The final interpretation of the exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. The report is expected in 1991.

Physical Examination Data

Composite Skin Test Diagnosis

For officers and for enlisted flyers, the unadjusted overall exposure index analyses comparing the relative frequencies of participants with possibly abnormal skin test reactions for the composite skin test diagnosis were borderline significant ($p=0.090$ and $p=0.100$, respectively). For the officers, the high versus low exposure contrast was borderline significant ($p=0.073$), with the low exposure category having a higher percentage of participants with possibly abnormal readings (8.6%) than the high exposure category (2.0%). For the enlisted flyers, the medium versus low exposure contrast was also borderline significant ($p=0.083$), with the low exposure category having a higher percentage of participants with possibly abnormal readings (15.0%) than the medium exposure category (2.3%). Although the unadjusted overall exposure index analysis for the enlisted groundcrew was not significant, the medium versus low exposure contrast was borderline significant ($p=0.087$), with the medium exposure category having a higher percentage of participants with possibly abnormal readings (12.4%) than the low exposure category (5.1%).

For officers, the adjusted exposure index analysis of the composite skin test diagnosis had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.017$) and a significant exposure index-by-current alcohol use interaction ($p=0.018$). Because of these interactions, the two covariates were trichotomized and contrasts performed within combinations of the covariate strata. For Ranch Hand officers with over 10 pack-years lifetime cigarette smoking history and a current alcohol use of zero to one drink per day, the relative frequency of participants with a possibly abnormal composite skin test was significant ($p=0.035$). The contrast of the high exposure category versus the low exposure category was marginally significant ($p=0.083$; 0.0% and 16.7%, respectively). Without the significant interactions of exposure index-by-lifetime cigarette smoking history and exposure index-by-current alcohol use in the adjusted model, a marginally significant contrast for the high exposure group versus the low exposure group ($p=0.070$) resulted; however, the contrast was not consistent with a dose-response relationship between exposure category and percent possibly abnormal.

For the Ranch Hand enlisted flyers, the adjusted exposure index analysis had a significant exposure index-by-lifetime alcohol history interaction ($p=0.037$). Because of this interaction, lifetime alcohol history was trichotomized on participants with lifetime alcohol history values of 0 drink-years, at most 40 drink-years, and over 40 drink-years. For Ranch Hand enlisted flyers with lifetime alcohol history values over 40 drink-years, the relative frequency of participants having possibly abnormal composite skin test results differed significantly ($p=0.049$) for the low, medium, and high exposure groups (25%, 0%, and 0%, respectively). An adjusted analysis without the exposure index-by-lifetime alcohol history interaction in the model was significant ($p=0.014$).

For the Ranch Hand enlisted groundcrew, the adjusted exposure index model contained two significant interactions: exposure index-by-lifetime alcohol history ($p=0.002$) and exposure index-by-current alcohol use ($p<0.001$). Because of these interactions, the two covariates were trichotomized and contrasts performed within combinations of the covariate strata. For Ranch Hand enlisted groundcrew with lifetime alcohol history values above 40 drink-years and current alcohol use between zero and one drink per day, the relative frequencies of participants with possibly abnormal composite skin test results differed significantly ($p=0.034$) across the low, medium, and high exposure groups (9.1%, 36.4%, and 0.0%, respectively).

None of these analyses was consistent with an expected dose-response relationship since the low dose category in all three analyses had a higher percentage of possibly abnormal skin test diagnoses than the high category.

Laboratory Examination Data: Quantitative Studies--Cell Surface Marker (Phenotypic) Studies

CD2 Cells

The unadjusted average CD2 cell counts were not significantly different among the exposure index categories in all three occupational categories.

For officers, the adjusted exposure index analysis of the CD2 cell counts was not significant.

The adjusted exposure index analysis for the enlisted flyers had a significant exposure index-by-current alcohol use interaction ($p=0.001$). To investigate this interaction, current alcohol use was dichotomized as zero or one drink per day, and over one drink per day. For both strata, neither the medium versus low exposure contrast nor the high versus low exposure contrast was significant.

For enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.017$). This interaction was investigated for the lifetime cigarette smoking history categories of 0 pack-years, at most 10 pack-years, and over 10 pack-years. For those Ranch Hand enlisted groundcrew with lifetime cigarette smoking values not exceeding 10 pack-years, the difference in the adjusted CD2 means for the low versus high exposure contrast was significant ($1,789.3$ cells/mm^3 vs. $1,308.9$ cells/mm^3, respectively; $p=0.010$). For those Ranch Hand enlisted groundcrew having lifetime cigarette smoking values over 10 pack-years, the adjusted mean CD2 level for the high exposure group was marginally greater than the low exposure group ($1,908.9$ cells/mm^3 vs. $1,522.5$ cells/mm^3; $p=0.061$). An adjusted analysis performed without the exposure index-by-lifetime cigarette smoking history interaction was not significant.

CD4 Cells

Stratifying by occupation, the unadjusted analyses of the CD4 cell counts showed no significant differences among the exposure index categories.

However, within the officer occupational strata, the medium versus low exposure contrast was marginally significant (p=0.100), with unadjusted CD4 means of 932.3 cells/mm^3 and 823.2 cells/mm^3, respectively.

For officers, the adjusted exposure index analysis of the CD4 cell counts was not significant.

For enlisted flyers, the adjusted exposure index analysis contained a significant exposure index-by-current alcohol use interaction (p=0.035). Exposure level contrasts were performed within dichotomized current alcohol use categories: zero to one drink per day, and over one drink per day. Within each of these strata, the adjusted CD4 means for the medium versus low exposure contrast and the high versus low contrast were not significant. For the enlisted flyers, an adjusted analysis of the CD4 counts, without the exposure index-by-current alcohol use interaction, was not significant.

For the enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.005). To explore the interaction, lifetime cigarette smoking history was categorized into 0 pack-years, at most 10 pack-years, and over 10 pack-years. For those Ranch Hand enlisted groundcrew with at most 10 pack-years smoking history, the high versus low exposure contrast of the adjusted CD4 means was significant (734.5 cells/mm^3 vs. 1,058.3 cells/mm^3, respectively; p=0.004).

CD8 Cells

The unadjusted exposure index analyses of the CD8 cell counts had no significant differences for any of the occupations.

For officers, the adjusted exposure index analysis of the CD8 cell counts had a significant exposure index-by-age interaction (p=0.002). To investigate this interaction, exposure index contrasts were performed within each of the following age strata: participants born in or after 1942, participants born between 1923 and 1941, and participants born in or before 1922. For the youngest category of Ranch Hand officers, the adjusted mean CD8 level for the high exposure level was greater than that of the low exposure level (690.7 cells/mm^3 vs. 405.5 cells/mm^3; p=0.015). For the oldest group of Ranch Hand officers, significant adjusted mean CD8 levels were found for the medium versus low exposure contrast (399.2 cells/mm^3 vs. 1,121.9 cells/mm^3, respectively; p<0.001) and the high versus low exposure contrast (466.1 cells/mm^3 vs. 1,121.9 cells/mm^3, respectively; p=0.036).

