%), low Ranch Hands (36.9%), and high Ranch Hands (20.0%).

No significant ($p\leq0.05$) associations were observed between asbestos exposure and the five estimates of dioxin exposure.

HEALTH VARIABLES

Results of tests of association between numerous measures related to a participant's health and the five estimates of dioxin exposure are presented in Table 8-6. Caloric intake in its continuous form was shown to be significantly associated with categorized dioxin in Model 3 ($p=0.018$). The mean caloric intake in the Comparison, background Ranch Hand, low Ranch Hand, and high Ranch Hand categories are 1,944.3 kcal/day; 2,046.9 kcal/day; 1,879.3 kcal/day; and 1,885.5 kcal/day respectively.

Statistically significant associations were found between body fat and dioxin for Model 2 ($p=0.015$), Model 3 ($p<0.001$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). In Model 3, the mean percent body fat in the Comparison, background Ranch Hands, low Ranch Hands, and high Ranch Hands categories was 22.63, 20.87, 23.27, and 23.83 respectively. Body fat increased as dioxin levels increased in Models 2 and 4, and Models 5 and 6. The examination of body fat when dichotomized into lean or normal (≤ 25 percent body fat) and obese (>25 percent body fat) showed a significant association with dioxin in Models 3 through 6 ($p<0.001$ for each model). In Model 3, a significant difference in the percentage of participants considered lean or normal was seen among Comparisons (73.7%), background Ranch Hands (85.8%), low Ranch Hands (69.6%), and high Ranch Hands (64.2%). The mean current dioxin levels were higher for the obese participants in Models 4 through 6.

Serum insulin in its continuous form showed a significant association with dioxin in Models 3 through 6 ($p\leq 0.001$ for each model). Model 3 revealed mean serum insulin levels of 97.57 mIU/ml for Comparisons, 87.98 mIU/ml for background Ranch Hands, 108.46 mIU/ml for low Ranch Hands, and 119.46 mIU/ml for high Ranch Hands. In Models 4 through 6, serum insulin levels increased as current dioxin levels increased. When stratified into either less than or equal to 56 mIU/ml or greater than 56 mIU/ml, serum insulin showed significant associations with dioxin in Model 3 ($p=0.033$), Model 4 ($p=0.005$), and Models 5 and 6 ($p<0.001$). In Model 3, a significant difference between the percentage of participants with serum insulin less than or equal to 56 mIU/ml was seen among Comparisons (42.5%), background Ranch Hands (50.5%), low Ranch Hands (42.7%), and high Ranch Hands (40.8%). The mean current dioxin levels were higher for participants with serum insulin greater than 56 mIU/ml in Models 4 through 6.

Analysis of cholesterol in both its continuous and discrete forms revealed highly significant positive associations with current dioxin in Models 5 and 6 ($p<0.001$ for cholesterol continuous; $p=0.003$ when cholesterol discrete). Cholesterol increased as the level of dioxin increased.

High-density lipoprotein (HDL) cholesterol showed highly significant associations in Model 2 ($p=0.006$), Model 3 ($p<0.001$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). HDL cholesterol levels decreased as the mean dioxin levels increased for Models 2, 4, 5, and 6. Model 3 revealed mean HDL cholesterol levels of 42.02 mg/dl for the Comparisons, 43.89 mg/dl for background Ranch Hands, 42.31 mg/dl for low Ranch Hands, and 39.52 mg/dl for high Ranch Hands. Stratifying participants into either less than or equal to 35 mg/dl or greater than 35 mg/dl, revealed significant associations between

Table 8-6.
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Caloric Intake (kcal/day) (Continuous)	--	n=950 $\bar{x}$=1,956.4	n=1,279 $\bar{x}$=1,952.7	n=518 r=-0.002
		p=0.912		p=0.957
Caloric Intake (kcal/day) (Discrete)		n=950	n=1,279	
	≤ 2000	58.8%	59.7%	$\bar{x}$=167.04 (n=324)
	> 2000	41.2%	40.3%	$\bar{x}$=163.51 (n=194)
		p=0.731		p=0.798
Body Fat (percent) (Continuous)	--	n=952 $\bar{x}$=22.41	n=1,281 $\bar{x}$=22.55	n=520 r=0.106
		p=0.529		p=0.015
Body Fat (percent) (Discrete)		n=952	n=1,281	
	Lean or Normal	74.6%	74.4%	$\bar{x}$=157.50 (n=348)
	Obese	25.4%	25.6%	$\bar{x}$=186.06 (n=172)
		p=0.960		p=0.052
Serum Insulin (mIU/ml) (Continuous)	--	n=952 $\bar{x}$=103.00	n=1,279 $\bar{x}$=97.51	n=520 r=0.059
		p=0.204		p=0.181
Serum Insulin (mIU/ml) (Discrete)		n=952	n=1,279	
	0-56	45.2%	43.5%	$\bar{x}$=164.02 (n=217)
	>56	54.8%	56.5%	$\bar{x}$=168.17 (n=303)
		p=0.450		p=0.761
Cholesterol (mg/dl) (Continuous)	--	n=952 $\bar{x}$=218.61	n=1,280 $\bar{x}$=218.30	n=520 r=0.052
		p=0.849		p=0.233
Cholesterol (mg/dl) (Discrete)		n=952	n=1,280	
	0-200	32.9%	32.0%	$\bar{x}$=155.28 (n=170)
	200-239	38.0%	41.6%	$\bar{x}$=176.67 (n=194)
	>239	29.1%	26.5%	$\bar{x}$=166.62 (n=156)
		p=0.202		p=0.412

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1 Ranch Hand	Model 1 Comparison	Model 2 Initial Dioxin (ppt)
HDL Cholesterol (mg/dl) (Continuous)	--	n=938 $\bar{x}$=42.06	n=1,268 $\bar{x}$=42.19	n=511 r=-0.120
		p=0.778		p=0.006
HDL Cholesterol (mg/dl) (Discrete)		n=938	n=1,268	
	0-35	28.3%	23.8%	$\bar{x}$=176.02 (n=158)
	>35	71.7%	76.2%	$\bar{x}$=161.21 (n=353)
		p=0.021		p=0.320
Cholesterol-HDL Cholesterol Ratio (Continuous)	--	n=938 $\bar{x}$=5.52	n=1,268 $\bar{x}$=5.45	n=511 r=0.127
		p=0.302		p=0.004
Cholesterol-HDL Cholesterol Ratio (Discrete)		n=938	n=1,268	
	0-5	41.3%	43.5%	$\bar{x}$=148.47 (n=188)
	>5	58.7%	56.5%	$\bar{x}$=176.56 (n=323)
		p=0.305		p=0.040
Physical Activity Index		n=952	n=1,279	
	Sedentary	57.6%	56.1%	$\bar{x}$=183.44 (n=313)
	Moderate	17.8%	18.5%	$\bar{x}$=145.91 (n=92)
	Very Active	24.7%	25.3%	$\bar{x}$=141.85 (n=115)
		p=0.791		p=0.012
Diabetic Class[a]		n=951	n=1,279	
	Normal	72.3%	75.4%	$\bar{x}$=159.44 (n=348)
	Impaired	12.5%	10.3%	$\bar{x}$=187.46 (n=74)
	Diabetic	15.1%	14.2%	$\bar{x}$=177.12 (n=98)
		p=0.187		p=0.296
Diabetic Severity[b]		n=144	n=182	
	No Treatment	54.2%	61.0%	$\bar{x}$=152.18 (n=48)
	Diet Only	21.5%	18.7%	$\bar{x}$=170.64 (n=23)
	Oral Hypoglycemic	12.5%	13.2%	$\bar{x}$=303.03 (n=18)
	Insulin Dependent	11.8%	7.1%	$\bar{x}$=149.55 (n=9)
		p=0.407		p=0.103

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin (ppt)
Family History of Diabetes		n=934	n=1,263	
	No	77.1%	75.5%	$\bar{x}$=159.42 (n=386)
	Yes	22.9%	24.5%	$\bar{x}$=187.84 (n=122)
		p=0.427		p=0.086
Family History of Heart Disease		n=939	n=1,267	
	No	40.8%	43.5%	$\bar{x}$=168.14 (n=222)
	Yes	59.2%	56.5%	$\bar{x}$=165.58 (n=290)
		p=0.220		p=0.853
Family History of Heart Disease Before Age 45		n=917	n=1,250	
	No	89.9%	88.7%	$\bar{x}$=162.86 (n=453)
	Yes	10.1%	11.3%	$\bar{x}$=202.22 (n=45)
		p=0.439		p=0.135
Currently Taking Blood Pressure Medication		n=952	n=1,281	
	No	78.9%	80.6%	$\bar{x}$=167.05 (n=410)
	Yes	21.1%	19.4%	$\bar{x}$=164.11 (n=110)
		p=0.333		p=0.858

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Caloric Intake (kcal/day) (Continuous)	--	n=1,061 $\bar{x}$=1,944.3	n=374 $\bar{x}$=2,046.9	n=260 $\bar{x}$=1,879.3	n=258 $\bar{x}$=1,885.5
			p=0.018		
Caloric Intake (kcal/day) (Discrete)		n=1,061	n=374	n=260	n=258
	≤2000	59.3%	54.8%	62.3%	62.8%
	>2000	40.7%	45.2%	37.7%	37.2%
			p=0.145		
Body Fat (percent) (Continuous)	--	n=1,063 $\bar{x}$=22.63	n=374 $\bar{x}$=20.87	n=260 $\bar{x}$=23.27	n=260 $\bar{x}$=23.83
			p<0.001		
Body Fat (percent) (Discrete)		n=1,063	n=374	n=260	n=260
	Lean or Normal	73.7%	85.8%	69.6%	64.2%
	Obese	26.3%	14.2%	30.4%	35.8%
			p<0.001		
Serum Insulin (mIU/ml) (Continuous)	--	n=1,062 $\bar{x}$=97.57	n=374 $\bar{x}$=87.98	n=260 $\bar{x}$=108.46	n=260 $\bar{x}$=119.46
			p=0.001		
Serum Insulin (mIU/ml) (Discrete)		n=1,062	n=374	n=260	n=260
	0-56	42.5%	50.5%	42.7%	40.8%
	>56	57.5%	49.5%	57.3%	59.2%
			p=0.033		
Cholesterol (mg/dl) (Continuous)	--	n=1,063 $\bar{x}$=217.74	n=374 $\bar{x}$=217.37	n=260 $\bar{x}$=217.70	n=260 $\bar{x}$=221.38
			p=0.533		
Cholesterol (mg/dl) (Discrete)		n=1,063	n=374	n=260	n=260
	0-200	31.7%	33.2%	35.0%	30.4%
	200-239	42.0%	39.0%	35.4%	39.2%
	>239	26.3%	27.8%	29.6%	30.4%
			p=0.504		

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
HDL Cholesterol (mg/dl) (Continuous)	--	n=1,053 $\bar{x}$=42.02	n=370 $\bar{x}$=43.89	n=256 $\bar{x}$=42.31	n=255 $\bar{x}$=39.52
			p<0.001		
HDL Cholesterol (mg/dl) (Discrete)		n=1,053	n=370	n=256	n=255
	0-35	24.4%	23.8%	29.3%	32.5%
	>35	75.6%	76.2%	70.7%	67.5%
			p=0.024		
Cholesterol-HDL Cholesterol Ratio (Continuous)	--	n=1,053 $\bar{x}$=5.45	n=370 $\bar{x}$=5.31	n=256 $\bar{x}$=5.46	n=255 $\bar{x}$=5.85
			p<0.001		
Cholesterol-HDL Cholesterol Ratio (Discrete)		n=1,053	n=370	n=256	n=255
	0-5	42.9%	47.3%	41.8%	31.8%
	>5	57.1%	52.7%	58.2%	68.2%
			p=0.001		
Physical Activity Index		n=1,061	n=374	n=260	n=260
	Sedentary	55.6%	53.5%	55.0%	65.4%
	Moderate	18.6%	19.0%	20.0%	15.4%
	Very Active	25.8%	27.5%	25.0%	19.2%
			p=0.092		
Diabetic Class[a]		n=1,062	n=373	n=260	n=260
	Normal	75.5%	79.9%	67.7%	66.2%
	Impaired	10.3%	8.8%	12.7%	15.8%
	Diabetic	14.2%	11.3%	19.6%	18.1%
			p=0.001		
Diabetic Severity[b]		n=151	n=42	n=51	n=47
	No Treatment	57.0%	61.9%	54.9%	42.6%
	Diet Only	21.2%	19.1%	23.5%	23.4%
	Oral Hypoglycemic	13.3%	0.0%	11.8%	25.5%
	Insulin Dependent	8.6%	19.1%	9.8%	8.5%
			p=0.050		

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Family History of Diabetes		n=1,048	n=368	n=254	n=254
	No	75.2%	79.1%	76.8%	75.2%
	Yes	24.8%	20.9%	23.2%	24.8%
			p=0.485		
Family History of Heart Disease		n=1,051	n=369	n=255	n=257
	No	43.6%	37.9%	44.7%	42.0%
	Yes	56.4%	62.1%	55.3%	58.0%
			p=0.244		
Family History of Heart Disease Before Age 45		n=1,035	n=361	n=249	n=249
	No	88.2%	88.6%	94.0%	88.0%
	Yes	11.8%	11.4%	6.0%	12.0%
			p=0.063		
Currently Taking Blood Pressure Medication		n=1,063	n=374	n=260	n=260
	No	80.3%	79.9%	79.2%	78.5%
	Yes	19.7%	20.1%	20.8%	21.5%
			p=0.911		

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Caloric Intake (kcal/day) (Continuous)	--	n=892 r=-0.062 p=0.064	n=892 r=-0.055 p=0.101
Caloric Intake (kcal/day) (Discrete)	≤2000 >2000	$\bar{x}$=15.21 (n=529) $\bar{x}$=13.46 (n=363) p=0.095	$\bar{x}$=86.69 (n=529) $\bar{x}$=77.45 (n=363) p=0.164
Body Fat (percent) (Continuous)	--	n=894 r=0.284 p<0.001	n=894 r=0.296 p<0.001
Body Fat (percent) (Discrete)	Lean or Normal Obese	$\bar{x}$=12.68 (n=669) $\bar{x}$=21.66 (n=225) p<0.001	$\bar{x}$=71.35 (n=669) $\bar{x}$=131.20 (n=225) p<0.001
Serum Insulin (mIU/ml) (Continuous)	--	n=894 r=0.134 p<0.001	n=894 r=0.153 p<0.001
Serum Insulin (mIU/ml) (Discrete)	0-56 >56	$\bar{x}$=12.98 (n=406) $\bar{x}$=15.95 (n=488) p=0.005	$\bar{x}$=71.00 (n=406) $\bar{x}$=94.92 (n=488) p<0.001
Cholesterol (mg/dl) (Continuous)	--	n=894 r=0.052 p=0.123	n=894 r=0.142 p<0.001
Cholesterol (mg/dl) (Discrete)	0-200 200-239 >239	$\bar{x}$=13.74 (n=294) $\bar{x}$=14.73 (n=340) $\bar{x}$=15.21 (n=260) p=0.521	$\bar{x}$=69.89 (n=294) $\bar{x}$=84.58 (n=340) $\bar{x}$=99.14 (n=260) p=0.003

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
HDL Cholesterol (mg/dl) (Continuous)	--	n=881 r=-0.157 p<0.001	n=881 r=-0.171 p<0.001
HDL Cholesterol (mg/dl) (Discrete)	0-35 >35	$\bar{x}$=16.86 (n=246) $\bar{x}$=13.59 (n=635) p=0.008	$\bar{x}$=101.25 (n=246) $\bar{x}$=75.48 (n=635) p=0.001
Cholesterol-HDL Cholesterol Ratio (Continuous)	--	n=881 r=0.145 p<0.001	n=881 r=0.211 p<0.001
Cholesterol-HDL Cholesterol Ratio (Discrete)	0-5 >5	$\bar{x}$=12.34 (n=363) $\bar{x}$=16.11 (n=518) p<0.001	$\bar{x}$=63.74 (n=363) $\bar{x}$=97.67 (n=518) p<0.001
Physical Activity Index	Sedentary Moderate Very Active	$\bar{x}$=15.93 (n=513) $\bar{x}$=13.68 (n=163) $\bar{x}$=12.23 (n=218) p=0.008	$\bar{x}$=91.67 (n=513) $\bar{x}$=78.27 (n=163) $\bar{x}$=69.30 (n=218) p=0.011
Diabetic Class[a]	Normal Impaired Diabetic	$\bar{x}$=13.18 (n=646) $\bar{x}$=19.31 (n=107) $\bar{x}$=18.41 (n=140) p<0.001	$\bar{x}$=73.55 (n=646) $\bar{x}$=117.54 (n=107) $\bar{x}$=113.81 (n=140) p<0.001
Diabetic Severity[b]	No Treatment Diet Only Oral Hypoglycemic Insulin Dependent	$\bar{x}$=16.04 (n=74) $\bar{x}$=20.52 (n=31) $\bar{x}$=49.76 (n=18) $\bar{x}$=9.25 (n=17) p<0.001	$\bar{x}$=96.76 (n=74) $\bar{x}$=142.30 (n=31) $\bar{x}$=325.16 (n=18) $\bar{x}$=50.08 (n=17) p<0.001

Table 8-6. (Continued)
Associations Between Health Variables and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin (ppt)	Models 5 and 6 Whole-Weight Current Dioxin (ppq)
Family History of Diabetes	No	$\bar{x}$=13.87 (n=677)	$\bar{x}$=78.65 (n=677)
	Yes	$\bar{x}$=16.60 (n=199)	$\bar{x}$=97.80 (n=199)
		p=0.038	p=0.023
Family History of Heart Disease	No	$\bar{x}$=15.39 (n=362)	$\bar{x}$=88.05 (n=362)
	Yes	$\bar{x}$=13.96 (n=519)	$\bar{x}$=79.90 (n=519)
		p=0.187	p=0.234
Family History of Heart Disease Before Age 45	No	$\bar{x}$=14.60 (n=773)	$\bar{x}$=83.31 (n=773)
	Yes	$\bar{x}$=13.17 (n=86)	$\bar{x}$=75.82 (n=86)
		p=0.404	p=0.489
Currently Taking Blood Pressure Medication	No	$\bar{x}$=14.36 (n=709)	$\bar{x}$=80.80 (n=709)
	Yes	$\bar{x}$=15.20 (n=185)	$\bar{x}$=93.08 (n=185)
		p=0.522	p=0.150

[a] Diabetic Class: Normal: <140 mg/dl 2-hour postprandial glucose.
Impaired: ≥140-<200 mg/dl 2-hour postprandial glucose.
Diabetic: Verified past history of diabetes or ≥200 mg/dl 2-hour postprandial glucose.

[b] Diabetic severity analyzed only for participants classified as diabetic.

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

group in Model 1 ($p=0.021$) and dioxin in Model 3 ($p=0.024$), Model 4 ($p=0.008$), and Models 5 and 6 ($p=0.001$) and HDL cholesterol. A significant difference between the percentage of participants in the lower HDL cholesterol category was seen between Ranch Hands (28.3%) and Comparisons (23.8%) in Model 1. In Model 3, a significant difference between the percentage of participants with lower HDL cholesterol levels was seen among Comparisons (24.4%), background Ranch Hands (23.8%), low Ranch Hands (29.3%), and high Ranch Hands (32.5%). The mean current dioxin levels were lower for participants with HDL cholesterol levels greater than 35 mg/dl in Models 4 through 6.

Statistically significant associations were found between the cholesterol-HDL ratio and dioxin for Model 2 ($p=0.004$), Model 3 ($p<0.001$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). As dioxin levels increased, the cholesterol-HDL cholesterol ratio increased in Models 2, 4, 5, and 6. In Model 3, the mean cholesterol-HDL cholesterol ratio in the Comparison, background Ranch Hand, low Ranch Hand, and high Ranch Hand categories was 5.45, 5.31, 5.46, and 5.85 respectively. Dichotomizing the cholesterol-HDL cholesterol ratio into less than or equal to five and greater than five revealed significant associations for Model 2 ($p=0.040$), Model 3 ($p=0.001$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). The mean dioxin levels were higher for participants with cholesterol-HDL cholesterol ratios greater than 5 in Models 2, 4, 5, and 6. In Model 3, a significant difference between the percentage of participants with a ratio less than five was seen among Comparisons (42.9%), background Ranch Hands (47.3%), low Ranch Hands (41.8%), and high Ranch Hands (31.8%).

The examination of the physical activity index showed a significant association with dioxin in Model 2 ($p=0.012$), Model 4 ($p=0.008$), and Models 5 and 6 ($p=0.011$). In each of these models, the mean dioxin levels were smaller as activity levels progressed from sedentary to moderate activity to very active. This relationship between the physical activity index and dioxin is most likely due to the relationship between dioxin and body fat, as discussed above.

A highly significant association between dioxin and diabetic class was revealed in Models 3 through 6 ($p\leq0.001$). In Model 3, a significant difference between the percentage of participants classified as normal, impaired, and diabetic was seen among Comparisons (75.5%, 10.3%, and 14.2%), background Ranch Hands (79.9%, 8.8%, and 11.3%), low Ranch Hands (67.7%, 12.7%, and 19.6%), and high Ranch Hands (66.2%, 15.8%, and 18.1%). In Models 4 through 6, participants classified as impaired or diabetic had higher mean current dioxin levels than participants classified as normal. This relationship between diabetic class and dioxin also may be due to the association between dioxin and body fat.

Examining the association between diabetic severity and dioxin in diabetics revealed significant relationships in the analysis of Model 3 ($p=0.050$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). In Model 3, a significant difference between the percentage of participants with no treatment for diabetes, treatment through diet only, oral hypoglycemic, and insulin dependent was seen among Comparisons (57.0%, 21.2%, 13.3%, and 8.6%), background Ranch Hands (61.9%, 19.1%, 0.0%, and 19.1%), low Ranch Hands (54.9%, 23.5%, 11.8%, and 9.8%), and high Ranch Hands (42.6%, 23.4%, 25.5%, and 8.2%). In Models 4, 5, and 6, the mean current dioxin level was highest for the oral hypoglycemic

participants followed by participants treating diabetes through diet only, participants with no treatment, and insulin dependent participants.