For the enlisted flyer Ranch Hands, the adjusted exposure index analysis of the CD8 cell counts had a significant exposure index-by-current alcohol use interaction (p<0.001). This interaction was explored by stratifying current alcohol use into two strata and contrasting exposure index groups on the adjusted mean CD8 levels within each of the strata. For Ranch Hand enlisted flyers not exceeding one drink per day, the adjusted CD8 mean for the high exposure level was greater than the mean of the low exposure level (674.9 cells/mm^3 vs. 499.6 cells/mm^3; p=0.044). For the Ranch Hand enlisted flyers having over one drink per day, the adjusted mean CD8 levels differed between the medium versus low exposure categories (569.6 cells/mm^3 vs. 244.2 cells/mm^3, respectively; p=0.015).

For the Ranch Hand enlisted groundcrew, the adjusted exposure index analysis had two significant interactions: exposure index-by-lifetime alcohol history ($p=0.008$) and exposure index-by-current alcohol use ($p=0.012$). These interactions were investigated by stratifying both of the alcohol use covariates. For those Ranch Hand enlisted groundcrew with lifetime alcohol history values above 40 drink-years and current alcohol use not exceeding one drink per day, the adjusted mean CD8 level of the medium exposure level was marginally greater than the low exposure level (572.0 cells/mm^3 vs. 339.3 cells/mm^3; $p=0.060$).

CD20 Cells

For each occupation, the unadjusted exposure index analysis of the CD20 cell counts displayed no significant differences.

For Ranch Hand officers, the adjusted exposure index analysis of the CD20 counts had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.009$) and a significant exposure index-by-current cigarette smoking interaction ($p=0.013$). Because of these interactions, both of the smoking covariates were stratified and contrasts performed within the combined strata. For each of the strata combinations, the adjusted means for the CD20 cell counts of the medium exposure versus low exposure groups, and the high versus low exposure groups, were not significant.

For Ranch Hand enlisted flyers, the adjusted exposure index analysis of the CD20 cell counts was not significant.

For Ranch Hand enlisted groundcrew, the adjusted exposure index analysis of the CD20 cells had a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.004$). As a followup to this interaction, exposure index contrasts were performed within the following strata of the lifetime smoking covariate: 0 pack-years, over 0 pack-years and at most 10 pack-years, and over 10 pack-years. Within the 0 pack-year strata, the adjusted mean CD20 level for the medium exposure category was marginally lower than the mean CD20 level of the low exposure category (134.3 cells/mm^3 vs. 206.4 cells/mm^3; $p=0.059$). For the middle smoking history strata, the high versus low exposure contrast was significant ($p=0.049$). The low exposure level had a higher adjusted mean than the high exposure level (227.5 cells/mm^3 vs. 158.0 cells/mm^3). For Ranch Hand enlisted groundcrew with over 10 pack-years smoking history, the medium versus low exposure contrast was marginally significant ($p=0.077$) and the high versus low exposure contrast was significant ($p=0.014$). Within the over 10 pack-year lifetime cigarette smoking history strata, the adjusted mean CD20 levels exhibited a dose-response relation with the exposure index (low: 150.9 cells/mm^3; medium: 204.5 cells/mm^3; high: 238.7 cells/mm^3).

CD14 Cells

For the unadjusted exposure index analyses of the CD14 cell counts, the enlisted flyers displayed a borderline significant difference ($p=0.078$). The unadjusted means were inversely related to the exposure index (low, 39.4 cells/mm^3; medium, 29.8 cells/mm^3; high, 22.9 cells/mm^3). The contrast

of high exposure versus low exposure of the CD14 cell counts was significant (p=0.025) for the enlisted flyers. No other unadjusted exposure index analyses were significant.

For Ranch Hand officers, the adjusted exposure index analysis of the CD14 cell counts was not significant.

For Ranch Hand enlisted flyers, the adjusted means of the CD14 cell counts did not differ significantly among exposure index categories. However, the high exposure versus low exposure contrast was borderline significant (20.3 cells/mm^3 vs. 32.0 cells/mm^3, respectively; p=0.075).

The adjusted exposure index analysis for the Ranch Hand enlisted groundcrew contained a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.020) and a significant exposure index-by-current alcohol use interaction (p=0.043). To explore these interactions, current alcohol use was dichotomized as zero or one drink per day and over one drink per day and lifetime cigarette smoking history was dichotomized as at most 10 pack-years and over 10 pack-years. For Ranch Hand enlisted groundcrew with lifetime cigarette smoking history values of at most 10 pack years and a current alcohol use value of zero to one drink per day, the adjusted mean for the medium exposure level (19.5 cells/mm^3) was significantly different (p=0.036) from that of the low exposure level (29.4 cells/mm^3). For Ranch Hand enlisted groundcrew with lifetime cigarette smoking history values over 10 pack-years and a current alcohol use value of zero or one drink per day, the medium exposure versus low exposure contrast was significant (36.5 cells/mm^3 and 21.6 cells/mm^3, respectively; p=0.023). Without the two specified interaction terms in the adjusted model, the adjusted exposure index analysis was not significant. No consistent patterns were evident in these interactions.

CD25 Cells

For the CD25 cell counts, the unadjusted exposure index analyses were not significant for any of the occupations. Similar to the core analyses, both the proportions of zero CD25 values and the means of the positive CD25 values were compared across exposure index categories. For the former, there were no significant differences in the proportions of zero CD25 values across exposure category for any occupation. For the latter, the high versus low exposure contrast was borderline significant (low, 13.8 cells/mm^3; medium, 11.1 cells/mm^3; high, 9.3 cells/mm^3; p=0.095) for the enlisted groundcrew.

For the Ranch Hand officers, the adjusted exposure index analysis on positive CD25 values had a significant exposure index-by-lifetime alcohol history interaction (p=0.012). The lifetime alcohol history covariate was trichotomized as 0 drink-years, not more than 40 drink-years, and over 40 drink-years. Within each of these strata, the adjusted mean CD25 levels were contrasted for medium versus low exposure and for high versus low exposure. For those Ranch Hand officers with over 40 drink-years for lifetime alcohol history, the high versus low exposure contrast of the adjusted CD25 means was borderline significant (46.5 cells/mm^3 vs. 12.7 cells/mm^3, respectively; p=0.051). Exposure index analyses were not significant without the exposure index-by-lifetime alcohol history interaction term in the adjusted model.

For both the Ranch Hand enlisted flyers and the enlisted groundcrew, no significant differences were found for the adjusted exposure index analysis of the positive CD25 cell counts.

HLA-DR Cells

For the unadjusted exposure index analysis of the HLA-DR cell counts, the overall exposure index comparisons were not significant for any of the occupations. However, for the enlisted flyers, the high versus low exposure contrast of the average HLA-DR cell counts was borderline significant and exhibited a dose-response relationship (low, 504.1 cells/mm^3; medium, 416.1 cells/mm^3; high, 389.0 cells/mm^3; p=0.069).

For the Ranch Hand officers and the enlisted flyers, the adjusted exposure index analyses of the HLA-DR cell counts were not significant.

For the Ranch Hand enlisted groundcrew, the adjusted exposure index analysis of the HLA-DR cell counts contained a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.011). After lifetime cigarette smoking history was trichotomized as 0 pack-years, not more than 10 pack-years, and over 10 pack-years, adjusted HLA-DR means were compared within each strata. For the zero pack-year strata, the adjusted HLA-DR cell mean contrast for the medium versus low exposure categories was significant (325.4 cells/mm^3 vs. 475.3 cells/mm^3, respectively; p=0.013). For the middle lifetime cigarette smoking history category, the high versus low exposure contrast was significant (369.7 cells/mm^3 vs. 491.5 cells/mm^3, respectively; p=0.022). For Ranch Hand enlisted groundcrew with over 10 pack-years lifetime cigarette smoking history, the adjusted HLA-DR mean for the medium exposure category was marginally greater (p=0.059) than the HLA-DR mean for the low exposure category, and the adjusted mean for the high exposure category was significantly greater (p=0.010) than the adjusted mean for the low exposure category (low: 383.9 cells/mm^3; medium: 476.9 cells/mm^3; high: 528.6 cells/mm^3). An adjusted analysis, performed without the exposure index-by-lifetime cigarette smoking history interaction, was not significant.

CD4/CD8 Ratio

No significant differences were found for the unadjusted exposure index analyses of the CD4/CD8 ratio values.

For the Ranch Hand officers, the adjusted exposure index analysis of the CD4/CD8 ratios had a significant exposure index-by-age interaction (p<0.001). Age was trichotomized as participants born in or after 1942, born between 1923 and 1941, and born in or before 1922 for investigation of this interaction. For the oldest Ranch Hand officers, the adjusted means for the CD4/CD8 ratios differed between the medium and low exposure groups (p=0.001) and between the high and low exposure groups (p=0.044). For these Ranch Hand officers, the adjusted CD4/CD8 ratio means for the low, medium, and high exposure groups were 0.54, 1.57, and 1.30, respectively.

For the Ranch Hand enlisted flyers, the adjusted overall exposure index analysis of the CD4/CD8 ratios was not significant. However, the contrast of

the adjusted means for the high exposure versus low exposure groups was borderline significant (1.58 vs. 1.98, respectively; p=0.080).

For the Ranch Hand enlisted groundcrew, the exposure index-by-current alcohol use interaction was significant (p=0.015) for the CD4/CD8 ratios. Because of this interaction, current alcohol use was dichotomized as zero to one drink per day, and over one drink per day. For those Ranch Hand enlisted groundcrew having more than one drink per day, the adjusted CD4/CD8 mean for the high exposure level differed marginally from the adjusted CD4/CD8 mean of the low exposure level (6.80 vs. 2.04, respectively; p=0.067). Exposure index analyses were not significant without the interaction term in the model.

Laboratory Examination Data: Quantitative Studies--TLC

No differences were detected in the unadjusted and adjusted analyses of the officer and enlisted flyer cohorts. In the unadjusted analysis of the enlisted groundcrew cohort, there was a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.004). Stratifying by lifetime cigarette smoking history, a significant difference (p=0.031) in the high versus low contrast was found for Ranch Hand smokers with a history of 10 pack-years or less and a marginally significant difference (p=0.058) in the high versus low exposure contrast for Ranch Hand smokers with a history of over 10 pack-years.

Laboratory Examination Data: Quantitative Studies--Quantitative Immunoglobulins

IgG

There were no significant differences identified in the unadjusted exposure index analyses of IgG. The adjusted analyses of the enlisted flyer cohort also revealed no significant differences.

In the adjusted analysis of the officer cohort, the overall and high versus low exposure contrasts were significant (p=0.032 and p=0.012, respectively). The adjusted means were 962.6 mg/dl, 1,032.7 mg/dl, and 1.242.6 mg/dl, for the low, medium, and high exposure categories, respectively.

For the enlisted groundcrew cohort, there was a significant exposure index-by-lifetime cigarette smoking history interaction (p=0.001). Stratifying by lifetime cigarette smoking history revealed a significant difference in the nonsmokers for the high versus low exposure contrast (adjusted means: 1,148.3 mg/dl for low, 1,208.2 mg/dl for medium, and 1,278.7 mg/dl for high; p=0.036). The high versus low exposure contrast for the heavy smokers was borderline significant (adjusted means: 1,219.3 mg/dl for low, 1,178.3 mg/dl for medium, and 1,149.7 mg/dl for high; p=0.086).

IgA

No significant differences were detected in the unadjusted analysis of the officer cohort. There were also no differences identified in the adjusted analysis without a significant exposure index-by-current cigarette smoking interaction (p=0.032). After stratifying by current smoking, the high versus low exposure contrast for the nonsmokers was significant (p=0.019), and the medium versus low exposure contrast was borderline significant (p=0.085). The adjusted means for the nonsmoking officers were 232.97 mg/dl, 196.15 mg/dl, and 184.98 mg/dl for the low, medium, and high exposure categories, respectively. The medium versus low exposure contrast for the heavy smokers was also significant (adjusted means: 228.23 mg/dl for low, 125.91 mg/dl for medium, and 185.50 mg/dl for high; p=0.002).

In the unadjusted analysis of the enlisted flyer cohort, the medium versus low exposure contrast was marginally significant (p=0.091). The mean of the low exposure category was 225.57 mg/dl, as compared to means of 195.85 mg/dl and 215.75 mg/dl for the medium and high exposure categories, respectively. The medium versus low exposure contrast of the adjusted analysis of the enlisted flyer cohort was also marginally significant (p=0.091).

For the enlisted groundcrew cohort, no differences were detected in the unadjusted analysis. In the adjusted analysis, there was a significant exposure index-by-lifetime alcohol history interaction (p=0.012). Stratifying by lifetime alcohol history to explore the interaction revealed no significant differences. Without the exposure index-by-lifetime alcohol history interaction in the model, there were no significant differences.

IgM

The unadjusted and adjusted exposure index analyses of IgM did not reveal any significant differences among exposure levels for the three occupational cohorts.

Laboratory Examination Data: Functional Stimulation Tests

Unstimulated PHA Responses

For each occupation, the unstimulated PHA responses of day 1 and day 2 were analyzed concurrently to assess differences among exposure index categories. The unadjusted exposure index analysis was performed using a two-factor model (containing exposure index, day, and exposure index-by-day interaction terms) assuming repeated measures across one factor (day). For each occupation, there were no significant differences among the unstimulated mean PHA responses of the high, medium, and low exposure index categories.

For the adjusted exposure index repeated measures analysis of the day 1 and day 2 unstimulated PHA responses, neither the officers nor the enlisted flyers had significant differences among the exposure index categories. For the enlisted groundcrew, the adjusted model had a significant exposure

index-by-current alcohol use interaction (p=0.047) and a significant exposure index-by-lifetime alcohol history interaction (p=0.027). Stratifying by current alcohol use and lifetime alcohol history, Ranch Hands having at most one drink per day and lifetime alcohol history above 40 drink-years had a significant medium versus low exposure contrast (1,767 cpm vs. 3,708 cpm, respectively; p=0.012). The adjusted analysis for the enlisted groundcrew was repeated without the two interaction terms included in the model. The adjusted means were not significantly different among the exposure index categories for this secondary model.

PHA Net Response for Day 1 at Concentration Level 1

For the PHA net responses for day 1 at concentration level 1, both the unadjusted and the adjusted analyses displayed no significant differences across exposure index categories for any occupation.