The analysis of family history of diabetes revealed significant associations with current dioxin in Models 4 ($p=0.038$) and Models 5 and 6 ($p=0.023$). In each model, the mean current dioxin level was higher for participants with a family history of diabetes, which may be due to the association between dioxin and body fat.

No significant ($p \leq 0.05$) associations were observed between family history of heart disease, family history of heart disease before age 45, or current use of blood pressure medication and any of the five estimates of dioxin exposure.

SUN-EXPOSURE VARIABLES

Results of tests of association between a participant's reaction to sun exposure and the estimates of dioxin exposure are shown in Table 8-7. These statistics are based on non-Black participants only, because the sun-exposure covariates were used in adjusted analyses of skin neoplasms only, and Blacks were excluded from the skin neoplasm analyses.

Model 2 showed a significant relationship between initial dioxin and hair color ($p=0.038$). The mean initial dioxin level was highest for participants with dark brown hair followed by black, light brown, blonde, and red hair colors.

The analysis of a participant's skin reaction to the sun after repeated exposure revealed a significant association with current dioxin in Models 5 and 6 ($p=0.034$). The mean current dioxin level was highest for participants who tan dark brown followed by participants who tan moderately, participants who tan mildly, and those who freckle but do not tan.

Analysis of average lifetime residential latitude revealed significant associations with group in Model 1 ($p=0.001$) and dioxin in Model 2 ($p=0.029$) and Model 3 ($p=0.005$). In Model 1, a significant difference between the percentage of participants living in areas less than 37 degrees latitude was seen between Ranch Hands (44.6%) and Comparisons (51.9%). In Model 2, the mean initial dioxin levels were greater for participants living south of 37 degrees latitude. In Model 3, a significant difference between the percentage of participants living south of 37 degrees latitude was seen among Comparisons (51.4%), background Ranch Hands (44.7%), low Ranch Hands (40.0%), and high Ranch Hands (45.3%).

No significant ($p \leq 0.05$) associations were observed between the five estimates of dioxin exposure and skin color, eye color, reaction of skin to sun after at least 2 hours, or a composite sun-reaction index.

OTHER MISCELLANEOUS COVARIATES

Results of tests of association between other miscellaneous covariates and the estimates of dioxin exposure are shown in Table 8-8. Examining the association between current total household income in both its continuous and discrete forms and dioxin revealed highly significant relationships in the analysis of Models 2 through 6 ($p<0.001$ for each model both

Table 8-7.
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure (Non-Blacks Only)

Covariate	Covariate Category	Model 1 Ranch Hand	Model 1 Comparison	Model 2 Initial Dioxin
Skin Color		n=895	n=1,202	
	Dark	0.0%	0.1%	(n=0)
	Medium	4.1%	2.8%	$\bar{x}$=153.73 (n=21)
	Pale	17.3%	17.6%	$\bar{x}$=168.36 (n=72)
	Dark Peach	55.2%	57.7%	$\bar{x}$=176.44 (n=285)
	Pale Peach	23.4%	21.9%	$\bar{x}$=157.46 (n=106)
		p=0.311		p=0.701
Hair Color		n=896	n=1,202	
	Black	18.5%	22.2%	$\bar{x}$=173.21 (n=90)
	Dark Brown	48.9%	47.4%	$\bar{x}$=189.93 (n=239)
	Light Brown	27.1%	24.7%	$\bar{x}$=144.13 (n=128)
	Blonde	4.9%	4.6%	$\bar{x}$=134.17 (n=24)
	Red	0.6%	1.0%	$\bar{x}$=96.56 (n=3)
	Bald	0.0%	0.1%	(n=0)
		p=0.231		p=0.038
Eye Color		n=896	n=1,200	
	Brown	28.7%	30.9%	$\bar{x}$=188.50 (n=149)
	Hazel	23.3%	20.4%	$\bar{x}$=155.34 (n=112)
	Green	5.1%	5.6%	$\bar{x}$=166.24 (n=28)
	Gray	4.7%	4.2%	$\bar{x}$=154.11 (n=23)
	Blue	38.2%	38.9%	$\bar{x}$=167.31 (n=172)
		p=0.487		p=0.526
Reaction of Skin to Sun After at Least Two Hours		n=895	n=1,203	
	No Reaction	37.8%	39.0%	$\bar{x}$=164.25 (n=191)
	Becomes Red	41.1%	39.1%	$\bar{x}$=170.34 (n=193)
	Burns	12.9%	15.7%	$\bar{x}$=204.62 (n=60)
	Painfully Burns	8.3%	6.2%	$\bar{x}$=150.85 (n=39)
		p=0.085		p=0.352
Reaction of Skin to Sun After Repeated Exposure		n=892	n=1,199	
	Tans Dark Brown	29.5%	28.7%	$\bar{x}$=164.62 (n=152)
	Tans Moderately	51.6%	51.5%	$\bar{x}$=172.24 (n=244)
	Tans Mildly	16.8%	17.8%	$\bar{x}$=181.98 (n=77)
	Freckles-No Tan	2.1%	2.1%	$\bar{x}$=91.69 (n=8)
		p=0.944		p=0.244

Table 8-7. (Continued)
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure (Non-Blacks Only)

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin
Composite Sun-Reaction Index[a]		n=895	n=1,204	
	High	8.9%	7.6%	$\bar{x}$=152.71 (n=41)
	Medium	20.2%	23.7%	$\bar{x}$=194.10 (n=97)
	Low	70.8%	68.8%	$\bar{x}$=166.01 (n=345)
		p=0.119		p=0.256
Average Lifetime Residential Latitude		n=893	n=1,187	
	< 37°	44.6%	51.9%	$\bar{x}$=189.57 (n=206)
	≥ 37°	55.4%	48.1%	$\bar{x}$=157.26 (n=276)
		p=0.001		p=0.029

Table 8-7. (Continued)
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure (Non-Blacks Only)

		Model 3			
Covariate	Covariate Category	Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Skin Color		n=1,008	n=358	n=237	n=247
	Dark	0.1%	0.0%	0.0%	0.0%
	Medium	2.8%	3.9%	4.2%	4.5%
	Pale	17.7%	18.7%	13.1%	16.6%
	Dark Peach	56.7%	52.0%	59.5%	58.3%
	Pale Peach	22.8%	25.4%	23.2%	20.7%
			p=0.628		
Hair Color		n=1,008	n=359	n=237	n=247
	Black	20.8%	17.8%	17.3%	19.8%
	Dark Brown	48.5%	47.4%	44.3%	54.3%
	Light Brown	24.5%	29.5%	31.2%	21.9%
	Blonde	5.0%	4.7%	6.3%	3.6%
	Red	1.1%	0.6%	0.8%	0.4%
	Bald	0.1%	0.0%	0.0%	0.0%
			p=0.411		
Eye Color		n=1,006	n=359	n=237	n=247
	Brown	29.6%	26.5%	27.4%	34.0%
	Hazel	20.6%	24.2%	23.6%	22.7%
	Green	5.7%	5.0%	5.1%	6.5%
	Gray	4.0%	4.5%	4.6%	4.9%
	Blue	40.2%	39.8%	39.2%	32.0%
			p=0.617		
Reaction of Skin to Sun After at Least 2 Hours		n=1,005	n=359	n=236	n=247
	No Reaction	38.5%	33.7%	38.1%	40.9%
	Becomes Red	39.7%	43.7%	40.7%	39.3%
	Burns	15.3%	13.4%	11.4%	13.4%
	Painfully Burns	6.5%	9.2%	9.8%	6.5%
			p=0.293		
Reaction of Skin to Sun After Repeated Exposure		n=1,002	n=358	n=235	n=246
	Tans Dark Brown	28.6%	25.7%	30.6%	32.5%
	Tans Moderately	51.6%	53.6%	50.6%	50.8%
	Tans Mildly	17.4%	17.9%	15.7%	16.3%
	Freckles-No Tan	2.4%	2.8%	3.0%	0.4%
			p=0.506		

Table 8-7. (Continued)
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure
(Non-Blacks Only)

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Composite Sun-Reaction Index[a]		n=1,006	n=359	n=236	n=247
	High	8.1%	10.0%	10.2%	6.9%
	Medium	23.5%	20.6%	19.1%	21.1%
	Low	68.5%	69.4%	70.8%	72.1%
			p=0.484		
Average Lifetime Residential Latitude		n=997	n=358	n=235	n=247
	< 37°	51.4%	44.7%	40.0%	45.3%
	≥ 37°	48.6%	55.3%	60.0%	54.7%
			p=0.005		

Table 8-7. (Continued)
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure (Non-Blacks Only)

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin	Models 5 and 6 Whole-Weight Current Dioxin
Skin Color	Dark	(n=0)	(n=0)
	Medium	$\bar{x}$=13.60 (n=35)	$\bar{x}$=75.41 (n=35)
	Pale	$\bar{x}$=13.37 (n=139)	$\bar{x}$=75.51 (n=139)
	Dark Peach	$\bar{x}$=15.61 (n=471)	$\bar{x}$=91.97 (n=471)
	Pale Peach	$\bar{x}$=13.11 (n=197)	$\bar{x}$=72.24 (n=197)
		p=0.194	p=0.070
Hair Color	Black	$\bar{x}$=15.14 (n=154)	$\bar{x}$=87.15 (n=154)
	Dark Brown	$\bar{x}$=15.60 (n=409)	$\bar{x}$=89.87 (n=409)
	Light Brown	$\bar{x}$=12.84 (n=234)	$\bar{x}$=74.10 (n=234)
	Blonde	$\bar{x}$=12.53 (n=41)	$\bar{x}$=67.88 (n=41)
	Red	$\bar{x}$=11.52 (n=5)	$\bar{x}$=64.98 (n=5)
	Bald	(n=0)	(n=0)
		p=0.205	p=0.247
Eye Color	Brown	$\bar{x}$=16.81 (n=244)	$\bar{x}$=100.14 (n=244)
	Hazel	$\bar{x}$=13.41 (n=199)	$\bar{x}$=76.22 (n=199)
	Green	$\bar{x}$=14.83 (n=46)	$\bar{x}$=79.96 (n=46)
	Gray	$\bar{x}$=14.38 (n=39)	$\bar{x}$=88.39 (n=39)
	Blue	$\bar{x}$=13.60 (n=315)	$\bar{x}$=76.53 (n=315)
		p=0.156	p=0.076
Reaction of Skin to Sun After at Least Two Hours	No Reaction	$\bar{x}$=15.52 (n=312)	$\bar{x}$=90.46 (n=312)
	Becomes Red	$\bar{x}$=13.90 (n=350)	$\bar{x}$=79.31 (n=350)
	Burns	$\bar{x}$=15.25 (n=108)	$\bar{x}$=86.57 (n=108)
	Painfully Burns	$\bar{x}$=12.46 (n=72)	$\bar{x}$=70.31 (n=72)
		p=0.344	p=0.313
Reaction of Skin to Sun After Repeated Exposure	Tans Dark Brown	$\bar{x}$=15.54 (n=244)	$\bar{x}$=88.00 (n=244)
	Tans Moderately	$\bar{x}$=14.61 (n=436)	$\bar{x}$=85.09 (n=436)
	Tans Mildly	$\bar{x}$=13.50 (n=141)	$\bar{x}$=77.34 (n=141)
	Freckles-No Tan	$\bar{x}$=7.57 (n=18)	$\bar{x}$=38.05 (n=18)
		p=0.053	p=0.034

Table 8-7. (Continued)
Associations Between Sun-Exposure Variables and Estimates of Dioxin Exposure (Non-Blacks Only)

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin	Models 5 and 6 Whole-Weight Current Dioxin
Composite Sun-Reaction Index[a]	High	$\bar{x}$=12.32 (n=77)	$\bar{x}$=69.83 (n=77)
	Medium	$\bar{x}$=15.01 (n=171)	$\bar{x}$=86.31 (n=171)
	Low	$\bar{x}$=14.69 (n=594)	$\bar{x}$=84.43 (n=594)
		p=0.380	p=0.395
Average Lifetime Residential Latitude	< 37°	$\bar{x}$=15.11 (n=366)	$\bar{x}$=87.37 (n=366)
	≥ 37°	$\bar{x}$=14.09 (n=474)	$\bar{x}$=80.46 (n=474)
		p=0.357	p=0.328

[a] Composite sun reaction index (from reaction of skin after at least 2 hours and reaction of skin after repeated exposure):

High: Burns painfully, freckles with no tan, or both.
Medium: Burns, tans mildly, or both.
Low: All other reactions.

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

Table 8-8.
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1 Ranch Hand	Model 1 Comparison	Model 2 Initial Dioxin
Current Total Household Income (Continuous)	--	n=941 $\bar{x}$=$60,550	n=1,263 $\bar{x}$=$59,293	n=516 r=-0.222
		p=0.268		p<0.001
Current Total Household Income (Discrete)		n=941	n=1,263	
	≤$55,000	47.2%	50.3%	$\bar{x}$=199.15 (n=275)
	>$55,000	52.8%	49.7%	$\bar{x}$=137.19 (n=241)
		p=0.163		p<0.001
Personality Type		n=951	n=1,280	
	A	44.1%	41.8%	$\bar{x}$=153.97 (n=215)
	B	55.9%	58.2%	$\bar{x}$=176.32 (n=304)
		p=0.305		p=0.099
Education		n=952	n=1,281	
	College	50.6%	53.1%	$\bar{x}$=138.46 (n=208)
	High School	49.4%	46.9%	$\bar{x}$=188.14 (n=312)
		p=0.269		p<0.001
Current Employment Status		n=952	n=1,279	
	No	22.7%	21.1%	$\bar{x}$=136.59 (n=111)
	Yes	77.3%	78.9%	$\bar{x}$=175.59 (n=409)
		p=0.400		p=0.011
Current Marital Status		n=952	n=1,279	
	Not Married	13.8%	14.9%	$\bar{x}$=161.02 (n=76)
	Married	86.2%	85.1%	$\bar{x}$=167.37 (n=444)
		p=0.504		p=0.735
Current Parental Status (child less than 18 years old)		n=952	n=1,281	
	No	75.9%	72.1%	$\bar{x}$=155.12 (n=382)
	Yes	24.1%	27.9%	$\bar{x}$=202.20 (n=138)
		p=0.048		p=0.004

Table 8-8. (Continued)
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 1		Model 2
		Ranch Hand	Comparison	Initial Dioxin
Worked with Vibrating Power Equipment or Tools		n=952	n=1,279	
	No	75.6%	79.4%	$\bar{x}$=162.76 (n=375)
	Yes	24.4%	20.6%	$\bar{x}$=176.28 (n=145)
		p=0.037		p=0.376
Composite Exposure to Heavy Metals		n=952	n=1,279	
	No	84.6%	84.4%	$\bar{x}$=163.26 (n=427)
	Yes	15.4%	15.6%	$\bar{x}$=181.75 (n=93)
		p=0.986		p=0.309

Table 8-8. (Continued)
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Current Total Household Income (Continuous)	--	n=1,048 $\bar{x}$=$60,000	n=367 $\bar{x}$=$67,800	n=256 $\bar{x}$=$61,328	n=260 $\bar{x}$=$50,346
			p<0.001		
Current Total Household Income (Discrete)		n=1,048	n=367	n=256	n=260
	≤$55,000	49.3%	37.9%	42.6%	63.8%
	>$55,000	50.7%	62.1%	57.4%	36.2%
			p<0.001		
Personality Type		n=1,062	n=374	n=259	n=260
	A	41.9%	46.8%	44.4%	38.5%
	B	58.1%	53.2%	55.6%	61.5%
			p=0.168		
Education		n=1,063	n=374	n=260	n=260
	College	53.2%	66.6%	49.6%	30.4%
	High School	46.8%	33.4%	50.4%	69.6%
			p<0.001		
Current Employment Status		n=1,061	n=374	n=260	n=260
	No	19.4%	24.3%	26.2%	16.5%
	Yes	80.6%	75.7%	73.8%	83.5%
			p=0.010		
Current Marital Status		n=1,061	n=374	n=260	n=260
	Not Married	13.7%	11.8%	13.8%	15.4%
	Married	86.3%	88.2%	86.2%	84.6%
			p=0.616		
Current Parental Status (child less than 18 years old)		n=1,063	n=374	n=260	n=260
	No	72.6%	79.4%	79.6%	67.3%
	Yes	27.4%	20.6%	20.4%	32.7%
			p=0.001		

Table 8-8. (Continued)
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 3			
		Comparison	Background Ranch Hand	Low Ranch Hand	High Ranch Hand
Worked With		n=1,061	n=374	n=260	n=260
Vibrating Power	No	80.0%	80.5%	73.8%	70.4%
Equipment or Tools	Yes	20.0%	19.5%	26.2%	29.6%
			p=0.002		
Composite		n=1,061	n=374	n=260	n=260
Exposure to Heavy	No	84.2%	88.5%	82.7%	81.5%
Metals	Yes	15.8%	11.5%	17.3%	18.5%
			p=0.071		

Table 8-8. (Continued)
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin	Models 5 and 6 Whole-Weight Current Dioxin
Current Total Household Income (Continuous)	--	n=883 r=-0.253 p<0.001	n=883 r=-0.240 p<0.001
Current Total Household Income (Discrete)	≤$55,000 >$55,000	$\bar{x}$=18.37 (n=414) $\bar{x}$=12.00 (n=469) p<0.001	$\bar{x}$=107.12 (n=414) $\bar{x}$=68.03 (n=469) p<0.001
Personality Type	A B	$\bar{x}$=13.34 (n=390) $\bar{x}$=15.53 (n=503) p=0.037	$\bar{x}$=76.76 (n=390) $\bar{x}$=88.57 (n=503) p=0.075
Education	College High School	$\bar{x}$=11.10 (n=457) $\bar{x}$=19.17 (n=437) p<0.001	$\bar{x}$=62.73 (n=457) $\bar{x}$=111.68 (n=437) p<0.001
Current Employment Status	No Yes	$\bar{x}$=12.21 (n=202) $\bar{x}$=15.28 (n=692) p=0.010	$\bar{x}$=69.22 (n=202) $\bar{x}$=87.78 (n=692) p=0.013
Current Marital Status	Not Married Married	$\bar{x}$=14.69 (n=120) $\bar{x}$=14.51 (n=774) p=0.907	$\bar{x}$=84.95 (n=120) $\bar{x}$=82.93 (n=774) p=0.837
Current Parental Status (child less than 18 years old)	No Yes	$\bar{x}$=13.48 (n=679) $\bar{x}$=18.40 (n=215) p<0.001	$\bar{x}$=77.16 (n=679) $\bar{x}$=105.51 (n=215) p<0.001

Table 8-8. (Continued)
Associations Between Other Miscellaneous Covariates and Estimates of Dioxin Exposure

Covariate	Covariate Category	Model 4 Lipid-Adjusted Current Dioxin	Models 5 and 6 Whole-Weight Current Dioxin
Worked With Vibrating Power Equipment or Tools	No	$\bar{x}$=13.82 (n=676)	$\bar{x}$=79.25 (n=676)
	Yes	$\bar{x}$=16.97 (n=218)	$\bar{x}$=96.75 (n=218)
		p=0.014	p=0.032
Composite Exposure to Heavy Metals	No	$\bar{x}$=13.98 (n=758)	$\bar{x}$=80.00 (n=758)
	Yes	$\bar{x}$=18.02 (n=136)	$\bar{x}$=103.53 (n=136)
		p=0.011	p=0.020

Note: Means for discrete covariates are transformed from the logarithmic (base 2) scale for initial dioxin in Model 2, and from the ($\log_2$ (X+1)) scale for current dioxin in Models 4, 5, and 6.

continuous and discrete). Current income was greater for those participants with lower dioxin levels in Models 2, 4, 5, and 6. In Model 3, a significant difference in the percentage of participants with an income less than or equal to $55,000 per year was observed for Comparisons (49.3%), background Ranch Hands (37.9%), low Ranch Hands (42.6%), and high Ranch Hands (63.8%). This relationship between current total household income and dioxin may be due to the association between dioxin and occupation, as discussed previously (officers tended to have higher current total household incomes than enlisted personnel).

Model 4 revealed a significant association between current lipid-adjusted dioxin and personality type ($p=0.037$). Participants with personality Type A had a lower mean current dioxin level than participants with personality Type B.

A significant relationship between education and dioxin was revealed for Models 2 through 6 ($p<0.001$ for each model). The mean dioxin levels in Models 2, 4, 5, and 6 were lower for participants with a college education than for participants with a high school education. In Model 3, a significant difference between the percentage of participants with a college education was seen among Comparisons (53.2%), background Ranch Hands (66.6%), low Ranch Hands (49.6%), and high Ranch Hands (30.4%). The relationship between education and dioxin in Models 2 through 6 is most likely due to the relationship between dioxin and military occupation, as discussed previously (a greater percentage of officers were college-educated, as compared to enlisted personnel).

Statistically significant associations were found between current employment status and dioxin for Model 2 ($p=0.011$), Model 3 ($p=0.010$), Model 4 ($p=0.010$), and Models 5 and 6 ($p=0.013$). In Models 2, 4, 5, and 6, participants who were currently employed had higher dioxin levels than those not currently employed (this group would contain retired participants as well). In Model 3, a significant difference between the percentage of participants not currently employed was seen among Comparisons (19.4%), background Ranch Hands (24.3%), low Ranch Hands (26.2%), and high Ranch Hands (16.5%).

Current parental status (having a child less than 18 years old: yes, no) was shown to have a significant relationship to group in Model 1 ($p=0.048$) and dioxin in Model 2 ($p=0.004$), Model 3 ($p=0.001$), Model 4 ($p<0.001$), and Models 5 and 6 ($p<0.001$). In Models 2, 4, 5, and 6, participants with children under the age of 18 had higher mean dioxin levels. In Model 1, a significant difference between the percentage of participants with no children under the age of 18 was seen between Ranch Hands (75.9%) and Comparisons (72.1%). In Model 3, a significant difference between the percentage of participants with no children under the age of 18 also was seen among Comparisons (72.6%), background Ranch Hands (79.4%), low Ranch Hands (79.6%), and high Ranch Hands (67.3%).