PHA Net Response for Day 1 at Concentration Level 2

For each occupation, the overall unadjusted exposure index comparisons of the PHA net responses for day 1 at concentration level 2 were not significant. However, among the enlisted flyers group, the medium versus low exposure contrast was marginally significant (low, 173,558 cpm; medium, 136,739 cpm; high, 171,800 cpm; p=0.077).

For the adjusted exposure index analysis, the enlisted flyers exhibited a borderline significant difference (p=0.053) on the PHA net responses for day 1 at concentration level 2. The average net responses for the low, medium, and high exposure groups were 149,371 cpm, 110,819 cpm, and 151,799 cpm, respectively. The medium versus low exposure contrast was borderline significant (p=0.053). Adjusted exposure index analyses for both the officers and the enlisted groundcrew were not significant for the PHA net responses of day 1 at concentration level 2.

PHA Net Response for Day 1 at Concentration Level 3

For enlisted flyers, the unadjusted exposure index analysis of the PHA net responses for day 1 at concentration level 3 was marginally significant (p=0.067). For the enlisted flyers, the medium versus low exposure contrast was significant (low, 165,631 cpm; medium, 126,209 cpm; high, 158,427 cpm; p=0.033). Neither the officers nor the enlisted groundcrew had significant unadjusted exposure index analyses for the PHA net responses for day 1 at concentration level 3.

The enlisted flyers had a borderline significant difference (p=0.056) for the overall exposure index analysis of the PHA net responses for day 1 at concentration level 3. The average net responses for the low, medium, and high exposure groups were 143,234 cpm, 109,316 cpm, and 145,490 cpm, respectively. The medium versus low exposure contrast was also borderline significant (p=0.057). Adjusted exposure index analyses for both the officers and the enlisted groundcrew were not significant for the PHA net responses of day 1 at concentration level 3.

PHA Net Response for Day 2 at Concentration Level 1

For the unadjusted exposure index analysis of the PHA net responses for day 2 at concentration level 1, no significant differences were found for any of the occupations.

For the adjusted exposure index analysis of the PHA net responses for day 2 at concentration level 1, no significant differences were found for either the officers or the enlisted flyers. For the enlisted groundcrew, the adjusted exposure index analysis had a significant exposure index-by-age interaction ($p=0.035$). To explore this interaction, age was dichotomized into those participants born in or after 1942 and those born before 1942. Within each age stratum, no significant contrasts were found. Without the exposure index-by-age interaction, the adjusted analysis for the enlisted groundcrew showed no significant difference for exposure index.

PHA Net Response for Day 2 at Concentration Level 2

For each occupation, the unadjusted and the adjusted exposure index analyses of the PHA net responses for day 2 at concentration level 2 were not significant.

PHA Net Response for Day 2 at Concentration Level 3

Unadjusted exposure index analyses of the PHA net responses for day 2 at concentration level 3 were not significantly different for any occupation.

For Ranch Hand enlisted flyers and enlisted groundcrew, the adjusted exposure index analysis of the PHA net responses for day 2 at concentration level 3 were not significant. For the Ranch Hand officers, the adjusted model had a significant exposure index-by-current cigarette smoking interaction ($p=0.014$). To investigate this interaction, the smoking covariate was stratified into four categories: 0 cigarettes per day--never smoked, 0 cigarettes per day--formerly smoked, at most 20 cigarettes per day, and over 20 cigarettes per day. For Ranch Hand officers who were former smokers, the adjusted mean PHA net response for the high exposure category was significantly lower than the mean for the low exposure category (94,234 cpm vs. 130,372 cpm; $p=0.023$). Also, for Ranch Hand officers who smoked over 20 cigarettes per day, the adjusted mean PHA net response for the medium exposure category was greater than that of the low exposure category (178,503 cpm vs. 81,091 cpm; $p=0.003$). An adjusted analysis performed without the interaction in the model did not result in a significant difference among exposure index categories.

Overall PHA Net Response

For the six PHA net responses of day 1 and day 2 at each of three concentration levels, unadjusted exposure index analyses were performed for each occupation assuming a three-factor repeated measures analysis framework (exposure index, day, concentration, associated two-factor interactions, and a three-factor interaction). The overall exposure index contrast was not significant for any of the occupations.

For the adjusted analysis using covariate information, the three-factor repeated measures analysis of all six PHA net responses simultaneously exhibited no significant difference across exposure category by occupation.

Maximum of Day and Concentration Level PHA Net Response

No significant differences were found in the unadjusted analyses or the adjusted analyses of each occupational cohort.

Unstimulated MLC Response

For each occupation, the unadjusted exposure index analyses were not significant for the unstimulated MLC responses.

For the Ranch Hand officers and enlisted groundcrew, the adjusted exposure index analysis comparisons of the unstimulated MLC response adjusted means were not significant across the low, medium, and high exposure categories. For enlisted flyers, the adjusted exposure index analysis had a significant exposure index-by-age interaction ($p=0.046$). Because of this interaction, age was dichotomized as participants born in or after 1942 and those born before 1942. Within each age stratum, there were no significant differences for either the medium versus low exposure contrast or the high versus low exposure contrast. An adjusted exposure index model was also used without the exposure index-by-age interaction term included. No significant differences were found for the overall contrast or the paired contrasts of medium versus low exposure and high versus low exposure for this secondary model.

MLC Net Response

For each occupation, the unadjusted and adjusted exposure index analyses of the MLC net responses did not display significant differences for either the overall contrast or the paired contrasts of medium versus low exposure and high versus low exposure.

NKCA 50/1 Net Response

For the NKCA 50/1 net response, the unadjusted exposure index analysis displayed no significant differences for any occupation.

For both Ranch Hand officers and enlisted groundcrew, the adjusted exposure index analysis of the NKCA 50/1 net response was not significant. For Ranch Hand enlisted flyers, the adjusted model contained a significant exposure index-by-lifetime cigarette smoking history interaction ($p=0.015$). Because of this interaction, exposure index contrasts were performed within each of three categorized levels of the lifetime cigarette smoking history covariate (0 pack-years, over 0 pack-years to 10 pack-years, and over 10 pack-years). For Ranch Hand enlisted flyers who had never smoked, the adjusted mean of the NKCA net response for the high exposure level was marginally less than the adjusted mean of the low exposure level (316.3 cpm

vs. 589.2 cpm; p=0.051). For Ranch Hand enlisted flyers with at most 10 pack-years lifetime smoking history, the adjusted mean of the medium exposure level was marginally greater than the adjusted mean of the low exposure level (571.4 cpm vs. 376.8 cpm; p=0.066). Without the exposure index-by-lifetime cigarette smoking history interaction in the adjusted model, the exposure index was not significant for the enlisted flyers.

NKCA 50/1 Percent Release

For each of the three occupations, the unadjusted exposure index analysis exhibited no significant differences for the NKCA 50/1 percent release.

For Ranch Hand officers and enlisted flyers, there were no significant differences for the adjusted exposure index analysis of the NKCA 50/1 percent release. However, for the Ranch Hand enlisted groundcrew, the adjusted model contained a significant exposure index-by-age interaction (p=0.014). As a result of that interaction, exposure index contrasts were performed within dichotimized strata of the age covariate (participants born in or after 1942 and those born before 1942). For those born before 1942, the adjusted mean percent release for the medium exposure category was significantly greater than the adjusted mean of the low exposure category (43.1 vs. 32.8; p=0.041). Without the exposure index-by-age interaction, the adjusted analysis was not significant.