The analysis of participants who reported having worked with vibrating power equipment or tools for 30 days or more revealed a significant relationship with group in Model 1 ($p=0.037$) and dioxin in Model 3 ($p=0.002$), Model 4 ($p=0.014$), and Models 5 and 6 ($p=0.032$). A significant difference between the percentage of participants who had not worked with vibrating power equipment was seen between Ranch Hands (75.6%) and Comparisons (79.4%) in Model 1. In Models 4, 5, and 6, participants who had worked with vibrating power equipment or tools had higher mean dioxin levels. In Model 3, a significant

difference between the percentage of participants who had not worked with vibrating power equipment was seen among Comparisons (80.0%), background Ranch Hands (80.5%), low Ranch Hands (73.8%), and high Ranch Hands (70.4%).

Testing the association between exposure to heavy metals (worked for 30 days or more with lead, mercury, chromium, nickel, copper, cadmium, manganese, arsenic, selenium, or molybdenum) and dioxin showed significant positive relationships in the analysis of Models 4 ($p=0.011$) and Models 5 and 6 ($p=0.020$). Participants who have been exposed to heavy metals had higher mean current dioxin levels than those participants who were not exposed.

No significant ($p \leq 0.05$) associations were observed between current marital status and the five estimates of dioxin exposure.

SUMMARY

The purpose of this chapter is to determine if the covariates used throughout this report are associated with the five estimates of dioxin exposure and, therefore, could potentially be confounding variables in subsequent statistical analyses in this report. However, the associations between covariates and the estimates of dioxin exposure were not adjusted for known and suspected confounders and, therefore, the results should not be interpreted as indicating causal relationships between dioxin exposure and covariate levels.

The demographic variables of age, race, and occupation were used as matching variables in the original study design. As expected, there were no significant differences between Ranch Hands and Comparisons for these three variables. As exhibited in previous study analyses, dioxin was significantly associated with military occupation. Officers had the lowest levels, followed by enlisted flyers and enlisted groundcrew. Because the Ranch Hand enlisted groundcrew tended to be younger on average than the Ranch Hand officers and enlisted flyers, a strong negative association also was seen between dioxin levels and age. Race was not significantly associated with dioxin.

Ranch Hands tended to serve in combat longer than Comparisons. This relationship is explained by the fact that the Ranch Hands were stationed in combat for their entire time of duty in SEA, whereas the Comparisons conducted missions in combat areas and then returned to a station outside of the combat zone. Also, approximately 25 percent of Comparisons did not serve in combat at all and approximately 80 percent of them served in combat less than 1 year. Positive associations were seen between dioxin and days in combat within the Ranch Hand cohort, indicating that Ranch Hands who had longer times of duty in Vietnam have the higher levels of dioxin. No significant associations were observed between the presence of post-SEA acne and group or dioxin.

Ranch Hands have higher levels of current wine use than Comparisons. Within the Ranch Hand cohort, participants with lower dioxin levels have greater amounts of wine consumption. This association also may be due to occupation because officers are more likely to drink wine than are enlisted personnel ($p<0.001$). No significant associations were seen between total current alcohol use or lifetime alcohol history and group or dioxin. No

significant associations were observed between either current cigarette smoking or lifetime cigarette smoking history and group or dioxin.

The percentage of Comparisons exposed to ionizing radiation was larger than the percentage of Ranch Hands exposed. However, a greater percentage of Ranch Hands were exposed to herbicides and insecticides. Questions were posed to the participants to capture post-SEA exposure to possible carcinogens. However the data appear to indicate that the participants may have included SEA exposures as well. Within the Ranch Hand cohort, higher dioxin levels were seen for those participants exposed to industrial chemicals and degreasing chemicals. No significant associations were observed between group or dioxin and asbestos exposure. Again, the significant associations between dioxin and industrial chemical exposure and between dioxin and degreasing chemical exposure may be related to occupation. A smaller percentage of Ranch Hand officers tended to be exposed to industrial chemicals and degreasing chemicals than Ranch Hand enlisted personnel.

The significant associations between dioxin and health measurements, such as HDL cholesterol and the cholesterol-HDL cholesterol ratio, can be partially explained by confounding with body fat. Higher body fat measurements correspond to higher dioxin levels, lower levels of HDL cholesterol, and higher cholesterol-HDL cholesterol ratio measurements. Also, higher body fat is more likely to occur with sedentary lifestyles.

Of covariates related to sun exposure or reaction to sun exposure, non-Black Ranch Hands with darker hair tended to have higher levels of initial dioxin than those with lighter-colored hair. Higher levels of current dioxin were seen in non-Black Ranch Hands who tanned easier. The relationship between dioxin and hair color also may be related to occupation, in that a greater percentage of Ranch Hand officers had light brown hair than did Ranch Hand enlisted personnel. Conversely, a larger percentage of Ranch Hand enlisted personnel had dark brown hair than did Ranch Hand officers. A larger percentage of Ranch Hands lived in latitudes farther from the equator than did Comparisons. However, within the Ranch Hand cohort, higher levels of initial dioxin were seen for those participants who live in more southerly latitudes. No other significant associations were observed with the other sun-exposure or reaction to sun exposure covariates.

The relationships between dioxin and current total household income, education, current employment status, and having a child less than 18 years old also may directly or indirectly relate to occupation and age. Officers currently make more money than enlisted personnel, and officers have the lowest dioxin levels; consequently, there is a negative association between income and dioxin. A larger percentage of Ranch Hand officers tended to be college graduates than enlisted personnel, and consequently college graduates have lower dioxin levels than high school graduates. More Ranch Hand enlisted groundcrew than Ranch Hand officers or enlisted flyers are currently employed, which may be due to their age, income, and level of education. More Ranch Hand enlisted groundcrew than officers or enlisted flyers have children under the age of 18, and participants with children under the age of 18 have higher dioxin levels.

CONCLUSION

The purpose of this chapter is to determine if the covariates used throughout this report are associated with the five estimates of dioxin exposure and, therefore, could potentially be confounding variables in subsequent statistical analyses in this report. However, the associations between covariates and the estimates of dioxin exposure were not adjusted for known and suspected confounders, and therefore, the results should not be interpreted as indicating causal relationships between dioxin exposure and covariate levels.

In general, the Ranch Hand and Comparison groups are similar for a number of the covariates. However, notable exceptions include duration of combat service, reported herbicide exposure, and HDL cholesterol. Ranch Hands tended to serve in combat longer than Comparisons, because Ranch Hands were stationed in combat areas for their entire time of duty in SEA, whereas Comparisons conducted missions in combat zones and then returned to a station outside of combat areas. A greater percentage of Ranch Hands than Comparisons reported herbicide exposure. A possible explanation for this association between group and herbicide exposure may have been the tendency of Ranch Hands to report their exposure to dioxin during their time of duty in SEA. The questionnaire had been structured to capture post-SEA exposure only. The relationship between group and HDL cholesterol is not quite as clear. The group means are not significantly different, but the percentage of Ranch Hand participants considered abnormal (less than 35 mg/dl) is significantly greater than the percentage of Comparisons considered abnormal. The analysis of HDL cholesterol as an endpoint is discussed in Chapter 13, Gastrointestinal Assessment.

Most of the significant associations between dioxin and the covariates in the Ranch Hand group can be attributed to, or partially explained by, the effects of occupation, age, or body fat. Of the three occupational cohorts, enlisted groundcrew have the highest levels of current and initial dioxin. Adjusted analyses in the clinical chapters (Chapters 9 through 20) fully account for group, age, body fat, and other potential confounders to further investigate significant associations between covariates and dioxin. The reader is referred to these chapters for a more complete assessment of the effect of dioxin on the relevant medical endpoints.

CHAPTER 9

GENERAL HEALTH ASSESSMENT

INTRODUCTION

Background

Though the potentially lethal consequences of acute phenoxy herbicide intoxication have been well documented (1-3), the long-term effects of herbicide exposure on human health remain undefined. Epidemiologic studies published in the scientific literature have focused on specific clinical endpoints, particularly malignancy, and have been based on cohorts of Vietnam veterans (4-9) and on civilian populations exposed to trichlorophenols by occupation (10-18) or as a consequence of industrial accidents (19-23). These studies and others have been addressed in several recent review articles (24-31).

In laboratory animals, dioxin toxicity is species- and strain-specific and appears to correlate with the presence of a stereospecific protein receptor, aryl hydrocarbon (Ah) receptor found in the cytosol of selected organs and capable of binding aromatic hydrocarbons (32-36). Research into the molecular and cellular mechanisms of dioxin toxicity has been summarized in the recent comprehensive literature reviews of the Veterans Health Services and Research Administration (37-39). Although Ah receptors have been isolated in the tissue of several human organs (40-45), the relevance of these observations to dioxin toxicity remains to be proven (46). Epidemiologic studies have focused on biologic endpoints defined in animal models including immunotoxicity, carcinogenicity, genetic and reproductive outcomes, hepatotoxicity, and neurotoxicity. In the chapters that follow, each of these endpoints will be considered in detail.

Common to all of the early epidemiologic studies of the effects of herbicides on human health was the inability to estimate dioxin exposure accurately. Currently available techniques permit the accurate detection (in parts per quadrillion [ppq]) of dioxin in human adipose tissue and in blood (47-49). In a preliminary study, based on serum levels in 36 subjects, a dioxin half-life of 7.1 years was derived (50). The extent of past exposure now can be derived objectively. More recent studies have established that obese subjects have longer dioxin half-lives than lean subjects (51,52), a finding that may prove relevant to the development of clinical endpoints related to obesity.

The importance of the serum dioxin assay to the credibility of this and other epidemiologic studies on the effects of dioxin on human health cannot be overemphasized. The Centers for Disease Control (CDC) study of serum dioxin levels demonstrated that all estimates of exposure employed previously in Vietnam veterans were imprecise, and that there was no significant difference in the current body burden of dioxin between most Vietnam and non-Vietnam veterans of the same era (53,54). Published reports leave no doubt that, of the approximately 3 million members of the Armed Forces who served in Southeast Asia (SEA), the 1,300 Air Force Ranch Hand personnel were among those most highly exposed to dioxin, and that, within this group, the enlisted groundcrew responsible for

handling the herbicide and for maintaining the herbicide spray equipment were at greatest risk (4,55).

Apart from the current study, a few other published reports on exposed populations include information on serum dioxin levels. These include occupational exposure occurring in the manufacture of dioxin-contaminated chemicals in the United States (10,56-58) and Germany (21,59) and civilians exposed as a consequence of an industrial explosion in Seveso, Italy (20,60). As the only other longitudinal epidemiologic studies that correlate clinical endpoints with the proven body burden of dioxin, these will receive special attention in the chapters that follow.

Finally, as will be discussed below, the Air Force Health Study (AFHS) has incorporated five variables into the current analyses including self-perception of health, appearance of illness or distress during the examination, relative age, percent body fat, and erythrocyte sedimentation rate. In the most recent Serum Dioxin Analysis Report (61), the first to correlate these indices with serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) levels, positive associations were noted with the perception of ill health and the percent body fat. Furthermore, a slight but statistically significant increase in the sedimentation rate was noted as initial dioxin levels increased. These results have raised the possibility of an occult dioxin-induced disease process and point to the need for surveillance in this and subsequent examination cycles.

Summary of Previous Analyses of the Air Force Health Study

1982 Baseline Study Summary Results

Five general health variables were included in the 1982 Baseline examination: self-perception of health, appearance of illness or distress, relative age, percent body fat, and sedimentation rate. In the analysis of the Baseline examination data, a statistically significant difference in self-perception of health was found between the Ranch Hand and Comparison groups, with a greater percentage of Ranch Hands reporting their health as fair or poor than Comparisons (20.6% vs. 14.2%). This was true in both the younger and older age groups (Est. RR=1.82, p=0.017 for individuals 40 or younger and Est. RR=1.35, p=0.025 for individuals older than 40). Since only 9 of 1,811 individuals were reported by the examining physician as appearing ill or distressed, this designation was apparently reserved for only very ill or distressed individuals. Nevertheless, eight of the nine individuals were Ranch Hands, the difference being of marginal significance (p=0.056). Conversely, more Ranch Hands than Comparisons were reported by the examiners as appearing younger than their actual ages (4.9% vs. 2.5%, p=0.029). No overall differences in percent body fat or sedimentation rate were found, although a significant interaction between group and age for sedimentation rate was noted; younger Ranch Hands had fewer sedimentation rate abnormalities than did Comparisons, whereas no difference was found in participants older than 40.

1985 Followup Study Summary Results

General physical health was evaluated by the same five measures used in the Baseline examination (self-perception of health, appearance of illness or distress, relative age, percent body fat, and sedimentation rate). The Ranch Hands again rated their health as fair or poor more often than the Comparisons (9.1% vs. 7.3% respectively), although this difference was not statistically significant. However, further analysis revealed a significant group-by-occupation interaction. Differences were largely confined to the enlisted groundcrew category where the adjusted relative risk was 1.90 ($p=0.003$).

Ten individuals were reported as appearing acutely ill or distressed at the 1985 followup examination. In contrast to the Baseline examination, four were Ranch Hands and six were Comparisons; thus, no group difference was suggested. Relative age, as determined by the examining physician, was not significantly different in the two groups.

The (geometric) mean sedimentation rates did not differ significantly, either unadjusted or after adjustment for age, race, occupation, personality score, and an age-by-personality score interaction. However, in the discrete analysis, 5.8 percent of the Ranch Hands had sedimentation rate abnormalities (>20 mm/hr), contrasted to 3.6 percent in the Comparison group. This difference was significant both unadjusted ($p=0.013$) and adjusted for age and personality score ($p=0.011$).

The mean percent body fat of the Ranch Hands was significantly lower than the Comparisons (21.10 vs. 21.54, $p=0.037$), and the difference was of nearly the same magnitude after adjustment for age, race, and occupation.

Longitudinal differences between the 1982 Baseline and the 1985 followup examination were assessed by analyses of two discrete variables: self-perception of health and sedimentation rate. Analysis of self-perception of health showed no significant group differences in the change over time, with the Ranch Hand and Comparison groups reporting symmetrical improvements in their perceptions over the 3-year period. The sedimentation rate analysis, however, revealed a highly significant group difference ($p=0.002$), due to a reversal of findings between examinations (i.e., a significant detriment in the [younger] Comparisons at the Baseline examination versus a significant detriment in the Ranch Hands at the followup examination).

1987 Followup Study Summary Results

The 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 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 were there 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 sedimentation rate in the two groups, but Ranch Hands had a significantly higher percentage of individuals with an abnormal sedimentation rate (>20 mm/hr) than Comparisons.

However, only three participants (two Ranch Hands and one Comparison) were found to have rates in excess of 100 mm/hr; one of these (a Comparison) proved to have lung cancer and died in early 1989. No diagnosis was established for either of the two Ranch Hands during the course of the 1987 examination. 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.

Serum Dioxin Analysis of 1987 Followup Study Summary Results

In general, percent body fat and sedimentation rate exhibited significant positive associations with initial dioxin. The other variables exhibited positive but nonsignificant associations with initial dioxin. The unadjusted and adjusted analyses of relative age exhibited significant interactions between current dioxin and time since tour of duty. For Ranch Hands with 18.6 years or less since the end of duty in SEA, the associations between relative age and current dioxin were positive and at least marginally significant for each analysis type and assumption. For the other variables, the current dioxin-by-time analyses generally displayed nonsignificant but positive associations with current dioxin.

In general, the unadjusted and adjusted analyses for the four current dioxin categories overall exhibited significant contrasts for percent body fat and sedimentation rate, and the high versus background contrast and the low versus background contrast were significant with the Ranch Hands exceeding Comparisons. The percent body fat results for the four current dioxin categories displayed an increasing association with dioxin within the Ranch Hands (i.e., unknown, low, and high categories); however, the background category for Comparisons exceeded the unknown category for Ranch Hands.

The longitudinal analyses of self-perception of health demonstrated significant positive associations with initial dioxin and current dioxin. However, the percentage of participants who reported fair or poor health decreased by more than 50 percent from 1982 to 1987. In the longitudinal analyses of sedimentation rate, the percentages of abnormalities in 1987 differed significantly among the current dioxin categories.

In summary, with the exception of the sedimentation rate, the data analyzed in the General Health Assessment did not reveal any health detriment consequent to herbicide exposure or to the current body burden of dioxin.

Parameters for the General Health Assessment

Dependent Variables

The General Health Assessment was based on data from the 1992 questionnaire, physical examination, and laboratory examination data.

Questionnaire Data

During the health interview administered through the 1992 National Opinion Research Center (NORC) Questionnaire, each study participant was asked, "Compared to other people your age, would you say your health is excellent, good, fair, or poor?" This self-reported perception was analyzed as a measure of the general health status of each participant, although it was recognized that the perception was susceptible to varying degrees of conscious and subconscious bias (most participants were aware of their serum dioxin levels). This variable was dichotomized as "excellent or good" and "fair or poor" for statistical analyses. No participants were excluded for medical reasons from the analysis of this variable.

Physical Examination Data

Three variables derived from the 1992 Scripps Clinic and Research Foundation (SCRF) physical examination were analyzed in the assessment of general health. For the first variable, the physician at the examination recorded the appearance of illness or distress (yes, no) of the study participant. For the second variable, the physician noted the appearance of the subject as younger than, older than, or the same as his stated age. This variable was dichotomized as "older than" and "same as or younger than" for statistical analyses. To the degree that the examining physicians are kept blind to the participant's group membership, these assessments were less subject to bias than the self-perception of health.

The third variable, body fat, was a measure of the relative body mass of an individual and was calculated from height (in meters) and weight (in kilograms) recorded at the physical examination. Non-ambulatory participants were weighed on a Scale-Tronix® 6006, which allowed a participant to be weighed in a wheelchair, if necessary. Body fat was calculated from a metric body mass index (62); the formula is

$$\textit{Body Fat (in percent)} = \frac{\textit{Weight (kg)}}{[\textit{Height (m)}]^2} \bullet 1.264 - 13.305.$$

This variable was analyzed in both the discrete and continuous forms. A natural logarithmic transformation was used to enhance normality. For purposes of discrete analyses, body fat was dichotomized as "lean or normal" ($\leq$25 percent) and "obese" (>25 percent). Lean participants (less than 10 percent body fat) were categorized with normal participants because few of the people in this study fit this definition (2 Ranch Hands and 4 Comparisons). This variable did not reflect changes in weight since time of duty in SEA.

To examine the association between body fat and exposure independent of the effects of diet, body fat also was analyzed adjusting for the covariate caloric intake. Caloric intake was not removed from the analysis during stepwise model reduction procedures; consequently, these results differed from the analysis results that do not consider caloric intake a covariate. This analysis is a further study motivated by the results observed from

the serum dioxin analysis of the 1987 followup examination data. No participants were excluded for medical reasons from the analyses of these three variables.

Laboratory Examination Data

The erythrocyte sedimentation rate (mm/hr), measured at the laboratory examination, was analyzed. Although nonspecific, a high sedimentation rate is a generally accepted indicator of an ongoing disease process. A natural logarithmic transformation was used to enhance normality. This variable was analyzed in both the discrete and continuous forms. Additionally, 0.1 was added to each measurement before the transformation due to the presence of zeros. No participants were excluded for medical reasons from the analysis of this variable.

Covariates

The effects of the covariates age, race (Black, non-Black), military occupation (officer, enlisted flyer, enlisted groundcrew), personality type (Type A, Type B), and caloric intake were examined in the assessment of general health in adjusted statistical analyses. Age, race, and occupation were used for analyses with all dependent variables. Age was used in its continuous form for all adjusted analyses. Personality type was used in the analysis of self-perception of health and sedimentation rate only. Personality type was determined from the Jenkins Activity Survey administered during the 1992 followup examination. This variable was derived from a discriminant-function equation based on questions that best discriminate men judged to be Type A from those judged to be Type B (63). Positive scores reflected the Type A direction; negative scores reflected the Type B direction. Personality type was dichotomized as Type A or Type B for all analyses of self-perception of health and sedimentation rate.

As mentioned above, body fat also was analyzed adjusting for the covariate caloric intake to examine the association between body fat and exposure independent of the effects of diet. The caloric intake variable was based on responses to the Diet Assessment Questionnaire administered along with the 1992 NORC Questionnaire. A measurement combining components of the Diet Assessment Questionnaire, based on a review of existing literature, was used to construct a caloric intake index (64).

Statistical Methods

Chapter 7, Statistical Methods, describes the basic statistical methods used throughout this report. Table 9-1 summarizes the statistical analyses performed for the General Health Assessment. The first part of this table describes the dependent variables and identifies the candidate covariates and the statistical methods. The second part of the table further describes the candidate covariates. The abbreviations used in the body of the table are defined at the end of the table. Table 9-2 provides participants with missing dependent variable and covariate data.

Cutpoints for sedimentation rate are age-dependent. Consequently, normal and abnormal levels for sedimentation rate are constructed according to a participant's laboratory

Table 9-1.
Statistical Analyses for the General Health Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analysis
Self-Perception of Health	Q-SR	D	Fair or Poor Excellent or Good	AGE,RACE, OCC,PERS	U:LR,CS A:LR L:LR
Appearance of Illness or Distress as Assessed by Physician	PE	D	Yes No	AGE,RACE, OCC	U:LR,CS A:LR L:LR
Relative Age Appearance as Assessed by Physician	PE	D	Older Same or Younger	AGE,RACE, OCC	U:LR,CS A:LR L:LR
Body Fat (percent)	PE	D/C	Obese: >25% Lean or Normal: ≤25%	AGE,RACE, OCC,CAL	U:LR,CS, GLM,TT A:LR,GLM L:LR,GLM
Sedimentation Rate (mm/hr)	LAB	D/C	Abnormal: >15 (40-49) >20 (≥50) Normal: ≤15 (40-49) ≤20 (≥50)	AGE,RACE, OCC,PERS	U:LR,CS, GLM,TT A:LR,GLM L:LR,GLM

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥ 1942 Born < 1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Personality Type (PERS)	PE	D	A Direction B Direction
Caloric Intake (CALINT) (kcal/day)	Q-SR	D/C	≤2,000 >2,000

Table 9-1. (Continued)
Statistical Analyses for the General Health Assessment

Abbreviations

Data Source:	LAB	= 1992 laboratory results
	MIL	= Air Force military records
	PE	= 1992 physical examination
	Q-SR	= 1992 health questionnaire (self-reported)
Data Form:	D	= Discrete analysis only
	D/C	= Discrete and continuous analysis for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates
Statistical Analyses:	U	= Unadjusted analyses
	A	= Adjusted analyses
	L	= Longitudinal analyses
Statistical Methods:	CS	= Chi-square contingency table analysis (continuity-adjusted for 2 x 2 tables)
	GLM	= General linear models analysis
	LR	= Logistic regression analysis
	TT	= Two-sample t-test

Table 9-2.
Number of Participants with Missing Data for the General Health Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Self-Perception of Health	DEP	0	2	0	0	0	2
Sedimentation Rate	DEP	0	1	0	0	0	0
Caloric Intake	COV	2	2	2	2	2	2
Personality Type	COV	1	1	1	1	1	1

Abbreviations: DEP = Dependent variable.
COV = Covariate.

Note: 952 Ranch Hands and 1,281 Comparisons;
520 Ranch Hands for initial dioxin; 894 Ranch Hands for current dioxin;
894 Ranch Hands and 1,063 Comparisons for categorized dioxin.

One Ranch Hand missing total lipids for current dioxin.

value and age at the physical examination. The age-specific cutpoints also are listed in Table 9-1, and the reference ages for these cutpoints are given in parentheses following the cutpoints.

Analyses of data collected at the 1987 followup study indicated that dioxin was associated with military occupation. In general, enlisted personnel had higher levels of dioxin than officers, with enlisted groundcrew having higher levels than enlisted flyers. Consequently, adjustment for military occupation in statistical models using dioxin as a measure of exposure may improperly mask an actual dioxin effect. However, occupation also can be a surrogate for socioeconomic effects. Failure to adjust for occupation could overlook important risk factors related to lifestyle. If occupation was found to be significantly associated with a dependent variable in the 1992 followup analyses and was retained in the final statistical models using dioxin as a measure of exposure, the dioxin effect was evaluated in the context of two models. Analyses were performed with and without occupation in the final models to investigate whether conclusions regarding the association between the health endpoint and dioxin differed.

The results of the analyses without occupation are presented in Appendix E-3 and are only discussed in the text if the level of significance differs from the original final adjusted model (significant versus nonsignificant).

Longitudinal Analysis

Longitudinal analyses on all of the variables described above (self-perception of health, appearance of illness or distress by the physician, relative age, body fat, and sedimentation rate) were conducted to evaluate the changes between the 1982 Baseline examination and the 1992 followup examination. Longitudinal analyses were conducted on body fat in the continuous and discrete forms but without adjustment for caloric intake. The absence of information on caloric intake from 1982 precludes this adjustment.

The sedimentation rate abnormal cutpoints differ by examination date and age. For the 1982 Baseline examination, the cutpoint was 12 mm/hr for all participants (that is, sedimentation rates greater than 12 mm/hr were considered abnormal). For the 1985, 1987, and 1992 followup examinations, the cutpoint was 15 mm/hr for participants younger than 50 and 20 mm/hr for participants at least 50 years old at the time of the examination. A participant is considered to be normal or abnormal based on his age and the cutpoint at the given examination for discrete analyses. Methods of compensation for the change in cutpoints over time for the continuous analyses include the use of age and the measurement in 1982 as covariates (see Chapter 7, Statistical Methods, for a further discussion of methods used in longitudinal analyses).

RESULTS

Dependent Variable-Covariate Associations

The covariate tests of association for self-perception of health showed that occupation and age were both significant covariates (Appendix Table E-1-1: $p=0.001$ and $p=0.082$

respectively). The percentages of officers, enlisted flyers, and enlisted groundcrew who perceived their health as fair or poor were 5.9, 11.2, and 10.2 respectively. Of the participants born before 1942, 9.6 percent reported their health as fair or poor in comparison to 7.4 percent of the participants born in or after 1942.

For appearance of illness or distress, tests of covariate association found age to be a significant covariate (Appendix Table E-1-1: $p=0.041$). For participants born before 1942, 2.4 percent appeared ill or distressed at the physical examination, whereas for participants born in or after 1942, 1.2 percent appeared ill or distressed.

Tests of covariate association found a high association between relative age appearance and both occupation ($p=0.001$) and race ($p=0.045$). The analysis of occupation revealed that 3.6 percent of the officers appeared older than their age, while 8.0 percent of the enlisted flyers and 7.2 percent of the enlisted groundcrew looked older than their actual age. The percentages of abnormalities for the Black and non-Black categories were 1.5 percent and 6.2 percent respectively.

The results of the tests of covariate association for body fat (discrete) revealed that occupation and caloric intake were statistically significant ($p=0.005$ and $p=0.048$ respectively). For the occupation analysis, the percentages of participants with body fat above 25 percent were 22.7 percent for officers, 23.3 percent for enlisted flyers, and 28.8 percent for enlisted groundcrew. The caloric intake analysis showed that 27.1 percent of the participants who consumed no more than 2,000 calories per day were obese, while 23.3 percent of the participants who consumed more than 2,000 calories per day were obese.

For body fat (continuous), tests of covariate association were significant for occupation ($p=0.039$) and caloric intake ($p=0.001$). Mean body fat was 21.64 percent in the officer category and 21.65 percent in the enlisted flyer category. For enlisted groundcrew, average body fat was 22.20 percent. For the caloric intake analysis, the correlation coefficient between body fat and caloric intake was -0.070.

The tests of covariate association for sedimentation rate (discrete) showed that both occupation and personality type were significant covariates ($p=0.001$ and $p=0.005$ respectively). The percentages of abnormalities for officers, enlisted flyers, and enlisted groundcrew were 14.0, 22.3, and 18.9 respectively. For those participants with a Type A personality, 14.9 percent had an abnormal sedimentation rate as compared to 19.5 percent of participants with a Type B personality.

In the covariate analysis of sedimentation rate (continuous), occupation, personality type, and age were statistically significant ($p=0.002$, $p<0.001$, and $p<0.001$ respectively). Average sedimentation rate was 7.64 mm/hr for officers, 9.27 mm/hr for enlisted flyers, and 8.15 mm/hr for enlisted groundcrew. In the analysis of personality type, the mean sedimentation rate was 7.46 mm/hr for Type A participants and 8.63 mm/hr for Type B participants. The test of covariate association for sedimentation rate and age revealed a statistically significant positive correlation between the two variables ($r=0.214$).

Exposure Analysis

The following section presents results of the statistical analyses of the dependent variables shown in Table 9-1. Dependent variables are grouped into three sections: those derived from the questionnaire administered in the 1992 followup examination, data obtained during the 1992 physical examination, and data derived from the laboratory portion of the 1992 followup examination.

Unadjusted and adjusted analyses of six models are presented for each variable. Model 1 examines the relationship between the dependent variable and group (Ranch Hand or Comparison). Model 2 explores the relationship between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. If a participant did not have a 1987 dioxin level, a 1992 level was used. A statistical adjustment for the percent of body fat at the participant's time of duty in SEA and the change in the percent of body fat from the time of duty in SEA to the date of the blood draw for dioxin is included in this model to account for body-fat-related differences in elimination rate (51). Model 3 dichotomies the Ranch Hands in Model 2 based on their initial dioxin measures; these two categories of Ranch Hands are referred to as the "low Ranch Hand" category and the "high Ranch Hand" category. These participants are added to Ranch Hands and Comparisons with current serum dioxin levels (1987, if available; 1992, if the 1987 level was not available) at or below 10 ppt to create a total of four categories. Ranch Hands with current serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. The relationship between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the "Comparison" category is examined. A fourth contrast, exploring the relationship of the dependent variable in the low Ranch Hand category and the high Ranch Hand category combined, also is conducted. This combination is referred to in the text and tables as the "low plus high Ranch Hand" category. As in Model 2, a statistical adjustment is made for the percent of body fat at the participant's time of duty in SEA and the change in the percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

Models 4, 5, and 6 examine the relationship between the dependent variable and 1987 dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, a 1992 measurement was utilized in determining the current dioxin level. The measure of dioxin in Model 4 is lipid-adjusted, whereas whole-weight current dioxin is used in Models 5 and 6. Model 6 differs from Model 5 in that a statistical adjustment for total lipids is included in Model 6. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7 respectively.

Results of investigations for group-by-covariate and dioxin-by-covariate interactions are referenced in the text, and tabular results are presented in Appendix E-2. As described previously, additional analyses were performed when occupation was retained in the final models for Models 2 through 6. Results excluding occupation from these models are tabled in Appendix E-3. Results from analyses excluding occupation are discussed in the text only if a meaningful change in the results occurred (that is, changes between significant results, marginally significant results, and nonsignificant results).

Questionnaire Variable

Self-Perception of Health

In the Model 1 unadjusted analysis of self-perception of health, a significant group difference existed between Ranch Hands and Comparisons (Table 9-3(a): p=0.017, Est. RR=1.45), with 10.4 percent of Ranch Hands and 7.4 percent of Comparisons reporting their health as fair or poor. Stratification by occupation revealed a significant estimated relative risk for enlisted groundcrew (p=0.031, Est. RR=1.60) but nonsignificant relative risks for officers and enlisted flyers. For the enlisted groundcrew stratum, 12.8 percent of the Ranch Hands perceived their health as fair or poor compared to 8.4 percent of the Comparisons. The Model 1 results of the adjusted analysis closely parallel those of the unadjusted analysis. The relative risk for Ranch Hands versus Comparisons was significant (Table 9-3(b): p=0.016, Adj. RR=1.44) and, of the three occupational strata, only enlisted groundcrew exhibited a significant adjusted relative risk (p=0.023, Adj. RR=1.62). Significant covariates included occupation and age.

The unadjusted analysis of self-perception of health for Model 2 uncovered a significant association with initial dioxin (Table 9-3(c): p=0.049, Est. RR=1.21). For the low, medium, and high initial dioxin categories, the percentages of Ranch Hands who reported their health as poor or fair were 10.3, 13.9, and 13.9 respectively. Although the relative risk was nonsignificant in the adjusted analysis (adjusted for age and occupation) (Table 9-3(d): p=0.120), removal of occupation from the final model caused the initial dioxin effect to become significant (Appendix Table E-3-1: p=0.010, Adj. RR=1.30).

In the unadjusted analysis for Model 3, the percentage of participants who perceived their health as fair or poor was significantly higher in both the high Ranch Hand dioxin category (15.0%) and low plus high Ranch Hand dioxin category (12.7%) than in the Comparison dioxin category (7.0%) (Table 9-3(e): high Ranch Hands vs. Comparisons: Est. RR=2.20, p<0.001, low plus high Ranch Hands vs. Comparisons: Est. RR=1.82, p=0.001). The adjusted analysis also uncovered significant differences between high Ranch Hands and Comparisons (Table 9-3(f): Adj. RR=1.84, p=0.005) as well as between low plus high Ranch Hands and Comparisons (Adj. RR=1.65, p=0.006). Age and occupation were significant covariates retained in the categorized dioxin adjusted analyses. In addition, the contrast involving low Ranch Hands and Comparisons became marginally significant after removing occupation from the final model (Appendix Table E-3-1: p=0.090, Adj. RR=1.50).

Each of the unadjusted analyses for Models 4, 5, and 6 revealed a significant relationship between self-perception of health and current dioxin (Table 9-3(g): p=0.002, p<0.001, and p=0.018 respectively). The current dioxin-by-age interaction was significant in all three adjusted analyses for Models 4, 5, and 6 (Table 9-3(h): p=0.039, p=0.021, and p=0.016 respectively), and occupation was also included in the final models. Appendix Table E-2-1 displays results stratified by age. After removing this interaction from the final models, current dioxin was marginally significant in Model 4 (Adj. RR=1.17, p=0.065) and significant in Model 5 (Adj. RR=1.18, p=0.024), but nonsignificant in Model 6 (p=0.291). In addition, once occupation was removed from each of the final models, the interaction of

Table 9-3.
Analysis of Self-Perception of Health

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Fair or Poor**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***10.4***	***1.45 (1.08,1.94)***	***0.017***
	Comparison	***1,279***	***7.4***		
Officer	Ranch Hand	367	6.0	1.04 (0.59,1.84)	0.999
	Comparison	502	5.8		
Enlisted Flyer	Ranch Hand	162	14.2	1.70 (0.88,3.27)	0.151
	Comparison	203	8.9		
Enlisted Groundcrew	Ranch Hand	423	12.8	1.60 (1.06,2.42)	0.031
	Comparison	574	8.4		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.44 (1.07,1.94)***	***0.016***	OCC ($p<0.001$) AGE ($p<0.001$)
Officer	1.03 (0.38,1.82)	0.926	
Enlisted Flyer	1.68 (0.87,3.25)	0.121	
Enlisted Groundcrew	1.62 (1.07,2.45)	0.023	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-3. (Continued)
Analysis of Self-Perception of Health

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Fair or Poor	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	10.3	1.21 (1.00,1.46)	0.049
Medium	173	13.9		
High	173	13.9		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	1.19 (0.96,1.47)	0.120	OCC (p=0.099) AGE (p=0.012)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-3. (Continued)
Analysis of Self-Perception of Health

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Fair or Poor	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,061	7.0		
Background RH	374	6.7	1.06 (0.66,1.70)	0.815
Low RH	260	10.4	1.47 (0.92,2.34)	0.107
High RH	260	15.0	2.20 (1.45,3.34)	<0.001
Low plus High RH	520	12.7	1.82 (1.28,2.60)	0.001

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,061			AGE (p<0.001) OCC (p<0.001)
Background RH	374	1.29 (0.79,2.11)	0.302	
Low RH	260	1.44 (0.90,2.31)	0.131	
High RH	260	1.84 (1.20,2.84)	0.005	
Low plus High RH	520	1.65 (1.15,2.36)	0.006	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-3. (Continued)
Analysis of Self-Perception of Health

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Fair or Poor/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	6.8 (295)	9.3 (300)	14.4 (299)	1.26 (1.09,1.45)	0.002
5	6.3 (300)	10.1 (297)	14.1 (297)	1.26 (1.11,1.43)	<0.001
6[c]	6.4 (299)	10.1 (297)	14.1 (297)	1.18 (1.03,1.36)	0.018

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	894	1.17 (0.99,1.38)**	0.065**	CURR*AGE (p=0.039) OCC (p<0.001)
5	894	1.18 (1.02,1.37)**	0.024**	CURR*AGE (p=0.021) OCC (p<0.001)
6[d]	893	1.09 (0.93,1.27)**	0.291**	CURR*AGE (p=0.016) OCC (p<0.001)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-1 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.
CURR = Log_2 (current dioxin + 1).

current dioxin and age became nonsignificant and was therefore removed from the supplemental model. In doing so, current dioxin was significant (Appendix Table E-3-1: $p \leq 0.003$ for Models 4 through 6).

Physical Examination Variables

Appearance of Illness or Distress

As shown in Table 9-4(a), the Model 1 unadjusted analysis of the physician's assessment as to whether the study participant displayed illness or distress at the physical examination uncovered no significant differences between Ranch Hands and Comparisons ($p > 0.25$ for all analyses). In the adjusted analysis, a marginally significant overall difference was detected between the two groups (Table 9-4(b): Adj. RR=1.44, p=0.093); however, this difference was not significant when examined within each of the three occupational strata. Interactions between age and race and between occupation and race were significant.

For Models 2 and 3, the results from the analysis of appearance of illness or distress are shown in Table 9-4(c-f). Neither the unadjusted or adjusted analyses detected any significant associations between initial or categorized dioxin and appearance of illness or distress ($p > 0.39$ for all analyses). The interaction of age and race was significant in the Model 2 adjusted analysis. In the Model 3 adjusted analysis, age was significant.

In each of the three unadjusted analyses for Models 4, 5, and 6, current dioxin was not significantly associated with appearance of illness or distress (Table 9-4(g): $p > 0.26$ for all analyses). The adjusted analyses uncovered a significant interaction effect between current dioxin and age for Models 4, 5, and 6 (Table 9-4(h): p=0.039, p=0.027, and p=0.028 respectively). The results stratified by each age category are shown in Appendix Table E-2-2. Removal of the interaction from the final models did not lead to a significant current dioxin effect ($p > 0.48$ for all models).

Relative Age Appearance

Table 9-5(a,b) displays the results from the analysis of relative age appearance for Model 1. No statistically significant group differences were detected in either the unadjusted or adjusted analyses ($p > 0.26$ for all analyses). Occupation and race were significant in the adjusted analysis.

The unadjusted analyses for Model 2 revealed a marginally significant association between initial dioxin and relative age appearance (Table 9-5(c): Est. RR=1.29, p=0.070). After adjusting for occupation, however, no statistically significant results were evident (Table 9-5(d): p=0.209). For Model 3, the relationship between categorized dioxin and relative age appearance was nonsignificant for both the unadjusted and adjusted analyses (Table 9-5(e,f): $p > 0.17$ for all contrasts). Significant covariates uncovered in the Model 3 adjusted analysis included race and occupation.

Table 9-4.
Analysis of Appearance of Illness or Distress

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Yes**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***2.3***	***1.49 (0.81,2.75)***	***0.258***
	Comparison	***1,281***	***1.6***		
Officer	Ranch Hand	367	2.5	2.08 (0.73,5.89)	0.254
	Comparison	502	1.2		
Enlisted Flyer	Ranch Hand	162	3.1	3.20 (0.61,16.72)	0.285
	Comparison	203	1.0		
Enlisted Groundcrew	Ranch Hand	423	1.9	0.91 (0.37,2.34)	0.999
	Comparison	576	2.1		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.44 (0.77,2.68)***	***0.093***	AGE*RACE ($p<0.001$) OCC*RACE ($p=0.006$)
Officer	1.85 (0.64,5.37)	0.258	
Enlisted Flyer	3.10 (0.60,16.07)	0.178	
Enlisted Groundcrew	0.91 (0.36,2.28)	0.841	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-4. (Continued)
Analysis of Appearance of Illness or Distress

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	1.7	0.90 (0.57,1.43)	0.648
Medium	173	2.3		
High	173	1.7		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	0.93 (0.56,1.54)	0.762	AGE*RACE (p=0.010)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-4. (Continued)
Analysis of Appearance of Illness or Distress

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	1.5		
Background RH	374	2.1	1.46 (0.61,3.47)	0.394
Low RH	260	2.3	1.41 (0.54,3.66)	0.482
High RH	260	1.5	0.95 (0.31,2.92)	0.924
Low plus High RH	520	1.9	1.18 (0.53,2.66)	0.685

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,063			AGE (p=0.021)
Background RH	374	1.38 (0.58,3.28)	0.473	
Low RH	260	1.32 (0.51,3.46)	0.570	
High RH	260	1.11 (0.36,3.44)	0.854	
Low plus High RH	520	1.23 (0.55,2.77)	0.618	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-4. (Continued)
Analysis of Appearance of Illness or Distress

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Yes/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.4 (295)	1.3 (300)	2.3 (299)	0.89 (0.63,1.24)	0.469
5	2.3 (300)	1.7 (297)	2.0 (297)	0.88 (0.67,1.16)	0.372
6[c]	2.3 (299)	1.7 (297)	2.0 (297)	0.89 (0.63,1.24)	0.268

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	894	0.95 (0.66,1.36)**	0.779**	CURR*AGE (p=0.039)
5	894	0.92 (0.69,1.24)**	0.596**	CURR*AGE (p=0.027)
6[d]	893	0.89 (0.65,1.22)**	0.484**	CURR*AGE (p=0.028)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-2 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 9-5.
Analysis of Relative Age Appearance

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Older**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***5.5***	***0.87 (0.61,1.24)***	***0.493***
	Comparison	***1,281***	***6.3***		
Officer	Ranch Hand	367	3.0	0.75 (0.35,1.57)	0.556
	Comparison	502	4.0		
Enlisted Flyer	Ranch Hand	162	9.3	1.38 (0.65,2.94)	0.526
	Comparison	203	6.9		
Enlisted Groundcrew	Ranch Hand	423	6.2	0.76 (0.46,1.24)	0.324
	Comparison	576	8.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.86 (0.60,1.23)***	***0.416***	OCC ($p<0.001$) RACE ($p=0.002$)
Officer	0.75 (0.35,1.58)	0.449	
Enlisted Flyer	1.36 (0.64,2.92)	0.425	
Enlisted Groundcrew	0.75 (0.46,1.24)	0.264	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-5. (Continued)
Analysis of Relative Age Appearance

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Older	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	4.6	1.29 (0.98,1.68)	0.070
Medium	173	6.4		
High	173	6.9		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	1.22 (0.90,1.65)	0.209	OCC (p=0.129)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-5. (Continued)
Analysis of Relative Age Appearance

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Older	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	6.2		
Background RH	374	4.3	0.71 (0.40,1.24)	0.229
Low RH	260	4.2	0.64 (0.33,1.23)	0.177
High RH	260	7.7	1.22 (0.22,2.06)	0.460
Low plus High RH	520	6.0	0.92 (0.59,1.43)	0.710

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,063			OCC (p=0.002) RACE (p=0.004)
Background RH	374	0.86 (0.48,1.53)	0.600	
Low RH	260	0.66 (0.34,1.27)	0.212	
High RH	260	0.97 (0.57,1.67)	0.925	
Low plus High RH	520	0.83 (0.53,1.30)	0.408	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-5. (Continued)
Analysis of Relative Age Appearance

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Older(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	5.4 (295)	2.7 (300)	7.7 (299)	1.08 (0.89,1.32)	0.430
5	5.3 (300)	3.0 (297)	7.4 (297)	1.04 (0.88,1.24)	0.618
6[c]	5.0 (299)	3.0 (297)	7.4 (297)	1.05 (0.87,1.27)	0.605

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	894	0.97 (0.78,1.21)**	0.785**	CURR*OCC (p=0.043)
5	894	0.95 (0.79,1.14)	0.591	OCC (p=0.010)
6[d]	893	0.95 (0.77,1.16)	0.599	OCC (p=0.023)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-3 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

As shown in Table 9-5(g), none of the unadjusted analyses for Models 4 through 6 uncovered a significant current dioxin effect in relation to the participant's relative age appearance ($p>0.43$ for all analyses). The adjusted analysis for Model 4 displayed a significant interaction between current dioxin and occupation (Table 9-5(h): $p=0.043$; see Appendix Table E-2-3 for the stratified results of this interaction). Analysis with the interaction removed did not reveal a significant association between current dioxin and relative age appearance ($p=0.785$). The adjusted analyses of Models 5 and 6 led to nonsignificant results ($p>0.59$). In both Models 5 and 6, occupation was significant.