NKCI 50/1 Net Response

For each of the three occupations, the unadjusted exposure index analyses for the NKCI 50/1 net response was not significant. However, for officers, the high versus low exposure index contrast was borderline significant (p=0.069).

For each occupation, the adjusted exposure index analyses of the NKCI net response were not significant.

NKCI 50/1 Percent Release

For the NKCI 50/1 percent release, the unadjusted exposure index analyses were not significant for each occupation.

For the Ranch Hand officers and enlisted flyers, the adjusted exposure index analyses of the NKCI percent releases were not significant. For the Ranch Hand enlisted groundcrew, there was a significant exposure index-by-age interaction (p=0.042). Age was dichotomized into participants born in or after 1942 and those born before 1942. For the latter stratum, the adjusted mean percent release of the medium exposure level was marginally greater than the adjusted mean of the low exposure level (71.4 vs. 64.9; p=0.094). An adjusted exposure index analysis was performed without the exposure index-by-age interaction in the model was not significant.

TABLE 19-14.

Longitudinal Analysis of CD4/CD8 Ratio:
A Contrast of 1985 Followup and 1987 Followup Examination Means

Variable	Examination	Group Means*		p-Value* (Equality of Differences)
		Ranch Hand	Comparison	
CD4/CD8 Ratio	1985 Followup	1.63	1.60	0.908
	1987 Followup	1.94	1.91	

Note: Summary statistics for the 1985 followup and the 1987 followup are based on 318 Ranch Hands and 417 Comparisons who took the immunologic examination at both the 1985 and 1987 followup examinations.

*Means transformed from the natural logarithm scale; hypothesis test performed on the natural logarithm scale.

Longitudinal Analysis

For the immunology assessment, the CD4/CD8 ratio was analyzed (unadjusted for any covariates) for longitudinal differences between the 1985 followup and the 1987 followup examinations. Table 19-14 shows that there was no significant difference in the change over time between Ranch Hands and Comparisons (p=0.908).

DISCUSSION

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

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

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

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

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

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

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

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

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

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

SUMMARY

For the 1987 followup immunologic assessment, a number of unadjusted and adjusted analyses were performed using physical examination (composite skin test diagnosis) and laboratory examination data (cell surface marker studies, TLC, quantitative immunoglobulin measurements, and functional stimulation tests). The results of the Ranch Hand and Comparison group contrasts performed using the physical examination and laboratory examination data are summarized in Table 19-15.

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

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

TABLE 19-15.

Overall Summary Results of Unadjusted and Adjusted Analyses of Immunologic Variables

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

TABLE 19-15. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses of Immunologic Variables

D: Discrete analysis performed.

** (0.011): Group-by-covariate interaction ($0.01<p\leq0.05$); significant ($p=0.011$) when interaction is deleted.

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

C: Continuous analysis performed.

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

--Analysis not done.

** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table P-3 for a detailed description of this interaction.

****: Group-by-covariate interaction ($p\leq0.01$); refer to Table P-3 for a detailed description of this interaction.

ratio; the remaining 1985 followup cell surface marker variables had significant group-by-covariate interactions in the adjusted models.

Unadjusted and adjusted group contrasts were not significant for TLC.

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

For the functional stimulation tests of the 1987 followup study, unadjusted and adjusted analyses were performed on a number of measures pertaining to responses after mitogen stimulation with PHA, mixed lymphocyte responses to stimulation from donor lymphocytes, and NKCA and NKCI.

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

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

For the PHA net response for day 1, the unadjusted group contrast at each of the three concentration levels was not significant. The adjusted group contrasts of the PHA net response for day 1 at concentration levels 2 and 3 were also not significant. However, the adjusted analysis of the PHA net

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

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

For the unstimulated MLC response, both the unadjusted and the adjusted group contrasts were not significant. For the MLC net response, the unadjusted group contrast was not significant and the adjusted analysis had a significant group-by-race interaction. Because of this interaction, group contrasts were performed within race strata. Among Blacks, the Ranch Hands had a marginally significantly lower average MLC net response than the Comparisons ($p=0.059$). An interaction with smoking history was seen in 1985.

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

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

For the exposure index analysis of the cell surface marker measures, the unadjusted analysis generally showed no significant difference for each occupation. For the adjusted exposure index analyses of an individual cell surface marker variable, an exposure index-by-covariate interaction was

generally found for at least one occupation. For the most part, the interactions involved the covariates of age, lifetime cigarette smoking history, current alcohol use, or lifetime alcohol history.

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

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

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

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

The unadjusted exposure index analyses of the NKCA and NKCI net responses and percent releases were not significant for each occupation. For the exposure index adjusted analysis of the NKCA net response, the enlisted flyers had a significant exposure index-by-lifetime cigarette smoking history

interaction. For the exposure index adjusted analyses of the NKCA and the NKCI percent release, the enlisted groundcrew had significant exposure index-by-age interactions. Overall, the exploration of covariate interactions in the exposure index analyses detected scattered increases and decreases in cell count and functional assays that are impossible to interpret in the absence of a consensus as to what is abnormal for these measures of immunity.

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

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

CHAPTER 19

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CHAPTER 20

PULMONARY DISEASE

INTRODUCTION

Background

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

Little research has been done on possible pulmonary effects of TCDD or other dioxin-related compounds. Animal studies have been limited to in vitro determination of the binding of TCDD to lung tissue components. Tissue obtained from the lung included cytosol from rat lung, which showed a high-affinity, low-capacity binding complex for TCDD.[1] Human lung cytosols from normal lung tissue taken from 53 adults were used to establish the Ah receptor for TCDD and other polycyclic aromatic hydrocarbons. Indications were obtained of a genetic basis for Ah receptor levels for these compounds (implying a genetic basis for chemically induced cancer).[2] Other studies have focused on the mechanism of cytochrome P-450 induction in rabbit pulmonary tissue; these results have not been extrapolated to possible health effects.[3-5]

In humans, lung cancers have been associated with MCPA [(2,4-dichlorophenoxy)-acetic acid] and 2,4,5-T exposures in a Danish study of phenoxy herbicides manufacturing workers, but other pulmonary diseases were not investigated.[6,7]

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

Only one contemporary morbidity study has attributed pulmonary dysfunction to phenoxy herbicide and TCDD exposure.[8] The percent abnormal pulmonary parameters of forced expiratory volume (FEV), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1)/FVC ratio, and forced mid-expiratory flow rate were significantly higher in exposed workers who currently smoke than in nonexposed workers who smoke. In considerable contrast, these test parameters were essentially equal in nonsmokers and former smokers of both the exposed and nonexposed groups. The effect of current smoking persisted after a logistic regression analysis adjusting for pack-years of cigarette smoking. Adjusted means of the test parameters FEV, FVC, and FEV_1/FVC also showed significant differences for current smokers but not for nonsmokers or former smokers.

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

Baseline Summary Results

The 1982 Baseline examination explored historical pulmonary disease by questionnaire and active pulmonary function by standardized spirometric technique. These areas were of significant interest because of suggested operational inhalation of Herbicide Orange by all Ranch Hand flying crewmen as well as ground maintenance personnel.