Body Fat (Continuous)

The results of the group analysis of body fat for Model 1 are shown in Table 9-6(a,b). The unadjusted and adjusted analyses did not reveal any significant differences in mean body fat between Ranch Hands and Comparisons ($p>0.13$ for all analyses). The age-by-occupation interaction was significant in the adjusted analysis.

No significant associations were detected between body fat and initial dioxin from the unadjusted or adjusted Model 2 analyses (Table 9-6(c,d): $p>0.12$ for all analyses). It is noted that the high R^2 values in these analyses ($R^2>0.72$) are due to the use of body fat at the time of duty in SEA and change in body fat from the time of duty in SEA to the date of the blood draw for dioxin as covariates in the analysis of this current body fat measure. For the Model 3 unadjusted analysis, a marginally significant relationship between categorized dioxin and body fat was evident from the contrast involving background Ranch Hands (21.76 percent) versus Comparisons (22.01 percent) (Table 9-6(e): difference=-0.25, $p=0.085$). However, no significant differences were revealed between the low Ranch Hands, the high Ranch Hands, or the low plus high Ranch Hands contrasts. After adjusting the Model 3 analysis for significant covariates, the difference between background Ranch Hands and Comparisons became nonsignificant (Table 9-6(f): $p=0.194$), but the difference between high Ranch Hands and Comparisons became marginally significant (difference=-0.30, $p=0.064$). Significant differences between low Ranch Hands and Comparisons and between low plus high Ranch Hands and Comparisons were not evident from this analysis ($p>0.40$). Age was a significant covariate retained in both adjusted analyses.

Highly significant positive associations between current dioxin and body fat were uncovered in the unadjusted analyses of Models 4 through 6 (Table 9-6(g): slope=0.05, $p<0.001$ for Model 4 and slope=0.04, $p<0.001$ for Models 5 and 6). The adjusted analysis of Model 4 detected a significant current dioxin-by-occupation interaction (Table 9-6(h): $p=0.023$). The stratified results of this interaction are shown in Appendix Table E-2-4. After deleting the interaction from the final model, a highly significant relationship still existed between current dioxin and body fat (Adj. slope=0.06, $p=0.001$). Analogous to the Model 5 and Model 6 unadjusted results, both adjusted analyses of Models 5 and 6 revealed highly significant associations between current dioxin and body fat (Adj. slope=0.05, $p<0.001$ for both models). The interaction of age and occupation was retained in both Models 4 and 5, while Model 6 adjusted only for occupation.

Table 9-6.
Analysis of Body Fat (Percent)
(Continuous)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value
All	***Ranch Hand***	***952***	***21.79***	***-0.17 --***	***0.448***
	Comparison	***1,281***	***21.96***		
Officer	Ranch Hand	367	21.78	0.25 --	0.432
	Comparison	502	21.54		
Enlisted Flyer	Ranch Hand	162	21.52	-0.24 --	0.656
	Comparison	203	21.76		
Enlisted Groundcrew	Ranch Hand	423	21.91	-0.50 --	0.159
	Comparison	576	22.41		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value	Covariate Remarks[c]
All	***Ranch Hand***	***952***	***21.75***	***-0.16 --***	***0.449***	AGE*OCC (p=0.012)
	Comparison	***1,281***	***21.91***			
Officer	Ranch Hand	367	21.61	0.23 --	0.511	
	Comparison	502	21.38			
Enlisted Flyer	Ranch Hand	162	21.71	-0.21 --	0.699	
	Comparison	203	21.91			
Enlisted Groundcrew	Ranch Hand	423	21.94	-0.50 --	0.131	
	Comparison	576	22.44			

[a] Transformed from natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-6. (Continued)
Analysis of Body Fat (Percent)
(Continuous)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	174	22.71	23.20	0.726	-0.0028 (0.0040)	0.484
Medium	173	22.55	22.83			
High	173	23.54	22.76			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	174	23.34	0.731	-0.0065 (0.0042)	0.123	AGE (p=0.004)
Medium	173	22.85				
High	173	22.60				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of body fat versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-6. (Continued)
Analysis of Body Fat (Percent)
(Continuous)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value
Comparison	1,063	22.05	22.01		
Background RH	374	20.36	21.76	-0.25 --	0.085
Low RH	260	22.69	22.09	0.08 --	0.616
High RH	260	23.17	21.82	-0.19 --	0.263
Low plus High RH	520	22.93	21.96	-0.05 --	0.691

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ad]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[e]	Covariate Remarks
Comparison	1,063	22.01			AGE ($p<0.001$)
Background RH	374	21.82	-0.19 --	0.194	
Low RH	260	22.14	0.13 --	0.415	
High RH	260	21.70	-0.30 --	0.064	
Low plus High RH	520	21.92	-0.08 --	0.509	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

[e] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-6. (Continued)
Analysis of Body Fat (Percent)
(Continuous)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	20.09 (295)	22.34 (300)	23.12 (299)	0.086	0.0471 (0.0051)	<0.001
5	20.01 (300)	22.34 (297)	23.26 (297)	0.096	0.0427 (0.0044)	<0.001
6[d]	20.11 (299)	22.34 (297)	23.17 (297)	0.092	0.0412 (0.0047)	<0.001

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	19.68** (295)	22.23** (300)	23.72** (299)	0.114	0.0619 (0.0059)**	0.001**	CURR*OCC (p=0.023) AGE*OCC (p=0.028)
5	19.63 (300)	22.25 (297)	23.84 (297)	0.123	0.0541 (0.0049)	<0.001	AGE*OCC (p=0.047)
6[e]	19.68 (299)	22.15 (297)	23.57 (297)	0.111	0.0521 (0.0053)	<0.001	OCC (p<0.001)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of body fat versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-4 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Body Fat (Continuous)—Adjusted for Caloric Intake

A second adjusted analysis of body fat was performed in which individual caloric intake was included as an additional covariate. This allowed the relationships between body fat and group and between body fat and dioxin to be explored independently of the effects of diet. The unadjusted analysis was not affected, thus unadjusted results in Table 9-7 are identical to those in Table 9-6. Adjusted results in Table 9-7 include caloric intake as a covariate.

In the Model 1 adjusted analysis of body fat, with adjustment for caloric intake, no significant differences, either overall or within occupation, were detected between Ranch Hands and Comparisons (Table 9-7(b): $p \geq 0.11$ for all contrasts). An age-by-occupation interaction and caloric intake were significant in the adjusted analysis.

The adjusted analysis of Model 2 did not show a significant relationship between body fat and initial dioxin (Table 9-7(d): $p=0.135$). In the adjusted analysis of body fat for Model 3, a highly significant categorized dioxin-by-caloric intake interaction was displayed (Table 9-7(f): $p=0.001$). Appendix Table E-2-5 shows the results from further exploration of this interaction. Analysis after removal of the interaction from the model showed a nonsignificant difference between background Ranch Hands and Comparisons ($p=0.183$), in contrast to the marginally significant unadjusted analysis. However, a marginally significant association between categorized dioxin and body fat was present for the participants in the high Ranch Hand category versus Comparison dioxin categories (difference=-0.29, $p=0.076$). Age was a significant covariate in both Model 2 and 3 adjusted analyses, and caloric intake was also significant in Model 2.

A significant interaction between current lipid-adjusted dioxin and occupation was uncovered in the adjusted analysis of body fat for Model 4 (Table 9-7(h): $p=0.013$). The results from analyzing the occupational levels separately are seen in Appendix Table E-2-5. Dropping the interaction from the final model resulted in a significant current lipid-adjusted dioxin effect (Adj. slope=0.06, $p=0.001$). The Models 5 and 6 current whole-weight dioxin adjusted analyses yielded very similar results. Highly significant results were evident in the results of both analyses (Table 9-7(h): Adj. slope=0.05, $p<0.001$ for both models). The age-by-occupation, age-by-caloric intake, and caloric intake-by-occupation interactions were significant in all three models.

Body Fat (Discrete)

For Model 1, the unadjusted analysis of the frequencies of obese Ranch Hands versus Comparisons did not reveal a significant difference between the two groups (Table 9-8(a): $p=0.960$). Likewise, no significant associations were found to exist between obesity and group after adjusting for covariate information (Table 9-8(b): $p>0.55$ for all analyses). The interaction of occupation and age was significant in the adjusted analysis.

Initial dioxin and categorized dioxin were nonsignificant when examined in relation to body fat in both unadjusted and adjusted analyses for Models 2 and 3 (Table 9-8(c-f): $p \geq 0.30$ for all analyses). Age was a significant covariate retained in both adjusted analyses.

Table 9-7.
Analysis of Body Fat (Percent) with Adjustment for Caloric Intake (Continuous)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value
All	***Ranch Hand***	***952***	***21.79***	***-0.17 --***	***0.448***
	Comparison	***1,281***	***21.96***		
Officer	Ranch Hand	367	21.78	0.25 --	0.432
	Comparison	502	21.54		
Enlisted Flyer	Ranch Hand	162	21.52	-0.24 --	0.656
	Comparison	203	21.76		
Enlisted Groundcrew	Ranch Hand	423	21.91	-0.50 --	0.159
	Comparison	576	22.41		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value	Covariate Remarks[c]
All	***Ranch Hand***	***950***	***21.72***	***-0.18 --***	***0.400***	AGE*OCC (p=0.012)
	Comparison	***1,279***	***21.90***			CALINT (p<0.001)
Officer	Ranch Hand	367	21.63	0.23 --	0.495	
	Comparison	502	21.39			
Enlisted Flyer	Ranch Hand	161	21.62	-0.26 --	0.626	
	Comparison	203	21.87			
Enlisted Groundcrew	Ranch Hand	422	21.94	-0.53 --	0.110	
	Comparison	574	22.46			

[a] Transformed from natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-7. (Continued)
Analysis of Body Fat (Percent) with Adjustment for Caloric Intake (Continuous)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	174	22.71	23.20	0.726	-0.0028 (0.0040)	0.484
Medium	173	22.55	22.83			
High	173	23.54	22.76			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	174	23.33	0.734	-0.0062 (0.0042)	0.135	AGE (p=0.003) CALINT (p=0.019)
Medium	173	22.83				
High	171	22.63				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of body fat versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-7. (Continued)
Analysis of Body Fat (Percent) with Adjustment for Caloric Intake (Continuous)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value
Comparison	1,063	22.01	22.01		
Background RH	374	20.36	21.76	-0.25 --	0.085
Low RH	260	22.69	22.09	0.08 --	0.616
High RH	260	23.17	21.82	-0.19 --	0.293
Low plus High RH	520	22.93	21.96	-0.05 --	0.691

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ad]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[e]	Covariate Remarks
Comparison	1,061	22.01**			DXCAT*CALINT (p=0.001) AGE (p<0.001)
Background RH	374	21.82**	-0.19 --**	0.183**	
Low RH	260	22.14**	0.13 --**	0.446**	
High RH	258	21.72**	-0.29 --**	0.076**	
Low plus High RH	518	21.93**	-0.08 --**	0.520**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

[e] P-value is based on difference of means on natural logarithm scale.

** Categorized dioxin-by-covariate interaction ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-5 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.
DXCAT = Categorized dioxin.

Table 9-7. (Continued)
Analysis of Body Fat (Percent) with Adjustment for Caloric Intake (Continuous)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	20.09 (295)	22.34 (300)	23.12 (299)	0.086	0.0471 (0.0051)	<0.001
5	20.11 (300)	22.34 (297)	23.26 (297)	0.096	0.0427 (0.0044)	<0.001
6[d]	20.01 (299)	22.34 (297)	23.17 (297)	0.092	0.0412 (0.0047)	<0.001

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	19.73** (295)	22.67** (300)	23.61** (297)	0.132	0.0604 (0.0059)**	0.001**	CURR*OCC (p=0.013) AGE*OCC (p=0.015) AGE*CALINT (p=0.001) CALINT*OCC (p=0.002)
5	19.67 (300)	22.32 (297)	23.71 (295)	0.140	0.0528 (0.0049)	<0.001	AGE*OCC (p=0.028) AGE*CALINT (p=0.003) CALINT*OCC (p=0.003)
6[e]	19.75 (299)	22.34 (297)	23.67 (295)	0.135	0.0527 (0.0050)	<0.001	AGE*OCC (p=0.032) AGE*CALINT (p=0.003) CALINT*OCC (p=0.003)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of body fat versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin +1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-5 for additional details of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 9-8.
Analysis of Body Fat
(Discrete)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Obese**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***25.4***	***0.99 (0.82,1.20)***	***0.960***
	Comparison	***1,281***	***25.6***		
Officer	Ranch Hand	367	22.3	0.97 (0.70,1.34)	0.909
	Comparison	502	22.9		
Enlisted Flyer	Ranch Hand	162	23.5	1.02 (0.62,1.66)	0.999
	Comparison	203	23.2		
Enlisted Groundcrew	Ranch Hand	423	28.8	1.00 (0.76,1.32)	0.999
	Comparison	576	28.8		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.99 (0.82,1.20)***	***0.927***	OCC*AGE (p=0.030)
Officer	1.04 (0.75,1.44)	0.805	
Enlisted Flyer	1.12 (0.68,1.83)	0.655	
Enlisted Groundcrew	1.09 (0.82,1.43)	0.558	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-8. (Continued)
Analysis of Body Fat
(Discrete)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Obese	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	28.2	0.99 (0.80,1.24)	0.950
Medium	173	34.1		
High	173	37.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	0.91 (0.72,1.16)	0.437	AGE (p=0.026)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-8. (Continued)
Analysis of Body Fat
(Discrete)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Obese	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	26.3		
Background RH	374	14.2	0.82 (0.49,1.35)	0.427
Low RH	260	30.4	1.19 (0.75,1.90)	0.464
High RH	260	35.8	1.23 (0.78,1.94)	0.377
Low plus High RH	520	33.1	1.21 (0.84,1.73)	0.300

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,063			AGE ($p<0.001$)
Background RH	374	0.88 (0.53,1.46)	0.623	
Low RH	260	1.24 (0.77,1.98)	0.374	
High RH	260	1.08 (0.68,1.72)	0.754	
Low plus High RH	520	1.15 (0.80,1.66)	0.442	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-8. (Continued)
Analysis of Body Fat
(Discrete)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Obese/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	11.9 (295)	27.0 (300)	36.5 (299)	1.41 (1.26,1.56)	<0.001
5	12.3 (300)	27.3 (297)	36.0 (297)	1.37 (1.25,1.51)	<0.001
6[c]	12.4 (299)	27.3 (297)	36.0 (297)	1.35 (1.22,1.50)	<0.001

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	894	1.45 (1.28,1.65)**	<0.001**	CURR*OCC (p=0.015) AGE*RACE (p=0.029)
5	894	1.37 (1.25,1.51)	<0.001	
6[d]	893	1.36 (1.22,1.51)	<0.001	AGE*RACE (p=0.049)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-6 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Each of the three unadjusted analyses for Models 4 through 6 detected a highly significant relationship between current dioxin and body fat (Table 9-8(g): $p<0.001$ for all unadjusted analyses). In the Model 4 adjusted analysis, the interaction of current dioxin and occupation was significant (Table 9-8(h): $p=0.015$). The results of further exploration of this interaction are shown in Appendix Table E-2-6. Deleting this interaction from the final model revealed a highly significant association between current dioxin and body fat (Table 9-8(h): Adj. RR=1.45, $p<0.001$). Likewise, current dioxin was significant in relation to body fat after adjusting for covariate information in the Model 6 analysis (Adj. RR=1.36, $p<0.001$). In both Model 4 and Model 6, the interaction of age and race was significant. In the Model 5 adjusted analysis, none of the candidate covariates were significant, and none were retained in the model; therefore, the results from this analysis are identical to those of the unadjusted Model 5 analysis.

Body Fat (Discrete)—Adjusted for Caloric Intake

A second adjusted analysis of body fat was performed in which individual caloric intake was included as an additional covariate. This allowed the relationships between body fat and group and between body fat and dioxin to be explored independently of the effects of diet. The unadjusted analysis was not affected, thus the unadjusted results in Table 9-9 are identical to those in Table 9-8. Adjusted results in Table 9-9 include caloric intake as a covariate.

For Model 1, adjusting for caloric intake in addition to the original covariates, age, race, and occupation, did not uncover any significant differences between Ranch Hands and Comparisons (Table 9-9(b): $p>0.79$ for all analyses). Caloric intake-by-race, age-by-race, and occupation-by-race interactions were significant in the adjusted analysis.

Examination of the adjusted results of body fat for Model 2 did not show any statistically significant associations between initial dioxin and body fat (Table 9-9(d): $p=0.460$). In the Model 3 adjusted analysis, no significant associations were seen between the percentage of obese Ranch Hands and the percentage in the Comparison category (Table 9-9(f): $p>0.44$ for all analyses). Model 2 analyses were adjusted for age and caloric intake. In Model 3, the adjusted analysis uncovered significant interactions between age and race and between race and caloric intake.

The results from investigating the relationship between body fat and current dioxin (Models 4 through 6) are displayed in Table 9-9(h). The current lipid adjusted dioxin-by-occupation interaction was significant in the Model 4 analysis ($p=0.021$; see Appendix Table E-2-7 for stratified results of the dioxin-by-occupation interaction). Deletion of this interaction from the final model found that current lipid-adjusted dioxin was significantly related to body fat (Adj. RR=1.44, $p<0.001$). Current whole-weight dioxin and body fat were also strongly associated for both Models 5 and 6 (Adj. RR=1.37, $p<0.001$ and Adj. RR=1.35, $p<0.001$ respectively). Caloric intake was included as a covariate in each of the Models 4 through 6 adjusted analysis. Also for Model 4, adjusting for covariate information revealed a significant interaction between age and race.

Table 9-9.
Analysis of Body Fat with Adjustment for Caloric Intake
(Discrete)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Obese**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***25.4***	***0.99 (0.82,1.20)***	***0.960***
	Comparison	***1,281***	***25.6***		
Officer	Ranch Hand	367	22.3	0.97 (0.70,1.34)	0.909
	Comparison	502	22.9		
Enlisted Flyer	Ranch Hand	162	23.5	1.02 (0.62,1.66)	0.999
	Comparison	203	23.2		
Enlisted Groundcrew	Ranch Hand	423	28.8	1.00 (0.76,1.32)	0.999
	Comparison	576	28.8		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.99 (0.82,1.21)***	***0.952***	CALINT*RACE (p=0.037) AGE*RACE (p=0.024) OCC*AGE (p=0.016)
Officer	0.96 (0.69,1.32)	0.792	
Enlisted Flyer	1.04 (0.64,1.70)	0.877	
Enlisted Groundcrew	1.01 (0.77,1.34)	0.926	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-9. (Continued)
Analysis of Body Fat with Adjustment for Caloric Intake
(Discrete)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Obese	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	28.2	0.99 (0.80,1.24)	0.950
Medium	173	34.1		
High	173	37.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
518	0.91 (0.72,1.16)	0.460	AGE (p=0.027) CALINT (p=0.816)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-9. (Continued)
Analysis of Body Fat with Adjustment for Caloric Intake
(Discrete)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Obese	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	26.3		
Background RH	374	14.2	0.82 (0.49,1.35)	0.427
Low RH	260	30.4	1.19 (0.75,1.90)	0.464
High RH	260	35.8	1.23 (0.78,1.94)	0.377
Low plus High RH	520	33.1	1.21 (0.84,1.73)	0.300

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,061			AGE*RACE (p=0.026) RACE*CALINT (p=0.010)
Background RH	374	0.91 (0.55,1.51)	0.707	
Low RH	260	1.20 (0.75,1.94)	0.441	
High RH	258	1.06 (0.66,1.69)	0.816	
Low plus High RH	518	1.13 (0.78,1.63)	0.521	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-9. (Continued)
Analysis of Body Fat with Adjustment for Caloric Intake
(Discrete)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Obese/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	11.9 (295)	27.0 (300)	36.5 (299)	1.41 (1.26,1.56)	<0.001
5	12.3 (300)	27.3 (297)	36.0 (297)	1.37 (1.25,1.51)	<0.001
6[c]	12.4 (299)	27.3 (297)	36.0 (297)	1.35 (1.22,1.50)	<0.001

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	892	1.44 (1.27,1.64)**	<0.001**	CURR*OCC (p=0.021) AGE*RACE (p=0.031) CALINT (p=0.335)
5	892	1.37 (1.24,1.50)	<0.001	CALINT (p=0.388)
6[d]	891	1.35 (1.22,1.49)	<0.001	CALINT (p=0.384)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table E-2-7 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Laboratory Examination Variable

Sedimentation Rate (Continuous)

In the Model 1 unadjusted analysis of sedimentation rate in its continuous form, the differences in means between Ranch Hands and Comparisons, overall and within occupations, were nonsignificant (Table 9-10(a): $p>0.10$ for all analyses). Although the adjusted analysis of sedimentation rate revealed no significant overall group difference (Table 9-10(b): $p=0.232$), stratification across occupation led to a marginally significant difference in adjusted means for enlisted groundcrew (Table 9-10(b): difference=0.84, $p=0.078$). After adjusting for covariate information, the interactions between occupation and personality type and between age and personality type were significant.

A significant association between initial dioxin and sedimentation rate was not evident from the results of the Model 2 unadjusted analysis (Table 9-10(c): $p=0.732$). However, the adjusted analysis uncovered a marginally significant relationship between initial dioxin and sedimentation rate (Table 9-10(d): Adj. slope=0.051, $p=0.089$). Age and personality type were retained in the Model 2 adjusted analysis.

The unadjusted categorized dioxin analysis of Model 3 detected marginally significant differences in means for low Ranch Hands versus Comparisons (Table 9-10(e): difference=0.85, $p=0.093$) and low plus high Ranch Hands versus Comparisons (difference=0.75, $p=0.057$). In the adjusted Model 3 analysis, the contrast involving low plus high Ranch Hands and Comparisons contained a marginally significant difference in adjusted means (Table 9-10(f): difference=0.71, $p=0.064$). Age-by-personality type and occupation-by-personality type interactions were retained in the Model 3 adjusted analysis. Once occupation was removed from the final model, significant differences in adjusted means were seen between high Ranch Hands and Comparisons and between low plus high Ranch Hands and Comparisons (Appendix Table E-3-8: $p=0.019$ and $p=0.017$ respectively).

The unadjusted current dioxin analyses of Models 4, 5, and 6 each revealed a statistically significant, or marginally significant, association between sedimentation rate and the current dioxin measurement (Table 9-10(g): $p\leq0.09$ for all unadjusted analyses). In the Model 4 adjusted analysis, sedimentation rate was significant in relation to dioxin (Table 9-10(h): Adj. slope=0.044, $p=0.045$). The Models 5 and 6 adjusted analyses led to conflicting results regarding the relationship between current whole-weight dioxin and sedimentation rate. For Model 5, the analysis uncovered a significant association between sedimentation rate and current whole-weight dioxin (Adj. slope=0.051, $p=0.006$), whereas for Model 6, which adjusts for total lipids, the relationship was nonsignificant (Adj. slope=0.027, $p=0.180$). Occupation was a covariate retained in each of the three adjusted analyses for Models 4, 5, and 6. Removing occupation from the final models did not change the status of the dioxin effects for Models 4 and 5, where dioxin was initially significant. However, in Model 6 the dioxin effect, originally nonsignificant, became significant once occupation was removed (Appendix Table E-3-7: $p=0.004$). Age, occupation, and personality were covariates retained in each of the current dioxin adjusted analyses.

Table 9-10.
Analysis of Sedimentation Rate (mm/hr)
(Continuous)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value
All	***Ranch Hand***	***952***	***8.32***	***0.35 --***	***0.248***
	Comparison	***1,280***	***7.97***		
Officer	Ranch Hand	367	7.63	-0.01 --	0.989
	Comparison	502	7.64		
Enlisted Flyer	Ranch Hand	162	9.31	0.07 --	0.939
	Comparison	202	9.24		
Enlisted Groundcrew	Ranch Hand	423	8.59	0.75 --	0.109
	Comparison	576	7.84		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value	Covariate Remarks[c]
All	***Ranch Hand***	***951***	***8.31***	***0.35 --***	***0.232***	OCC*PERS (p=0.034)
	Comparison	***1,279***	***7.96***			AGE*PERS (p=0.001)
Officer	Ranch Hand	367	6.93	0.02 --	0.946	
	Comparison	502	6.91			
Enlisted Flyer	Ranch Hand	161	8.75	-0.05 --	0.945	
	Comparison	202	8.80			
Enlisted Groundcrew	Ranch Hand	423	9.27	0.84 --	0.078	
	Comparison	575	8.43			

[a] Transformed from natural logarithm scale of sedimentation rate + 0.1.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale of sedimentation rate + 0.1.

[c] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-10. (Continued)
Analysis of Sedimentation Rate (mm/hr)
(Continuous)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	174	8.51	8.56	0.007	0.0070 (0.0099)	0.732
Medium	173	9.86	9.92			
High	173	8.77	8.67			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	173	7.97	0.071	0.0506 (0.0297)	0.089	AGE ($p<0.001$) PERS ($p=0.017$)
Medium	173	9.62				
High	173	9.16				

[a] Transformed from natural logarithm scale of sedimentation rate of + 0.1.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of sedimentation rate + 0.1 versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-10. (Continued)
Analysis of Sedimentation Rate (mm/hr)
(Continuous)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value
Comparison	1,063	8.06	8.05		
Background RH	374	7.60	7.89	-0.16 --	0.697
Low RH	260	9.09	8.91	0.85 --	0.093
High RH	260	8.97	8.70	0.64 --	0.203
Low plus High RH	520	9.03	8.80	0.75 --	0.057

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ad]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[e]	Covariate Remarks
Comparison	1,062	8.02			AGE*PERS (p=0.002) OCC*PERS (p=0.027)
Background RH	374	8.01	-0.01 --	0.980	
Low RH	259	8.70	0.68 --	0.163	
High RH	260	8.76	0.74 --	0.145	
Low plus High RH	519	8.73	0.71 --	0.064	

[a] Transformed from natural logarithm scale of sedimentation rate + 0.1.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale of sedimentation rate + 0.1.

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

[e] P-value is based on difference of means on natural logarithm scale of sedimentation rate + 0.1.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-10. (Continued)
Analysis of Sedimentation Rate (mm/hr)
(Continuous)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	7.52 (295)	8.69 (300)	9.06 (299)	0.007	0.0490 (0.0199)	0.014
5	7.47 (300)	8.68 (297)	9.16 (297)	0.011	0.0541 (0.0170)	0.001
6[d]	7.84 (299)	8.72 (297)	8.65 (297)	0.029	0.0309 (0.0182)	0.090

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	7.68 (295)	8.38 (299)	8.93 (299)	0.077	0.0443 (0.0220)	0.045	AGE ($p<0.001$) OCC ($p=0.009$) PERS ($p=0.020$)
5	7.58 (300)	8.40 (296)	9.03 (297)	0.081	0.0507 (0.0186)	0.006	AGE ($p<0.001$) OCC ($p=0.017$) PERS ($p=0.019$)
6[e]	7.98 (299)	8.47 (296)	8.48 (297)	0.095	0.0269 (0.0200)	0.180	AGE ($p<0.001$) OCC ($p=0.011$) PERS ($p=0.009$)

[a] Transformed from natural logarithm scale of sedimentation rate + 0.1.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of sedimentation rate + 0.1 versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Sedimentation Rate (Discrete)

For Model 1, neither the unadjusted nor the adjusted group analyses of sedimentation rate detected any significant differences between Ranch Hands and Comparisons (Table 9-11(a,b): $p>0.78$ for all analyses). Occupation and the interaction of age and personality type were significant in the adjusted analysis.

Models 2 and 3 examined the association between initial and categorized dioxin and sedimentation rate. No significant results were uncovered in the unadjusted or adjusted analyses of each model (Table 9-11(c-f): $p>0.12$ for all analyses). Age and personality type were included in the final Model 2 adjusted analysis. In Model 3, occupation and the interaction of age and personality type were retained in the adjusted analysis. However, removal of occupation from the final Model 3 adjusted analysis revealed a marginally significant association between sedimentation rate and initial dioxin for the low plus high Ranch Hand category versus the Comparison category (Appendix Table E-3-8: $p=0.086$).

Each of the unadjusted analyses of Models 4 through 6 detected a significant, or marginally significant, current dioxin effect in relation to sedimentation rate. For Model 4, where current dioxin is lipid-adjusted, the estimated relative risk was 1.15 (Table 9-11(g): $p=0.019$). Sedimentation rate and current whole-weight dioxin were associated in both the Model 5 and Model 6 unadjusted analyses. The respective estimated relative risks were 1.15 ($p=0.009$) and 1.10 ($p=0.082$). In the Model 4 adjusted analyses of sedimentation rate, a marginally significant relationship was seen between current lipid-adjusted dioxin and sedimentation rate (Table 9-11(h): Adj. RR=1.12, $p=0.090$). Although the adjusted analyses of Model 5 uncovered a statistically significant adjusted relative risk (Adj. RR=1.19, $p=0.001$), examination of the results of the Model 6 analysis showed that additionally adjusting for total lipids led to nonsignificant results (Adj. RR=1.08, $p=0.223$). Also, in the Model 6 adjusted analysis, occupation was retained in the final model. The deletion of this variable from the final model caused current whole-weight dioxin to become significant (Appendix Table E-3-8: Adj. RR=1.15, $p=0.021$). Age was retained in each of the adjusted analyses of Models 4 through 6 as a significant covariate. Additionally, in Models 5 and 6, race was included.

Longitudinal Analysis

Longitudinal analyses were conducted on five variables—self-perception of health, appearance of illness or distress, relative age, body fat, and sedimentation rate—to examine whether changes across time differed with respect to group membership (Model 1), initial dioxin (Model 2), and categorized dioxin (Model 3). Models 4, 5, and 6 were not examined in longitudinal analyses because current dioxin, the measure of exposure in these models, changes over time and is not available for all participants for 1982 or 1992. Discrete analyses were performed for all variables, and continuous analyses were performed for body fat and sedimentation rate. The longitudinal analyses for all of these variables investigated the difference between the 1982 examination and the 1992 examination. Participants considered abnormal in 1982 were not included. These analyses were used to investigate the temporal effects of dioxin during the 10-year period between 1982 and 1992. Participants considered abnormal in 1982 were already abnormal before this period; consequently, only

Table 9-11.
Analysis of Sedimentation Rate
(Discrete)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Abnormal**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***17.8***	***1.02 (0.82,1.28)***	***0.883***
	Comparison	***1,280***	***17.4***		
Officer	Ranch Hand	367	14.2	1.02 (0.69,1.50)	0.999
	Comparison	502	13.9		
Enlisted Flyer	Ranch Hand	162	22.2	1.00 (0.61,1.64)	0.999
	Comparison	202	22.3		
Enlisted Groundcrew	Ranch Hand	423	19.2	1.03 (0.75,1.41)	0.938
	Comparison	576	18.8		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.02 (0.82,1.28)***	***0.839***	OCC ($p<0.001$) AGE*PERS ($p=0.008$)
Officer	1.06 (0.71,1.56)	0.782	
Enlisted Flyer	0.96 (0.58,1.58)	0.859	
Enlisted Groundcrew	1.03 (0.75,1.42)	0.859	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 9-11. (Continued)
Analysis of Sedimentation Rate
(Discrete)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	19.5	1.02 (0.87,1.19)	0.835
Medium	173	23.1		
High	173	20.2		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
519	1.06 (0.89,1.25)	0.509	AGE (p=0.048) PERS (p=0.136)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 9-11. (Continued)
Analysis of Sedimentation Rate
(Discrete)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	17.2		
Background RH	374	13.4	0.79 (0.56,1.11)	0.174
Low RH	260	21.5	1.29 (0.92,1.81)	0.136
High RH	260	20.4	1.17 (0.83,1.65)	0.373
Low plus High RH	520	21.0	1.23 (0.94,1.61)	0.128

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,062			OCC (p=0.004) AGE*PERS (p=0.007)
Background RH	374	0.87 (0.61,1.23)	0.423	
Low RH	259	1.27 (0.90,1.79)	0.169	
High RH	260	1.10 (0.77,1.57)	0.616	
Low plus High RH	519	1.18 (0.90,1.56)	0.224	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 9-11. (Continued)
Analysis of Sedimentation Rate
(Discrete)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	12.5 (295)	20.3 (300)	20.4 (299)	1.15 (1.02,1.29)	0.019
5	13.0 (300)	19.2 (297)	21.2 (297)	1.15 (1.03,1.27)	0.009
6[c]	13.0 (299)	19.2 (297)	21.2 (297)	1.10 (0.99,1.23)	0.082

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	894	1.12 (0.98,1.28)	0.090	OCC (p=0.109) AGE (p<0.001)
5	894	1.19 (1.07,1.33)	0.001	AGE (p=0.002) RACE (p=0.086)
6[d]	893	1.08 (0.95,1.21)	0.223	AGE (p=0.001) OCC (p=0.114) RACE (p=0.118)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

participants normal at the 1982 examination were considered to be at risk when the effects of dioxin over this period of time are explored. The rate of abnormalities under this restriction approximates an incidence rate between 1982 and 1992. Summary statistics are provided for reference purposes for the 1985 and 1987 examinations.

The longitudinal analyses for the discrete variables examined relative risks at the 1992 exam for participants who were classified as normal at the 1982 exam. The adjusted relative risks estimated from each of the three models were used to investigate the change in the dependent variable over time. All three models were adjusted for age; Models 2 and 3 were also adjusted for percent body fat at the tour of duty and change in percent body fat from the tour of duty to the date of the blood draw for dioxin.

The longitudinal analysis for the two continuous variables examined the paired difference between the measurements from 1982 and 1992. These paired differences measured the change in body fat or sedimentation rate over time. Each of the three models used in the longitudinal analysis were adjusted for age and the dependent variable as measured in 1982 (see Statistical Methods, Chapter 7). The analyses of Models 2 and 3 were also adjusted for percent body fat at the tour of duty and change in percent body fat from the tour of duty to the date of the blood draw for dioxin. A logarithmic transformation was applied to both of these variables for analytic purposes.

The cutpoints for abnormal sedimentation rate differ by examination data and age. For the 1982 Baseline examination, the cutpoint was 12 mm/hr for all participants. For the 1985, 1987, and 1992 followup examinations, the cutpoint was 15 mm/hr for participants younger than 50 and 20 mm/hr for participants at least 50 years old at the time of the examination.

Questionnaire Variable

Self-Perception of Health

Percentages of participants who reported their health as fair or poor for the 1992 examination were examined longitudinally for an association with group and current and initial dioxin levels. Only those participants who reported a good or excellent perception of health in 1982 were included in the longitudinal study. The results of this analysis are shown in Table 9-12.

In the Model 1 analyses, overall and occupationally-stratified longitudinal analyses of participants with good or excellent health in 1982 showed that the percentage of Ranch Hands who reported their health as fair or poor in the 1992 examination did not differ significantly from the percentage of Comparisons (Table 9-12(a): $p>0.14$ for each analysis).

Conditioned on good or excellent health in 1982, the Model 2 longitudinal analysis detected a significant positive association between initial dioxin and the percentage of Ranch Hands with a fair or poor self-perception of health in 1992 (Table 9-12(b): Adj. RR=1.38, $p=0.031$). Of the Ranch Hands with a good or excellent self-perception of health in 1982,

Table 9-12.
Longitudinal Analysis of Self-Perception of Health

a) MODEL 1: RANCH HANDS VS. COMPARISONS					
		Percent Fair or Poor/(n) Examination			
Occupational Category	Group	1982	1985	1987	1992
All	***Ranch Hand***	***18.2 (899)***	***8.3 (877)***	***6.0 (868)***	***10.6 (899)***
	Comparison	***14.8 (1,061)***	***6.6 (1,038)***	***6.0 (1,034)***	***7.8 (1,061)***
Officer	Ranch Hand	10.6 (339)	4.2 (334)	4.2 (333)	6.5 (339)
	Comparison	10.2 (403)	4.8 (395)	2.8 (390)	5.7 (403)
Enlisted Flyer	Ranch Hand	20.9 (158)	6.4 (156)	5.9 (153)	13.3 (158)
	Comparison	18.9 (175)	8.1 (172)	6.3 (174)	9.1 (175)
Enlisted Groundcrew	Ranch Hand	23.6 (402)	12.7 (387)	7.6 (382)	12.9 (402)
	Comparison	17.2 (483)	7.4 (471)	8.5 (470)	9.1 (483)

		Excellent or Good in 1982			
Occupational Category	Group	n in 1992	Percent Fair or Poor in 1992	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	***Ranch Hand***	***735***	***5.6***	***1.22 (0.78,1.90)***	***0.385***
	Comparison	***904***	***4.7***		
Officer	Ranch Hand	303	2.3	0.59 (0.23,1.48)	0.261
	Comparison	362	3.9		
Enlisted Flyer	Ranch Hand	125	9.6	1.59 (0.64,3.92)	0.317
	Comparison	142	6.3		
Enlisted Groundcrew	Ranch Hand	307	7.2	1.60 (0.85,3.04)	0.146
	Comparison	400	4.8		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1992 results; results adjusted for age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had an excellent or good self-perception of health in 1982 (see Chapter 7, Statistical Methods).

Table 9-12. (Continued)
Longitudinal Analysis of Self-Perception of Health

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN				
	Percent Fair or Poor/(n) Examination			
Initial Dioxin	1982	1985	1987	1992
Low	16.3 (166)	8.6 (163)	4.9 (165)	10.2 (166)
Medium	24.4 (168)	11.7 (162)	8.5 (164)	13.7 (168)
High	19.1 (168)	13.9 (166)	8.0 (162)	13.7 (168)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Excellent or Good in 1982			
Initial Dioxin	n in 1992	Percent Fair or Poor in 1992	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	139	4.3	1.38 (1.03,1.85)	0.031
Medium	127	9.5		
High	136	8.1		

[a] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had an excellent or good self-perception of health in 1982 (see Chapter 7, Statistical Methods).

Table 9-12. (Continued)
Longitudinal Analysis of Self-Perception of Health

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY				
	Percent Fair or Poor/(n) Examination			
Dioxin Category	1982	1985	1987	1992
Comparison	14.2 (915)	6.2 (904)	5.9 (904)	7.3 (915)
Background RH	16.1 (342)	3.8 (339)	3.9 (336)	7.0 (342)
Low RH	18.9 (249)	9.1 (243)	6.5 (247)	10.4 (249)
High RH	21.0 (253)	13.7 (248)	7.8 (244)	14.6 (253)
Low plus High RH	19.9 (502)	11.4 (491)	7.1 (491)	12.6 (502)

	Excellent or Good in 1982			
Dioxin Category	n in 1992	Percent Fair or Poor in 1992	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	785	4.6		
Background RH	287	3.1	0.73 (0.34,1.55)	0.409
Low RH	202	5.0	0.97 (0.47,2.01)	0.940
High RH	200	9.5	2.24 (1.23,4.09)	0.008
Low plus High RH	402	7.2	1.54 (0.92,2.57)	0.101

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤10 ppt.
Background (Ranch Hand): Current Dioxin ≤10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin > 143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had an excellent or good self-perception of health in 1982 (see Chapter 7, Statistical Methods).

the percentages of Ranch Hands who reported their health as fair or poor in 1992 were 4.3, 9.5, and 8.1 for the low, medium, and high categories of initial dioxin respectively.

For the Model 3 longitudinal analysis, there was a highly significant difference between Ranch Hands in the high dioxin category and Comparisons for participants who perceived their health as fair or poor in 1992 (Table 9-12(e): Adj. RR=2.24, p=0.008). Of the participants who reported good or excellent health in the 1982 examination, 9.5 percent of the high Ranch Hands and 4.6 percent of the Comparisons reported a fair or poor perception of health in 1992. For background, low, and low plus high Ranch Hands, the percentages were 3.1, 5.0, and 7.2 respectively. However, none of these categories was significantly different from the Comparison category ($p>0.10$ for each contrast).

Physical Examination Variables

Appearance of Illness of Distress

Longitudinal analyses for the physician's evaluation as to whether the participant appeared ill or distressed at the physical examination were conducted. These analyses were performed for participants who did not appear ill or distressed at the 1982 examination. Table 9-13 displays the results of these analyses.

For the Model 1 longitudinal analysis, no significant overall group effect existed for participants who appeared ill or distressed at the 1992 examination (Table 9-13(a): p=0.468). This nonsignificant result remained after longitudinal analyses were performed within each of the three levels of occupation ($p>0.22$ for each stratum). The percentage of Ranch Hands with an unhealthy appearance in 1992 was not significantly associated with initial dioxin in the Model 2 longitudinal analysis (Table 9-13(b): p=0.789). For the participants who appeared healthy at the 1982 physical examination, the Model 3 longitudinal analyses did not detect a significant difference in the 1992 percentages of participants who appeared ill or distressed between the Comparison and Ranch Hand categories of dioxin (Table 9-13(c): $p>0.57$ for each contrast).

Relative Age Appearance

Longitudinal analyses investigating associations between either group or dioxin and participants who appeared older than their age were performed. Only those participants who appeared as old as or younger than their stated age in 1982 were included in this analysis. The results of the longitudinal analyses of relative age appearance are shown in Table 9-14.

No significant difference in relative age appearance in 1992 between Ranch Hands and Comparisons was detected in either the overall or stratified Model 1 longitudinal analyses (Table 9-14(a): $p>0.23$). The percentage of participants with an abnormal relative age appearance in 1992 was significantly associated with initial dioxin in the Model 2 longitudinal analysis (Table 9-14(b): Adj. RR=1.33, p=0.050). Of those participants with a normal relative age appearance in 1982, the percentages of Ranch Hands who appeared older than their age at the 1992 examination were 4.8, 6.6, and 7.4 for the low, medium, and high categories of initial dioxin. In the Model 3 longitudinal analysis, for participants

Table 9-13.
Longitudinal Analysis of Appearance of Illness or Distress

a) MODEL 1: RANCH HANDS VS. COMPARISONS					
		Percent Yes/(n) Examination			
Occupational Category	Group	1982	1985	1987	1992
All	***Ranch Hand***	***0.2 (899)***	***0.2 (875)***	***0.4 (868)***	***2.5 (899)***
	Comparison	***0.1 (1,059)***	***0.4 (1,036)***	***0.4 (1,032)***	***1.9 (1,059)***
Officer	Ranch Hand	0.3 (340)	0.3 (335)	0.3 (334)	2.7 (340)
	Comparison	0.0 (402)	0.0 (394)	0.3 (390)	1.5 (402)
Enlisted Flyer	Ranch Hand	0.0 (159)	0.6 (157)	0.0 (154)	3.1 (159)
	Comparison	0.0 (173)	1.2 (170)	0.6 (172)	1.2 (173)
Enlisted Groundcrew	Ranch Hand	0.3 (400)	0.0 (383)	0.5 (380)	2.0 (400)
	Comparison	0.2 (484)	0.4 (472)	0.4 (470)	2.5 (484)

		No in 1982			
Occupational Category	Group	n in 1992	Percent Yes in 1992	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	***Ranch Hand***	***897***	***2.3***	***1.26 (0.68,2.34)***	***0.468***
	Comparison	***1,058***	***1.9***		
Officer	Ranch Hand	339	2.4	1.61 (0.55,4.70)	0.381
	Comparison	402	1.5		
Enlisted Flyer	Ranch Hand	159	3.1	2.81 (0.53,14.87)	0.223
	Comparison	173	1.2		
Enlisted Groundcrew	Ranch Hand	399	2.0	0.83 (0.33,2.05)	0.681
	Comparison	483	2.5		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1992 results; results adjusted for age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who did not appear ill or distressed in 1982 (see Chapter 7, Statistical Methods).