The questionnaire revealed no group differences for historical diagnoses of tuberculosis and fungal infections, pneumonia, cancer, or chronic sinusitis and upper respiratory disease. At the physical examination, the unadjusted means for FEV_1 (percent predicted), FVC, and the FEV_1/FVC ratio were almost identical between the Ranch Hands and Comparisons. Adjusted mean values were not calculated due to significant interactions (group-by-age for FEV_1 and FVC; group-by-smoking with FEV_1/FVC).

Detailed exposure analyses showed two significant associations in the enlisted flyer and enlisted groundcrew strata, but neither was indicative of a linear dose response. Attempts to adjust the means of the pulmonary function values for age and smoking revealed several interactions, but essentially negative results.

Overall, there were no pulmonary disease or pulmonary function data or associations of concern.

1985 Followup Study Summary Results

Because of the essentially negative pulmonary analyses from the Baseline examination, pulmonary function (spirometric) studies were not performed during the 1985 followup examination. Collection of pulmonary data was limited to a questionnaire history of respiratory disease, physical examination of the thorax and lungs, and pulmonary abnormalities detected on a routine chest x ray. Mortality due to respiratory disease was also evaluated.

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

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

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

Parameters of the 1987 Pulmonary Assessment

Dependent Variables

Questionnaire, physical examination, and laboratory data were used in the pulmonary assessment for the 1987 followup.

Questionnaire Data

In the self-administered family and personal history section, each study participant was asked whether he had ever experienced the following conditions: asthma, bronchitis, pleurisy, pneumonia, and tuberculosis. These five variables, based on self-reported and unverified information, were analyzed as a measure of the pulmonary health status of each participant.

No participants were excluded for medical reasons from the analysis of these variables.

Physical Examination Data

Part of the pulmonary assessment was based on the results of the physical examination of the thorax and lungs, and pulmonary abnormalities detected on a routine chest x ray. The following seven variables from the radiologic and physical examinations were analyzed in the pulmonary assessment: asymmetrical expansion, hyperresonance, dullness, wheezes, rales, thorax and lung abnormalities (a composite variable including all of the previous conditions), and x-ray interpretation. These variables were coded as normal/abnormal for x-ray interpretation, and as yes/no for the other variables.

No participants were excluded for medical reasons from the analysis of these variables.

Laboratory Examination Data

The 1987 assessment included the analysis of pulmonary physiologic data collected during the physical examination employing standard spirometric techniques. Numerous indices were derived including (1) FVC, a measurement of the amount of air in liters expelled from maximum inspiration to full expiration; (2) FEV, in liters, an index derived from the FVC that quantifies the amount of air expelled at 1 second (FEV_1), 2 seconds (FEV_2), and 3 seconds (FEV_3); and (3) forced expiratory flow (FEFmax), an index of peak instantaneous flow in liters per second during a forced expiration. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. In addition, the ratio of FEV_1 to FVC was calculated as an index reflective of obstructive airways disease. For these indices, lower values indicate greater compromise in the lung function. These variables were analyzed as continuous variables. For the ratio of observed FEV in 1 second to observed FVC, the natural logarithm of 1 minus the ratio transformation was used. Loss of vital capacity and obstructive abnormality were classified as none, mild, moderate, or severe and were analyzed as part

of the 1987 pulmonary assessment. Results judged to be between none and mild were classified as mild for all analyses. A similar methodology was used for results between mild and moderate, and between moderate and severe, where the next most abnormal category was applied. Due to the low frequencies in the moderate and severe categories, these two categories were combined in the analysis.

As a guide for determining abnormal pulmonary function, readings below the 95th percentile are considered abnormal for the FVC and FEV_1. For men above 36 years of age, the corresponding percent of predicted is 74 percent for the FVC and 73 percent for the FEV_1. An FVC or FEV_1 below 40 percent of predicted is considered severely impaired, as recommended by the American Thoracic Society. The division between mild, moderate, and severe impairment is arbitrarily defined by dividing the interval between severe impairment and the lower limit of normal into two equal bands. That is, the cutpoint between mild and moderate impairment is at 57 percent of the predicted value. Although the other spirometric indices (FEV_2, FEV_3, FEFmax, FEV_1/FVC) and the appearance of the flow volume curve are useful to the physician interpreting the test, there are no good statistical data to support arbitrary lower limits of normal or cutpoints to classify impairment as mild, moderate, or severe.

No participants were excluded for medical reasons from the analysis of these variables.

Covariates

The effects of age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history were examined in the assessment of pulmonary function, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Current cigarette smoking and lifetime cigarette smoking history were based on self-reported questionnaire data.

In the discussion of the smoking covariates, the different classes of current cigarette smoking are (1) nonsmokers (those who never smoked cigarettes, shown as 0-Never in Table 20-1); (2) former smokers (those who used to smoke cigarettes but currently do not, shown as 0-Former); (3) moderate smokers (those who smoke, on the average, more than 0 but not more than 20 cigarettes per day); and (4) heavy smokers (those who smoke, on the average, more than 20 cigarettes per day). The categories of lifetime cigarette smoking history are (1) 0 pack-years or nonsmokers; (2) greater than 0 but not more than 10 pack-years, which will be referred to as moderate smokers; and (3) greater than 10 pack-years or heavy smokers.

Age and lifetime cigarette smoking history were used in the continuous form for modeling purposes in all general linear models and logistic regression analyses; these variables were discretized for use in log-linear analyses. These covariates were also discretized for presentation purposes (e.g., dependent variable-covariate associations and interaction summaries). Current cigarette smoking was discretized in adjusted analyses for eight dependent variables (asthma, bronchitis, pleurisy, pneumonia, rales, x ray, loss of vital capacity, and obstructive abnormality) and was used in its continuous form for adjusted analyses of the other dependent variables.

Several relationships between group and the covariates and among covariates are of special interest in interpreting subsequent analyses. As discussed in Chapter 2, Ranch Hands currently smoke more cigarettes per day,

on the average, than Comparisons (p=0.014). Enlisted flyers and enlisted groundcrew smoke more cigarettes per day (means of 11.1 and 10.4, respectively) than officers (4.7). In terms of lifetime cigarette smoking history, enlisted flyers have, on the average, smoked more (a mean of 19.2 pack-years) than either the enlisted groundcrew or officers (14.0 pack-years and 12.8 pack-years, respectively). Associations for both smoking variables with occupation are significant ($p<0.001$). Nonblacks also have a stronger history of cigarette smoking than Blacks.

Relation to Baseline and 1985 Followup Studies

In general, the same variables that were analyzed in the 1987 followup study were analyzed at Baseline, although a slightly different classification of reported pulmonary disease was used in the Baseline analyses. In the 1985 followup, the pulmonary physiology data were not collected. The questionnaire and physical examination data analyzed in the 1987 followup were analyzed for the 1985 followup.

In the longitudinal analysis, group differences in the changes from Baseline in the ratio of observed FEV in 1 second to observed FVC were analyzed.