Table 9-13. (Continued)
Longitudinal Analysis of Appearance of Illness or Distress

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN				
	Percent Yes/(n) Examination			
Initial Dioxin	1982	1985	1987	1992
Low	0.0 (167)	0.0 (164)	0.0 (166)	1.8 (167)
Medium	0.0 (168)	0.6 (161)	0.0 (164)	2.4 (168)
High	0.6 (167)	0.0 (164)	0.6 (161)	1.8 (167)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	No in 1982			
Initial Dioxin	n in 1992	Percent Yes in 1992	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	167	1.8	0.94 (0.57,1.53)	0.789
Medium	168	2.4		
High	166	1.8		

[a] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who did not appear ill or distressed in 1982 (see Chapter 7, Statistical Methods).

Table 9-13. (Continued)
Longitudinal Analysis of Appearance of Illness or Distress

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY				
	Percent Yes/(n) Examination			
Dioxin Category	1982	1985	1987	1992
Comparison	0.0 (915)	0.3 (904)	0.3 (904)	1.8 (915)
Background RH	0.0 (342)	0.3 (339)	0.3 (336)	2.3 (342)
Low RH	0.0 (249)	0.4 (243)	0.0 (247)	2.4 (249)
High RH	0.4 (253)	0.0 (246)	0.4 (244)	1.6 (253)
Low plus High RH	0.2 (502)	0.2 (489)	0.2 (491)	2.0 (502)

	No in 1982			
Dioxin Category	n in 1992	Percent Yes in 1992	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	915	1.8		
Background RH	342	2.3	1.29 (0.54,3.07)	0.571
Low RH	249	2.4	1.17 (0.45,3.08)	0.743
High RH	252	1.6	0.97 (0.31,3.01)	0.957
Low plus High RH	501	2.0	1.08 (0.48,2.46)	0.845

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤10 ppt.
Background (Ranch Hand): Current Dioxin ≤10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin > 143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who did not appear ill or distressed in 1982 (see Chapter 7, Statistical Methods).

Table 9-14.
Longitudinal Analysis of Relative Age Appearance

a) MODEL 1: RANCH HANDS VS. COMPARISONS					
		Percent Older/(n) Examination			
Occupational Category	Group	1982	1985	1987	1992
All	*Ranch Hand*	*1.7 (901)*	*3.5 (878)*	*5.1 (870)*	*5.8 (901)*
	Comparison	*2.2 (1,061)*	*4.1 (1,038)*	*4.6 (1,035)*	*6.1 (1,061)*
Officer	Ranch Hand	0.9 (340)	1.5 (335)	3.6 (334)	3.2 (340)
	Comparison	1.5 (402)	0.3 (394)	2.6 (390)	3.7 (402)
Enlisted Flyer	Ranch Hand	0.0 (159)	3.2 (157)	7.1 (154)	9.4 (159)
	Comparison	3.4 (175)	8.7 (172)	8.1 (174)	7.4 (175)
Enlisted Groundcrew	Ranch Hand	3.0 (402)	5.4 (386)	5.5 (382)	6.5 (402)
	Comparison	2.3 (484)	5.5 (472)	5.1 (471)	7.6 (484)

		Same or Younger in 1982			
Occupational Category	Group	n in 1992	Percent Older in 1992	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	*Ranch Hand*	*886*	*5.8*	*1.05 (0.71,1.55)*	*0.808*
	Comparison	*1,038*	*5.5*		
Officer	Ranch Hand	337	3.3	0.99 (0.44,2.25)	0.988
	Comparison	396	3.3		
Enlisted Flyer	Ranch Hand	159	9.4	1.66 (0.72,3.80)	0.234
	Comparison	169	5.9		
Enlisted Groundcrew	Ranch Hand	390	6.4	0.89 (0.52,1.51)	0.659
	Comparison	473	7.2		

[a] Relative risk, confidence interval, and p-value are in reference to a contrast of 1982 and 1992 results; results adjusted for age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who appeared as old as or younger than their age in 1982 (see Chapter 7, Statistical Methods).

Table 9-14. (Continued)
Longitudinal Analysis of Relative Age Appearance

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN				
	Percent Older/(n) Examination			
Initial Dioxin	1982	1985	1987	1992
Low	0.6 (167)	3.1 (164)	4.2 (166)	4.8 (167)
Medium	1.8 (169)	3.7 (163)	4.2 (165)	6.5 (169)
High	3.0 (168)	6.7 (165)	4.3 (162)	7.1 (168)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Same or Younger in 1982			
Initial Dioxin	n in 1992	Percent Older in 1992	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	166	4.8	1.33 (1.01,1.75)	0.050
Medium	166	6.6		
High	163	7.4		

[a] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who appeared as old as or younger than their age in 1982 (see Chapter 7, Statistical Methods).

Table 9-14. (Continued)
Longitudinal Analysis of Relative Age Appearance

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY				
	Percent Older/(n) Examination			
Dioxin Category	1982	1985	1987	1992
Comparison	2.3 (916)	3.9 (905)	4.6 (906)	6.1 (916)
Background RH	1.2 (342)	2.4 (339)	5.7 (336)	4.7 (342)
Low RH	0.4 (250)	3.3 (244)	3.2 (248)	4.4 (250)
High RH	3.2 (254)	5.7 (248)	5.3 (245)	7.9 (254)
Low plus High RH	1.8 (504)	4.5 (492)	4.3 (493)	6.2 (504)

	Same or Younger in 1982			
Dioxin Category	n in 1992	Percent Older in 1992	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	895	5.5		
Background RH	338	4.4	0.83 (0.46,1.52)	0.553
Low RH	249	4.4	0.78 (0.40,1.52)	0.458
High RH	246	8.1	1.44 (0.83,2.51)	0.191
Low plus High RH	495	6.3	1.10 (0.69,1.76)	0.689

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin $\leq$143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin > 143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who appeared as old as or younger than their age in 1982 (see Chapter 7, Statistical Methods).

who appeared as old as or younger than their age in 1982, no statistically significant associations were seen between the percentage of Comparisons who appeared older than their age in 1992 versus background, low, and high Ranch Hands who appeared older (Table 9-14(c): $p>0.19$).

Body Fat (Continuous)

Longitudinal analyses that examined the mean difference in body fat between 1982 and 1992 were performed to explore associations with group and dioxin. The results of the longitudinal analysis are seen in Table 9-15.

The Model 1 longitudinal analysis of body fat did not detect a significant overall difference in the average change in body fat from 1982 to 1992 between Ranch Hands and Comparisons (Table 9-15(a): $p=0.325$). However, when stratified across the levels of occupation, the category of enlisted groundcrew revealed a marginally significant difference in body fat between the two groups over time (difference = -0.35, $p=0.053$). A marginally significant negative association between initial dioxin and the change in body fat between 1982 and 1992 was evident in the Model 2 longitudinal analysis (Table 9-15(b): Slope= -0.0075, $p=0.075$). The Model 3 longitudinal analysis of the mean change in body fat between 1982 and 1992 revealed a significant negative association with categorized dioxin for high Ranch Hands versus Comparisons (Table 9-15(c): difference = -0.23, $p=0.025$). The remaining three contrasts between Ranch Hands and Comparisons did not reveal significant associations between body fat and categorized dioxin.

Body Fat (Discrete)

For the longitudinal analyses, the percentages of participants with elevated (i.e., >25%) body fat at the 1992 examination were examined for associations with group and dioxin. Only those participants with less than 25 percent body fat at the 1982 Baseline examination were included in these analyses. Table 9-16 presents the results of the longitudinal analyses for body fat.

Neither the overall nor stratified Model 1 longitudinal analyses detected a significant difference in the percentages of abnormal body fat in 1992 between Ranch Hands and Comparisons (Table 9-16(a): $p>0.70$). Of the participants with a 1982 body fat measurement less than 25 percent, the relationship between initial dioxin and Ranch Hands with an abnormal body fat measurement in 1992 was nonsignificant for the Model 2 longitudinal analysis (Table 9-16(b): $p=0.696$). For the Model 3 longitudinal analysis there were no significant differences in the percentages among the participants with abnormal body fat measurements in 1992 for the four current dioxin categories (Table 9-16(c): $p\geq0.51$ for all contrasts).

Table 9-15.
Longitudinal Analysis of Body Fat (Percent)
(Continuous)

a) MODEL 1: RANCH HANDS VS. COMPARISONS								
		Mean[a]/(n) Examination						
Occupational Category	Group	1982	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	***Ranch Hand***	***19.92 (901)***	***20.73 (879)***	***21.08 (870)***	***21.82 (901)***	***1.91***	***-0.12***	***0.325***
	Comparison	***19.99 (1,063)***	***20.99 (1,040)***	***21.23 (1,037)***	***22.01 (1,063)***	***2.02***		
Officer	Ranch Hand	20.07 (340)	20.86 (335)	21.15 (334)	21.85 (340)	1.78	0.03	0.827
	Comparison	19.90 (403)	20.87 (395)	21.00 (391)	21.65 (403)	1.74		
Enlisted Flyer	Ranch Hand	19.66 (159)	20.56 (157)	20.83 (154)	21.48 (159)	1.82	0.17	0.623
	Comparison	19.86 (175)	20.43 (172)	20.76 (174)	21.51 (175)	1.65		
Enlisted Groundcrew	Ranch Hand	19.89 (402)	20.68 (387)	21.11 (382)	21.94 (402)	2.05	-0.35	0.053
	Comparison	20.11 (485)	21.30 (473)	21.59 (472)	22.51 (485)	2.40		

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of body fat; results adjusted for natural logarithm of body fat in 1982 and age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-15. (Continued)
Longitudinal Analysis of Body Fat (Percent)
(Continuous)

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN						
	Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]	
	Mean[a]/(n) Examination					
Initial Dioxin	1982	1985	1987	1992	Adj. Slope (Std. Error)	p-Value
Low	20.55 (167)	21.48 (164)	21.67 (166)	22.67 (167)	-0.0075 (0.0042)	0.075
Medium	20.74 (169)	21.68 (163)	21.86 (165)	22.50 (169)		
High	21.82 (168)	22.84 (166)	23.11 (162)	23.64 (168)		

[a] Transformed from natural logarithm scale.

[b] Results based on difference between natural logarithm of 1992 body fat and natural logarithm of 1982 body fat versus log_2 (initial dioxin); results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of 1982 body fat, and age in 1992.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-15. (Continued)
Longitudinal Analysis of Body Fat (Percent)
(Continuous)

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY							
	Mean[a]/(n) Examination						
Dioxin Category	1982	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
Comparison	20.10 (917)	21.08 (906)	21.37 (907)	22.16 (917)	2.06		
Background RH	18.42 (342)	19.14 (339)	19.60 (336)	20.35 (342)	1.93	-0.13	0.432
Low RH	20.67 (250)	21.57 (244)	21.83 (248)	22.64 (250)	1.97	-0.09	0.654
High RH	21.39 (254)	22.41 (249)	22.57 (245)	23.22 (254)	1.83	-0.23	0.025
Low plus High RH	21.03 (504)	21.99 (493)	22.20 (493)	22.93 (504)	1.90	-0.16	0.251

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of body fat; results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of body fat in 1982, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin $\leq$143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin >143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-16.
Longitudinal Analysis of Body Fat
(Discrete)

a) MODEL 1: RANCH HANDS VS. COMPARISONS					
		Percent Obese/(n) Examination			
Occupational Category	Group	1982	1985	1987	1992
All	***Ranch Hand***	***14.4 (901)***	***18.8 (879)***	***20.0 (870)***	***25.6 (901)***
	Comparison	***14.6 (1,063)***	***20.2 (1,040)***	***22.6 (1,037)***	***26.6 (1,063)***
Officer	Ranch Hand	12.7 (340)	17.6 (335)	18.0 (334)	23.5 (340)
	Comparison	10.4 (403)	14.9 (395)	17.7 (391)	23.6 (403)
Enlisted Flyer	Ranch Hand	12.0 (159)	16.6 (157)	18.8 (154)	23.3 (159)
	Comparison	14.9 (175)	20.4 (172)	20.7 (174)	21.7 (175)
Enlisted Groundcrew	Ranch Hand	16.9 (402)	20.7 (387)	22.3 (382)	28.4 (402)
	Comparison	17.9 (485)	24.5 (473)	27.3 (472)	30.9 (485)

		Lean or Normal in 1982			
Occupational Category	Group	n in 1992	Percent Obese in 1992	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	***Ranch Hand***	***771***	***15.7***	***0.99 (0.76,1.29)***	***0.966***
	Comparison	***908***	***15.8***		
Officer	Ranch Hand	297	15.8	1.00 (0.66,1.53)	0.989
	Comparison	361	15.8		
Enlisted Flyer	Ranch Hand	140	14.3	1.14 (0.58,2.24)	0.702
	Comparison	149	12.8		
Enlisted Groundcrew	Ranch Hand	334	16.2	0.95 (0.64,1.40)	0.788
	Comparison	398	16.8		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1992 results; results adjusted for age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who were lean or had normal body fat in 1982 (see Chapter 7, Statistical Methods).

Table 9-16. (Continued)
Longitudinal Analysis of Body Fat
(Discrete)

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN				
	Percent Obese/(n) Examination			
Initial Dioxin	1982	1985	1987	1992
Low	16.2 (167)	20.1 (164)	20.5 (166)	27.0 (167)
Medium	17.2 (169)	24.5 (163)	25.5 (165)	33.1 (169)
High	23.2 (168)	30.7 (166)	30.3 (162)	37.5 (168)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Lean or Normal in 1982			
Initial Dioxin	n in 1992	Percent Obese in 1992	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	140	16.4	0.95 (0.71,1.25)	0.696
Medium	140	22.9		
High	129	21.7		

[a] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who were lean or had normal body fat in 1982 (see Chapter 7, Statistical Methods).

Table 9-16. (Continued)
Longitudinal Analysis of Body Fat
(Discrete)

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY				
	Percent Obese/(n) Examination			
Dioxin Category	1982	1985	1987	1992
Comparison	14.5 (917)	20.0 (906)	22.6 (907)	27.4 (917)
Background RH	8.2 (342)	10.6 (339)	12.2 (336)	15.2 (342)
Low RH	17.6 (250)	22.1 (244)	23.0 (248)	29.2 (250)
High RH	20.1 (254)	28.1 (249)	27.8 (245)	35.8 (254)
Low plus High RH	18.9 (504)	25.2 (493)	25.4 (493)	32.5 (504)

	Lean or Normal in 1982			
Dioxin Category	n in 1992	Percent Obese in 1992	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	784	16.6		
Background RH	314	8.9	0.88 (0.49,1.58)	0.675
Low RH	206	17.0	1.03 (0.60,1.79)	0.905
High RH	203	23.7	1.19 (0.71,2.02)	0.510
Low plus High RH	409	20.3	1.11 (0.73,1.69)	0.611

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin $\leq$143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin >143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who were lean or had normal body fat in 1982 (see Chapter 7, Statistical Methods).

Laboratory Variable

Sedimentation Rate (Continuous)

The change in sedimentation rate between 1982 and 1992 was examined for an association with group and dioxin. Table 9-17 presents the results of the analysis.

The overall and stratified Model 1 longitudinal analyses of the mean difference in sedimentation rate between 1982 and 1992 did not uncover a significant group effect for Ranch Hands versus Comparisons (Table 9-17(a): $p>0.13$). The association between initial dioxin and change in sedimentation rate from 1982 to 1992 was nonsignificant in the Model 2 longitudinal analyses (Table 9-17(b): $p=0.334$). The Model 3 longitudinal analysis detected a marginally significant association between categorized dioxin and the mean difference in sedimentation rate between the Baseline and the 1992 followup examinations for Ranch Hands in the high dioxin category (Table 9-17(c): difference = 0.75, $p=0.060$) and low plus high dioxin category (difference = 0.77, $p=0.066$) versus Comparisons. The contrasts involving background and low Ranch Hands versus Comparisons were nonsignificant ($p>0.25$).

Sedimentation Rate (Discrete)

Longitudinal analyses were conducted to investigate associations between abnormal sedimentation rates at the 1992 examination and dioxin or group. The longitudinal study was conditioned on participants with normal sedimentation rates at the 1982 Baseline examination. The results of the analysis for sedimentation rate are shown in Table 9-18.

For participants with normal sedimentation rates in 1982, Model 1 analyses investigating the overall and stratified differences between Ranch Hands and Comparisons with abnormal sedimentation rates in 1992 were not significant (Table 9-18(a): $p>0.64$). The Model 2 longitudinal analysis of Ranch Hands with normal sedimentation rates in 1982 did not reveal a significant association between initial dioxin and the percentage of Ranch Hands in 1992 with abnormal sedimentation rates (Table 9-18(b): $p=0.272$). There were no significant differences in patterns of sedimentation rate changes over time for participants in the four current dioxin categories in the Model 3 longitudinal analysis (Table 9-18(c): $p\geq0.12$).

DISCUSSION

In ambulatory medicine, the assessment of an individual's general state of health is based on subjective and objective indices including the individual's history, physical examination, and laboratory testing. The variables analyzed in this chapter are frequently employed by clinicians in outpatient practice and were selected to be sensitive to the overall state of health rather than specific to any organ system.

As in the 1982 and 1985 examinations (though not in 1987), Ranch Hand participants perceive themselves to be less healthy than Comparisons, particularly those who as a group were known to have had the highest level of dioxin exposure, the enlisted groundcrew. In the unadjusted analysis, 10.4 percent of Ranch Hands viewed their health as fair or poor

Table 9-17.
Longitudinal Analysis of Sedimentation Rate (mm/hr)
(Continuous)

a) MODEL 1: RANCH HANDS VS. COMPARISONS								
		Mean[a]/(n) Examination						
Occupational Category	Group	1982	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	*Ranch Hand*	*1.82 (901)*	*4.94 (879)*	*5.22 (869)*	*8.35 (901)*	*6.53*	*0.25*	*0.570*
	Comparison	*1.63 (1,063)*	*4.83 (1,040)*	*5.05 (1,035)*	*7.91 (1,063)*	*6.28*		
Officer	Ranch Hand	1.85 (340)	4.94 (335)	5.06 (333)	7.75 (340)	5.90	-0.32	0.198
	Comparison	1.48 (403)	4.79 (395)	4.88 (391)	7.70 (403)	6.22		
Enlisted Flyer	Ranch Hand	1.97 (159)	5.18 (157)	5.93 (154)	9.26 (159)	7.29	0.52	0.348
	Comparison	2.29 (175)	5.34 (172)	5.39 (174)	9.06 (175)	6.77		
Enlisted Groundcrew	Ranch Hand	1.74 (402)	4.84 (387)	5.09 (382)	8.53 (402)	6.79	0.64	0.132
	Comparison	1.57 (485)	4.69 (473)	5.08 (470)	7.71 (485)	6.14		

[a] Transformed from natural logarithm of sedimentation rate + 0.1 scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of sedimentation rate + 0.1; results adjusted for natural logarithm of sedimentation rate + 0.1 in 1982 and age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-17. (Continued)
Longitudinal Analysis of Sedimentation Rate (mm/hr)
(Continuous)

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN						
Initial Dioxin Category Summary Statistics					Analysis Results for Log_2 (Initial Dioxin)[b]	
	Mean[a]/(n) Examination					
Initial Dioxin	1982	1985	1987	1992	Adj. Slope (Std. Error)	p-Value
Low	1.76 (167)	5.12 (164)	5.37 (166)	8.52 (167)	0.0247 (0.0256)	0.334
Medium	2.20 (169)	5.64 (163)	5.94 (165)	9.76 (169)		
High	1.70 (168)	4.93 (166)	5.58 (162)	8.74 (168)		

[a] Transformed from natural logarithm of sedimentation rate + 0.1 scale.

[b] Results based on difference between natural logarithm of 1992 sedimentation rate + 0.1 and natural logarithm of 1982 sedimentation rate + 0.1 versus log_2 (initial dioxin); results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of 1982 sedimentation rate + 0.1, and age in 1992.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-17. (Continued)
Longitudinal Analysis of Sedimentation Rate (mm/hr)
(Continuous)

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY							
	Mean[a]/(n) Examination				Exam. Mean	Difference of Exam. Mean	
Dioxin Category	1982	1985	1987	1992	Change[b]	Change	p-Value[c]
Comparison	1.65 (917)	4.84 (906)	5.10 (906)	8.00 (917)	6.35		
Background RH	1.79 (342)	4.71 (339)	4.81 (335)	7.72 (342)	5.93	-0.41	0.250
Low RH	1.92 (250)	5.37 (244)	5.60 (248)	9.06 (250)	7.13	0.78	0.327
High RH	1.83 (254)	5.08 (249)	5.65 (245)	8.93 (254)	7.10	0.75	0.060
Low plus High RH	1.88 (504)	5.22 (493)	5.62 (493)	8.99 (504)	7.12	0.77	0.066

[a] Transformed from natural logarithm of sedimentation rate + 0.1 scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of sedimentation rate + 0.1; results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of sedimentation rate + 0.1 in 1982, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤10 ppt.
Background (Ranch Hand): Current Dioxin ≤10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin >143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations.