Statistical Methods

Table 20-1 summarizes the statistical analyses performed for the 1987 pulmonary assessment. The first part of this table lists the dependent variables analyzed, the source of the data, the form of the data (discrete/continuous), cutpoints (if applicable), the candidate covariates, and the statistical methods. The basic statistical analysis methods used are described in Chapter 7. The second part of this table provides a further description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Due to the low number of abnormalities, adjusted analyses of tuberculosis, asymmetric expiration, and dullness were not conducted.

Although no participants were excluded for medical reasons in the pulmonary assessment, dependent variable data were missing in some cases. The number of participants with missing data is provided in Table 20-2 by group and variable.

RESULTS

Ranch Hand and Comparison Group Contrast

Questionnaire Variables

The results of the unadjusted and adjusted Ranch Hand and Comparison group contrasts for the questionnaire variables of the pulmonary assessment are summarized in Tables 20-3 and 20-4, respectively. Table Q-1 of Appendix Q

TABLE 20-1.

Statistical Analysis for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Asthma	Q-SR	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Bronchitis	Q-SR	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Pleurisy	Q-SR	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Pneumonia	Q-SR	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Tuberculosis	Q-SR	D	No Yes	--	UC:FT UE:CS,FT
Thorax and Lung Abnormalities	PE	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Asymmetric Expansion	PE	D	No Yes	--	UC:FT UE:CS,FT
Hyperresonance	PE	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 20-1. (continued)

Statistical Analysis for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Dullness	PE	D	No Yes	--	UC:FT UE:CS,FT
Wheezes	PE	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Rales	PE	D	No Yes	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
X-Ray Interpretation	PE	D	Normal Abnormal	AGE RACE OCC CSMOK PACKYR	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Forced Vital Capacity (FVC) (percent of predicted)	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM
Forced Expiratory Volume in 1 Second (FEV_1) (percent of predicted)	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM
Forced Expiratory Volume in 2 Seconds (FEV_2) (percent of predicted)	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM
Forced Expiratory Volume in 3 Seconds (FEV_3) (percent of predicted)	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM

TABLE 20-1. (continued)

Statistical Analysis for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Forced Expiratory Flow Maximum (FEFmax) (percent of predicted)	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM
Ratio of Observed FEV$_1$ to Observed FVC	LAB	C	--	AGE RACE OCC CSMOK PACKYR	UC:TT AC:GLM CA:GLM,CC UE:GLM,TT AE:GLM L:RM
Loss of Vital Capacity	LAB	D	None Mild Moderate/ Severe	AGE RACE OCC CSMOK PACKYR	UC:CS,FT AC:LL CA:CS UE:CS,FT AE:LL
Obstructive Abnormality	LAB	D	None Mild Moderate/ Severe	AGE RACE OCC CSMOK PACKYR	UC:CS,FT AC:LL CA:CS UE:CS,FT AE:LL

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born $\geq$1942 Born 1923-1941 Born $\leq$1922
Race (RACE)	MIL	D	Nonblack Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew

TABLE 20-1. (continued)

Statistical Analysis for the Pulmonary Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Current Cigarette Smoking (CSMOK)(cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10

Abbreviations:

Data Source:
LAB--1987 SCRF laboratory results
MIL--Air Force military records
PE--1987 SCRF physical examination
Q-SR--1987 NORC questionnaire (self-reported)

Data Form:
C--Continuous analysis only
D--Discrete analysis only
D/C--Appropriate form for analysis (either discrete or continuous)

Statistical Analyses:
UC--Unadjusted core analyses
AC--Adjusted core analyses
CA--Dependent variable-covariate associations
UE--Unadjusted exposure index analyses
AE--Adjusted exposure index analyses
L--Longitudinal analyses

Statistical Methods:
CC--Pearson's product moment correlation coefficient
CS--Chi-square contingency table test
FT--Fisher's exact test
GLM--General linear models analysis
LL--Log-linear models analysis
LR--Logistic regression analysis
RM--Repeated measures analysis
TT--Two-sample t-test

TABLE 20-2.

Number of Participants With Missing Data for the Pulmonary Assessment by Group

Variable	Analysis Use	Group		Total
		Ranch Hand	Comparison	
Asthma	DEP	0	1	1
Bronchitis	DEP	1	1	2
Pleurisy	DEP	2	3	5
Pneumonia	DEP	0	1	1
Tuberculosis	DEP	0	1	1
X-Ray Interpretation	DEP	4	4	8
FVC	DEP	2	0	2
FEV_1	DEP	2	0	2
FEV_2	DEP	2	0	2
FEV_3	DEP	2	0	2
FEFmax	DEP	2	0	2
Ratio of Observed FEV_1 to Observed FVC	DEP	2	0	2
Loss of Vital Capacity	DEP	2	0	2
Obstructive Abnormality	DEP	2	0	2

Abbreviations: DEP--Dependent variable (missing data)

TABLE 20-3.

Unadjusted Analysis for Pulmonary Questionnaire Variables by Group

Variable	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
Asthma	n	995		1,298			
	Number/%						
	Yes	58	5.8%	62	4.8%	1.23 (0.85,1.78)	0.304
	No	937	94.2%	1,236	95.2%		
Bronchitis	n	994		1,298			
	Number/%						
	Yes	187	18.8%	240	18.5%	1.02 (0.83,1.26)	0.886
	No	807	81.2%	1,058	81.5%		
Pleurisy	n	993		1,296			
	Number/%						
	Yes	60	6.0%	7	5.9%	1.03 (0.73,1.46)	0.926
	No	933	94.0%	1,220	94.1%		
Pneumonia	n	995		1,298			
	Number/%						
	Yes	220	22.1%	321	24.7%	0.86 (0.71,1.05)	0.157
	No	775	77.9%	977	75.3%		
Tuberculosis	n	995		1,298			
	Number/%						
	Yes	9	0.9%	8	0.6%	1.47 (0.57,3.83)	0.578
	No	986	99.1%	1,290	99.4%		

TABLE 20-4.

Adjusted Analysis for Pulmonary Questionnaire Variables by Group

Variable	Statistic	Group		Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
		Ranch Hand	Comparison			
Asthma	n	995	1,298	1.29 (0.89,1.87)	0.178	OCC*CSMOK (p=0.007)
Bronchitis	n	994	1,298	1.01 (0.82,1.25)	0.898	RACE*PACKYR (p=0.005)
Pleurisy	n	993	1,296	1.02 (0.72,1.44)	0.932	PACKYR (p=0.005)
Pneumonia	n	995	1,298	****	****	GRP*PACKYR (p=0.004) AGE (p<0.001) OCC*PACKYR (p=0.033)

GRP: Group (Ranch Hand, Comparison).

****Group-by-covariate interaction ($p \leq 0.01$)--adjusted relative risk, confidence interval, and p-value not presented.

contains the dependent variable-covariate associations. The summary of the group-by-covariate interactions for the group contrasts on the pulmonary variables can be found in Table Q-2 of Appendix Q.

Asthma

As shown in Table 20-3, no difference between the Ranch Hands and Comparisons was detected in the unadjusted analysis of asthma (p=0.304).

Based on pooled group data, none of the covariate tests of association with asthma were significant.

In the adjusted analysis of asthma, there was no significant difference between the two groups (p=0.178). In the adjusted model, the occupation-by-current cigarette smoking interaction was significant (p=0.007).

Bronchitis

No significant group difference was identified in the unadjusted analysis of bronchitis (p=0.886).