Table 9-18.
Longitudinal Analysis of Sedimentation Rate
(Discrete)

a) MODEL 1: RANCH HANDS VS. COMPARISONS					
		Percent Abnormal/(n) Examination			
Occupational Category	Group	1982	1985	1987	1992
All	***Ranch Hand***	***2.9 (901)***	***6.5 (879)***	***7.5 (869)***	***17.9 (901)***
	Comparison	***4.5 (1,063)***	***5.3 (1,040)***	***5.4 (1,035)***	***17.6 (1,063)***
Officer	Ranch Hand	3.2 (340)	4.8 (335)	5.4 (333)	14.7 (340)
	Comparison	4.0 (403)	4.3 (395)	4.1 (391)	14.4 (403)
Enlisted Flyer	Ranch Hand	2.5 (159)	8.3 (157)	9.7 (154)	22.0 (159)
	Comparison	8.0 (175)	7.6 (172)	5.8 (174)	21.7 (175)
Enlisted Groundcrew	Ranch Hand	2.7 (402)	7.2 (387)	8.4 (382)	18.9 (402)
	Comparison	3.7 (485)	5.3 (473)	6.4 (470)	18.8 (485)

		Normal in 1982			
Occupational Category	Group	n in 1992	Percent Abnormal in 1992	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	***Ranch Hand***	***872***	***16.0***	***1.04 (0.81,1.33)***	***0.767***
	Comparison	***1,015***	***15.6***		
Officer	Ranch Hand	329	12.5	0.96 (0.62,1.50)	0.863
	Comparison	387	12.9		
Enlisted Flyer	Ranch Hand	155	20.7	1.14 (0.65,1.99)	0.647
	Comparison	161	18.6		
Enlisted Groundcrew	Ranch Hand	391	17.1	1.05 (0.73,1.51)	0.779
	Comparison	467	16.7		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1992 results; results adjusted for age in 1992.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had a normal sedimentation rate ($\leq$12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

Table 9-18. (Continued)
Longitudinal Analysis of Sedimentation Rate
(Discrete)

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN				
	Percent Abnormal/(n) Examination			
Initial Dioxin	1982	1985	1987	1992
Low	6.0 (167)	9.2 (164)	7.2 (166)	19.2 (167)
Medium	1.8 (169)	8.6 (163)	10.9 (165)	23.1 (169)
High	2.4 (168)	8.4 (166)	9.3 (162)	20.2 (168)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Normal in 1982			
Initial Dioxin	n in 1992	Percent Abnormal in 1992	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	157	15.9	1.11 (0.92,1.33)	0.272
Medium	166	21.7		
High	164	18.9		

[a] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had a normal sedimentation rate ($\leq$12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

Table 9-18. (Continued)
Longitudinal Analysis of Sedimentation Rate
(Discrete)

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY				
	Percent Abnormal/(n) Examination			
Dioxin Category	1982	1985	1987	1992
Comparison	4.3 (917)	5.4 (906)	5.1 (906)	17.7 (917)
Background RH	2.3 (342)	3.8 (339)	4.8 (335)	13.7 (342)
Low RH	4.8 (250)	9.4 (244)	8.1 (248)	21.2 (250)
High RH	2.0 (254)	8.0 (249)	10.2 (245)	20.5 (254)
Low plus High RH	3.4 (504)	8.7 (493)	9.1 (493)	20.8 (504)

	Normal in 1982			
Dioxin Category	n in 1992	Percent Abnormal in 1992	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	878	15.7		
Background RH	334	12.0	0.74 (0.51,1.09)	0.126
Low RH	238	18.5	1.18 (0.80,1.72)	0.403
High RH	249	19.3	1.34 (0.93,1.95)	0.120
Low plus High RH	487	18.9	1.26 (0.94,1.69)	0.128

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA, change in body fat from the time of duty in SEA to the date of the blood draw for dioxin, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤10 ppt.
Background (Ranch Hand): Current Dioxin ≤10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin >143 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1992 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Statistical analyses are based only on participants who had a normal sedimentation rate (≤12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

versus 7.4 percent of Comparisons, percentages very similar to the 1985 examination (9.1% vs. 7.3%) and reflecting a symmetrical decline from the Baseline examination (20.0% vs. 14.2%).

Dependent variable-covariate analyses confirmed several associations that have been documented in previous examination cycles. As a group, officers continue to appear healthier than enlisted personnel by several indices including subjective perception of health, appearance of illness or distress, relative age appearance, and percent body fat. In covariate analyses of sedimentation rate, older participants had more abnormally elevated results than younger participants. With occupation as a covariate, enlisted participants appeared to be at detriment relative to officers, but the pattern did not suggest a dose response effect by either continuous or discrete analysis.

The highly significant ($p<0.001$) association in Ranch Hands of the current level of serum dioxin with a negative self-perception of health deserves comment. Subsequent to the 1987 examinations, when no group differences with respect to this variable were defined, serum dioxin data were incorporated in the analyses and individual serum level results were provided to the participants. As noted in Chapter 12, Psychological Assessment, numerous reports have documented the negative psychological and subjective consequences associated with the perception of dioxin exposure. Given that the degree of prior exposure is now established rather than perceived, it is not surprising to find an elevated prevalence of negative self-perceptions of health in those Ranch Hands with the highest levels of serum dioxin. In contrast, as recorded by examining physicians, no group differences were noted in the appearance of illness or distress or relative age appearance.

The percent body fat is easily derived as an objective index related to general health and, to the extent that it can reflect significant weight gain or loss, can serve as a valuable clinical clue to the presence of occult disease. In the current study, the prevalence of obesity was similar in the Ranch Hands and Comparison cohorts. In Ranch Hands, a consistent and highly significant positive association was found in all occupational categories between percent body fat and the current serum dioxin whether calculated on a whole-weight or lipid-adjusted basis. Although a mobile equilibrium exists between serum dioxin and adipose tissue, the current results point strongly to a difference in dioxin pharmacokinetics in obese versus lean individuals. Clinically, it would be difficult to explain the finding of higher levels of dioxin in relatively obese participants on the basis of any health detriment. It is not clear whether a causal relationship exists between dioxin exposure and increased body fat.

In the analyses relating current caloric intake to obesity, 27.1 percent of the participants who reported consuming less than 2,000 calories/day were obese, while only 23.3 percent of the participants who consumed more than 2,000 calories/day were obese. This apparent inconsistency is most likely reflective of the recognized tendency for overweight individuals to underestimate their caloric intake on self-reporting nutrition inventory questionnaires.

The sedimentation rate can be a sensitive, although 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 millimeters per hour is considered within the range of normal at age 65. Extreme elevations in the sedimentation rate are consistently associated with serious underlying

disease, usually malignancy. In prior examinations, Ranch Hands were found to have a significantly higher prevalence of elevated sedimentation rates than Comparisons in a pattern consistent with a dose-response effect. In the current study, no significant differences between Ranch Hands and Comparisons (Model 1) were defined by either discrete or continuous analyses. In the occupation at highest risk, the enlisted groundcrew, Ranch Hands had a slightly higher mean sedimentation rate than Comparisons, but the difference (9.27 mm/hr vs. 8.43 mm/hr) is not clinically significant. In the models employing current serum dioxin, several of the analyses yielded results that were consistent with a subtle dose-response effect, but the differences were slight and the biologic significance is uncertain.

The longitudinal analyses yielded some results that were at variance with previous examinations. Between 1982 and 1987, despite advancing age, a greater than 50-percent reduction occurred in the percentage of Ranch Hands and Comparisons reporting ill health and the initial difference between the cohorts had narrowed to nil. The 1992 examinations revealed reversals in these trends most prominently in those Ranch Hands in the medium and high categories of current and calculated initial levels of serum dioxin. In contrast, in neither the appearance of illness or distress nor relative age appearance were there any significant associations with the current body burden of dioxin. Again the potentially negative subjective effect of established prior exposure is raised.

In the 1985 and 1987 examinations, Ranch Hands were noted to have a significantly higher percentage of abnormal sedimentation rates than Comparisons raising the possibility of a subtle inflammatory effect related to dioxin exposure. In the current study, no significant group differences were defined and the differences in the means across dioxin categories were not biologically significant.

In summary, the general health of the Ranch Hand and Comparison cohorts appears comparable by all objective indices, although significant and increasing group differences in the self-perception of health were evident in the 1992 data.

SUMMARY

Five dependent variables were analyzed in the General Health Assessment, including self-perception of health, appearance of illness or distress, relative age appearance, percent body fat, and sedimentation rate. These five health endpoints were analyzed for associations with group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), current lipid-adjusted dioxin (Model 4), and current whole-weight dioxin (Models 5 and 6). Each of the five variables were analyzed in discrete form; additionally, percent body fat and sedimentation rate were analyzed on a continuous scale. All variables were examined longitudinally. The results of the group, initial dioxin, categorized dioxin, and current dioxin analyses are summarized in Tables 9-19 through 9-22. A summary of group-by-covariate and dioxin-by-covariate interactions is found in Table 9-23.

Table 9-19.
Summary of Group Analyses (Model 1) for General Health Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Questionnaire				
Self-Perception of Health (D)	+0.017	NS	NS	+0.031
Physical Examination				
Appearance of Illness or Distress (D)	NS	NS	NS	ns
Relative Age Appearance (D)	ns	ns	NS	ns
Body Fat (C)	ns	NS	ns	ns
Body Fat (D)	ns	ns	NS	NS
Laboratory				
Sedimentation Rate (C)	NS	ns	NS	NS
Sedimentation Rate (D)	NS	NS	NS	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
NS or ns: Not significant ($p > 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or differences of means nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00 for discrete analyses or difference of means negative for continuous analyses.

Table 9-19. (Continued)
Summary of Group Analyses (Model 1) for General Health Variables
(Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Questionnaire				
Self-Perception of Health (D)	+0.016	NS	NS	+0.023
Physical Examination				
Appearance of Illness of Distress (D)	NS*	NS	NS	ns
Relative Age Appearance (D)	ns	ns	NS	ns
Body Fat (C)	ns	NS	ns	ns
Body Fat with Adjustment for Caloric Intake (C)	ns	NS	ns	ns
Body Fat (D)	ns	NS	NS	NS
Body Fat with Adjustment for Caloric Intake (D)	ns	ns	NS	NS
Laboratory				
Sedimentation Rate (C)	NS	NS	ns	NS*
Sedimentation Rate (D)	NS	NS	ns	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
NS or ns: Not significant ($p > 0.10$).
NS*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or differences of means nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00 for discrete analyses or difference of means negative for continuous analyses.

Table 9-20.
Summary of Initial Dioxin Analyses (Model 2) for General Health Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Questionnaire		
Self-Perception of Health (D)	+0.049	NS
Physical Examination		
Appearance of Illness of Distress (D)	ns	ns
Relative Age Appearance (D)	NS*	NS
Body Fat (C)	ns	ns
Body Fat with Adjustment for Caloric Intake (C)	--	ns
Body Fat (D)	ns	ns
Body Fat with Adjustment for Caloric Intake (D)	--	ns
Laboratory		
Sedimentation Rate (C)	NS	NS*
Sedimentation Rate (D)	NS	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
NS or ns: Not significant ($p>0.10$).
NS*: Marginally significant ($0.05<p\leq0.10$).
--: Not applicable for unadjusted analysis.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or slope nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00 for discrete analyses or slope negative for continuous analyses.

Table 9-21.
Summary of Categorized Dioxin Analyses (Model 3) for General Health Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Questionnaire				
Self-Perception of Health (D)	NS	NS	+ <0.001	+0.001
Physical Examination				
Appearance of Illness or Distress (D)	NS	NS	ns	NS
Relative Age Appearance (D)	ns	ns	NS	ns
Body Fat (C)	ns*	NS	ns	ns
Body Fat (D)	ns	NS	NS	NS
Laboratory				
Sedimentation Rate (C)	ns	NS*	NS	NS*
Sedimentation Rate (D)	ns	NS	NS	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or differences of means nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00 for discrete analyses or difference of means negative for continuous analyses.

Table 9-21. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for General Health Variables (Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Questionnaire				
Self-Perception of Health (D)	NS	NS	+0.005	+0.006
Physical Examination				
Appearance of Illness of Distress (D)	NS	NS	NS	NS
Relative Age Appearance (D)	ns	ns	ns	ns
Body Fat (C)	ns	NS	ns*	ns
Body Fat with Adjustment for Caloric Intake (C)	**(ns)	**(NS)	**(ns*)	**(ns)
Body Fat (D)	ns	NS	NS	NS
Body Fat with Adjustment for Caloric Intake (D)	ns	NS	NS	NS
Laboratory				
Sedimentation Rate (C)	ns	NS	NS	NS*
Sedimentation Rate (D)	ns	NS	NS	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns): Categorized dioxin-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix E-2 for further analysis of this interaction.
**(ns*): Categorized dioxin-by-covariate interaction ($p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix E-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or differences of means for nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00 for discrete and analyses or difference of means negative for continuous analyses.

Table 9-22.
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for General Health Variables (Ranch Hands Only)

	UNADJUSTED		
Variable	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Questionnaire			
Self-Perception of Health (D)	+0.002	+ <0.001	+0.018
Physical Examination			
Appearance of Illness or Distress (D)	ns	ns	ns
Relative Age Appearance (D)	NS	NS	NS
Percent Body Fat (C)	+ <0.001	+ <0.001	+ <0.001
Percent Body Fat (D)	+ <0.001	+ <0.001	+ <0.001
Laboratory			
Sedimentation Rate (C)	+0.014	+0.001	NS*
Sedimentation Rate (D)	+0.019	+0.009	NS*

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00 for discrete analyses; slope nonnegative for continuous analyses.
NS or ns: Not significant.
NS*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or slope nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00.

Table 9-22. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for General Health Variables (Ranch Hands Only)

Variable	ADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Questionnaire			
Self-Perception of Health (D)	**(NS*)	**(+0.024)	**(NS)
Physical Examination			
Appearance of Illness of Distress (D)	**(ns)	**(ns)	**(ns)
Relative Age Appearance (D)	**(ns)	ns	ns
Body Fat (C)	**(+0.001)	+ <0.001	+ <0.001
Body Fat with Adjustment for Caloric Intake (C)	**(+0.001)	+ <0.001	+ <0.001
Body Fat (D)	**(+ <0.001)	+ <0.001	+ <0.001
Body Fat with Adjustment for Caloric Intake (D)	**(+ <0.001)	+ <0.001	+ <0.001
Laboratory			
Sedimentation Rate (C)	+0.045	+0.006	NS
Sedimentation Rate (D)	NS*	+0.001	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00 for discrete analysis; slope nonnegative for continuous analysis.
NS or ns: Not significant.
NS*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns): Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table E-2 for further analysis of this interaction.
**(NS*): Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix E-2 for further analysis of this interaction.
**(...): Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix E-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analyses or slope nonnegative for continuous analyses. A lower case "ns" denotes relative risk less than 1.00.

Table 9-23.
Summary of Dioxin-by-Covariate Interactions from Analyses of General Health Variables

Model	Variable	Covariate
3[a]	Body Fat with Adjustment for Caloric Intake (C)	Caloric Intake
4[b]	Self-Perception of Health (D)	Age
	Appearance of Illness or Distress (D)	Age
	Relative Age Appearance (D)	Occupation
	Body Fat (C)	Occupation
	Body Fat with Adjustment for Caloric Intake (C)	Occupation
	Body Fat (D)	Occupation
	Body Fat with Adjustment for Caloric Intake (D)	Occupation
5[c]	Self-Perception of Health (D)	Age
	Appearance of Illness or Distress (D)	Age
6[d]	Self-Perception of Health (D)	Age
	Appearance of Illness or Distress (D)	Age

C: Continuous analysis.
D: Discrete analysis.

[a] Categorized Dioxin.
[b] Ranch Hands—Log_2 (Current Lipid-Adjusted Dioxin).
[c] Ranch Hands—Log_2 (Current Whole-Weight Dioxin).
[d] Ranch Hands—Log_2 (Current Whole-Weight Dioxin), Adjusted for Total Lipids.

Model 1: Group Analysis

In the unadjusted analysis, the percentage of Ranch Hands that reported their self-perception of health as poor or fair was significantly greater than the percentage of Comparisons that reported their health as poor or fair. Stratification across the three occupational levels revealed a significant difference in self-perception of health between Ranch Hands and Comparisons for the enlisted groundcrew stratum only. The unadjusted analyses of the remaining four variables did not reveal significant group differences.

The adjusted analysis of self-perception of health displayed a significant positive difference between Ranch Hands and Comparisons both overall and for the enlisted groundcrew category. For appearance of illness or distress, a marginally significant group effect was revealed, but this difference was not evident when examined within each of the three occupations. In the continuous adjusted analysis of sedimentation rate, a marginally significant difference was found to exist between Ranch Hands and Comparisons in the enlisted groundcrew stratum with Ranch Hands having a higher mean sedimentation rate than Comparisons. The adjusted results for the remaining dependent variables were nonsignificant. Adjusting the percent body fat analyses for caloric intake did not change the significance of the results.

Model 2: Initial Dioxin Analysis

For the unadjusted analysis of self-perception of health, there was a significant association with initial dioxin with an estimated relative risk of 1.21. In the unadjusted analysis of relative age appearance, a marginally significant increased relative risk of appearing older than one's stated age was found with an increase in initial dioxin. The remaining three dependent variables displayed nonsignificant associations with initial dioxin for the unadjusted analyses.

The adjusted analysis of self-perception of health revealed a nonsignificant relative risk; however, removal of occupation from the final model caused the initial dioxin effect to become significant.

A marginally significant positive relationship between initial dioxin and sedimentation rate in its continuous form was revealed in the adjusted analysis. These were the only relationships of significance in the adjusted analyses of the dependent general health variables. Adjustments for caloric intake in the analyses of percent body fat did not change the significance of the results.

Model 3: Categorized Dioxin Analysis

In the unadjusted analysis of self-perception of health, highly significant differences were seen between the high Ranch Hand and Comparison dioxin categories and for the low plus high Ranch Hand versus Comparison dioxin categories. For both contrasts, the percentage of participants who perceived their health as poor or fair was greater in the Ranch Hand categories than in the Comparison category. For body fat measured in the continuous form, the unadjusted analysis revealed a negative association of marginal significance for

background Ranch Hands versus Comparisons. Marginally significant differences between low Ranch Hands and Comparisons and between low plus high Ranch Hands and Comparisons were revealed in the unadjusted analysis of sedimentation rate in its continuous form. For both of these contrasts, the Ranch Hands exceeded the Comparisons in mean sedimentation rate.

The adjusted analysis of self-perception of health yielded results very similar to the unadjusted analysis. The difference in categorized dioxin between high Ranch Hands and Comparisons was highly significant as was the difference between low plus high Ranch Hands and Comparisons. The relative risk exceeded 1.5 in each of these contrasts.

For the adjusted analysis of body fat expressed in continuous form, the difference between the dioxin categories of high Ranch Hands and Comparisons was marginally significant with mean body fat percentages of 21.70 and 22.01 respectively. No significant differences between the dioxin categories were revealed in the discrete body fat analysis.

For the continuous analysis of body fat with adjustment for caloric intake, there was a significant interaction between categorized dioxin and caloric intake. After removing the interaction from the final model, the difference between the dioxin categories of high Ranch Hands and Comparisons was marginally significant with Comparisons exceeding Ranch Hands. In the discrete analysis of body fat with adjustment for caloric intake, no significant difference between the dioxin categories was observed.

Models 4, 5, and 6: Current Dioxin Analyses

For self-perception of health, each of the Models 4 through 6 unadjusted analyses exhibited a significant positive relationship with current dioxin, where the percentage of abnormalities increased with each level of dioxin. In the Models 4 through 6 unadjusted analyses of body fat in either form, a strong positive association between current dioxin and body fat was displayed. Both the continuous and discrete unadjusted analyses of sedimentation rate revealed a positive significant dioxin effect for Models 4 and 5. The Model 6 unadjusted analyses of sedimentation rate led to marginally significant results.

The Models 4 through 6 adjusted analyses of self-perception of health found the interaction of current dioxin and age to be significant. Removal of the interaction from the final model led to marginally significant and significant positive associations between current dioxin and self-perception of health for Models 4 and 5 only. In addition, the removal of occupation, retained in each of the adjusted analyses, led to a significant current dioxin effect in all three models.

In the adjusted analyses of appearance of illness or distress for Models 4 through 6, a significant interaction between current dioxin and age was evident. After deleting the interaction from the final models, negative associations between current dioxin and appearance of illness or distress were detected, but these associations were nonsignificant.

The adjusted analyses of relative age appearance showed the current dioxin-by-occupation interaction to be significant for Model 4. A significant dioxin effect did not

remain after the interaction was deleted from the final model. The adjusted analyses of Models 5 and 6 led to nonsignificant results.

For both the discrete and continuous adjusted analyses of body fat, a current dioxin-by-occupation interaction was significant for Model 4. Once the interaction was removed from each of the final models, a highly significant positive relationship between current dioxin and body fat remained. Regardless of form, the Models 5 and 6 adjusted analyses displayed highly significant positive associations between current whole-weight dioxin and body fat. Adjusting the analyses of body fat for caloric intake did not change the significance of the results.

For both continuous and discrete analyses of sedimentation rate, positive associations with current dioxin were evident from the results of the adjusted analyses of Models 4 and 5. Both continuous and discrete adjusted analyses of Model 6 showed that the association between sedimentation rate and current dioxin, albeit positive, was nonsignificant. However, the deletion of occupation, retained in the each of the adjusted analyses, yielded a significant current dioxin effect in Models 4, 5, and 6.

CONCLUSION

In the assessment of general health, significant differences between Ranch Hands and Comparisons, the enlisted groundcrew in particular, were evident for self-perception of health. Significant associations between negative self-perception of health and initial and current levels of dioxin were also evident. Because participants were aware of their serum dioxin levels, the possibility of bias in these results should be considered. Participants who knew they possessed an elevated dioxin level or whose occupation implied a greater risk for exposure (i.e., enlisted groundcrew) may consciously or subconsciously have perceived their health to be poorer than did their Comparisons. These results are consistent with the 1985 and 1987 followup examinations. In contrast to self-perception of health, no significant results were found for the appearance of illness or distress and relative age appearance, which were objectively recorded by the examining physicians.

The analyses of percent body fat displayed a significant positive association with current dioxin, whether calculated on a whole-weight or lipid-adjusted basis. These results seem to imply a difference in the dioxin pharmacokinetics in obese versus lean participants but would be difficult to explain clinically. Also, it is not clear whether a causal relationship exists. Sedimentation rate also displayed a significant positive association with current dioxin levels.

In the longitudinal analysis, the increase in the percentage of Ranch Hands who perceived their health to be poor in 1992 from those that were normal in 1982 was significantly associated with initial dioxin levels. Relative age appearance also displayed a significant positive association with initial dioxin. The change in percent body fat from 1982 to 1992 was significantly associated with initial dioxin, and a significant difference between Ranch Hands and Comparisons also was found, especially in enlisted groundcrew.

In conclusion, self-perception of health displayed an association with herbicide exposure, but the results are subject to considerable bias. Percent body fat and sedimentation rate displayed significant associations with current serum dioxin levels.

CHAPTER 9
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