The covariate tests of association showed that race, current cigarette smoking, and lifetime cigarette smoking history were statistically significant (p=0.002, p=0.009, and p=0.042, respectively). A higher percentage of non-blacks reported having had bronchitis than Blacks (19.3% vs. 8.8%). For current cigarette smoking, 22.2 percent of the heavy smokers and 20.6 percent of the former smokers reported having experienced bronchitis in the past, as contrasted to 15.8 percent of the nonsmokers and 15.4 percent of the moderate smokers. For lifetime cigarette smoking history, the percentage of reported bronchitis increased with the frequency of smoking (15.7% for nonsmokers, 18.2% for moderate smokers, and 20.7% for heavy smokers).

The adjusted analysis of bronchitis also did not detect a significant difference between the Ranch Hands and the Comparisons (p=0.898). The race-by-lifetime cigarette smoking history interaction was significant (p=0.005).

Pleurisy

The results of the unadjusted analysis of pleurisy did not detect a significant group difference (p=0.926).

Based on pooled group data, the covariate associations with pleurisy showed that age, current cigarette smoking, and lifetime cigarette smoking history were borderline significant (p=0.091, p=0.052, and p=0.055, respectively). The rate of pleurisy increased with age (5.1% for those born in or after 1942, 6.3% for those born between 1923 and 1941, and 10.7% for those born in or before 1922). For current cigarette smoking, 4.5 percent of the nonsmokers, 7.0 percent of the former smokers, 4.4 percent of the moderate smokers, and 7.6 percent of the heavy smokers responded yes to having experienced pleurisy. Based on lifetime cigarette smoking history, the rates of pleurisy were 4.5, 5.4, and 7.2 percent for nonsmokers, moderate smokers, and heavy smokers, respectively.

In the adjusted analysis, no significant difference between the two groups was detected (p=0.932). In the adjusted model, lifetime cigarette smoking history was significant (p=0.005).

Pneumonia

In the unadjusted analysis of pneumonia, no significant difference between the Ranch Hands and the Comparisons was found (p=0.157).

Four of the five covariate tests of association with pneumonia were significant: age (p<0.001), race (p=0.020), current cigarette smoking (p=0.003), and lifetime cigarette smoking history (p=0.024). The number of participants who reported having had pneumonia increased with age (18.4% for those born in or after 1942, 27.0% for those born between 1923 and 1941, and 32.1% for those born in or before 1922). The rate for nonblacks was higher than for Blacks (24.1% vs. 15.3%). Based on current cigarette smoking, 20.7 percent of the nonsmokers, 26.5 percent of the former smokers, 18.7 percent of the moderate smokers, and 26.6 percent of the heavy smokers reported yes to having had pneumonia. For lifetime cigarette smoking history, the rate of pneumonia was found to increase with smoking intensity (20.7% for nonsmokers, 22.3% for moderate smokers, and 26.2% for heavy smokers).

The results of the adjusted analysis of pneumonia showed a significant group-by-lifetime cigarette smoking history interaction (p=0.004). Age and occupation-by-lifetime cigarette smoking history were significant terms in the model (p<0.001 and p=0.033, respectively). As shown in Table Q-2 of Appendix Q, the Comparisons in the heavy smoking category had a significantly higher reported history of pneumonia than the Ranch Hands (29.6% vs. 21.9%; Adj. RR: 0.66, 95% C.I.: [0.50,0.88], p=0.005). No significant differences were detected between the Ranch Hands and the Comparisons in the nonsmoking and moderate smoking strata (p=0.690 and p=0.266, respectively).

Tuberculosis

The unadjusted analysis of tuberculosis did not detect a significant difference between the Ranch Hands and the Comparisons (p=0.578). Only nine Ranch Hands and eight Comparisons reported having had tuberculosis. Due to the low frequency of occurrence, an adjusted analysis was not conducted.

Physical Examination Variables

The unadjusted and adjusted results of the physical examination variables are presented in Tables 20-5 and 20-6, respectively. The dependent variable-covariate associations and group-by-covariate interactions are provided in Appendix Q in Tables Q-1 and Q-2, respectively.

Thorax and Lung Abnormalities

The unadjusted analysis of thorax and lung abnormalities showed a significant difference between the Ranch Hands and the Comparisons (Est. RR:

TABLE 20-5.

Unadjusted Analysis for Pulmonary Physical Examination Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Thorax and Lung Abnormalities	n	995		1,299			
	Number/%						
	Yes	74	7.4%	65	5.0%	1.53 (1.08,2.15)	0.020
	No	921	92.6%	1,234	95.0%		
Asymmetric Expansion	n	995		1,299			
	Number/%						
	Yes	0	0.0%	1	0.1%	--[a]	0.999
	No	995	100.0%	1,298	99.9%		
Hyperresonance	n	995		1,299			
	Number/%						
	Yes	40	4.0%	35	2.7%	1.51 (0.96,2.40)	0.100
	No	955	96.0%	1,264	97.3%		
Dullness	n	995		1,299			
	Number/%						
	Yes	2	0.2%	1	0.1%	2.61 (0.24,28.87)	0.802
	No	993	99.8%	1,298	99.9%		
Wheezes	n	995		1,299			
	Number/%						
	Yes	30	3.0%	25	1.9%	1.58 (0.93,2.71)	0.121
	No	965	97.0%	1,274	98.1%		

TABLE 20-5. (continued)

Unadjusted Analysis for Pulmonary Physical Examination Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Rales	n	995		1,299			
	Number/%						
	Yes	14	1.4%	16	1.2%	1.14 (0.56,2.36)	0.850
	No	981	98.6%	1,283	98.8%		
X-Ray Interpretation	n	991		1,295			
	Number/%						
	Abnormal	48	4.8%	71	5.5%	0.88 (0.60,1.28)	0.560
	Normal	943	95.2%	1,224	94.5%		

--[a]Relative risk/confidence interval not given due to a cell with zero frequency.

TABLE 20-6.

Adjusted Analysis for Pulmonary Physical Examination Variables by Group

Variable	Statistic	Group		Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
		Ranch Hand	Comparison			
Thorax and Lung Abnormalities	n	995	1,299	1.39 (0.97,2.00)	0.072	AGE (p<0.001) OCC (p<0.001) CSMOK (p<0.001) PACKYR (p=0.030)
Hyper-resonance	n	995	1,299	1.36 (0.84,2.20)**	0.208**	GRP*OCC (p=0.017) AGE (p<0.001) CSMOK (p<0.001)
Wheezes	n	995	1,299	1.37 (0.79,2.38)	0.267	AGE (p=0.004) PACKYR (p=0.035) CSMOK (p<0.001)
Rales	n	995	1,299	1.05 (0.50,2.21)	0.895	AGE (p<0.001) CSMOK (p=0.001)
X-Ray Interpretation	n	991	1,295	0.84 (0.57,1.23)**	0.367**	GRP*RACE (p=0.023) AGE (p<0.001) CSMOK (p=0.002)

**Group-by-covariate interaction ($0.01 < p \leq 0.05$)--relative risk and p-value derived from a model fitted after deletion of this interaction.

1.53, 95% C.I.: [1.08,2.15], p=0.020). Among the Ranch Hands, 7.4 percent had abnormalities, as contrasted with 5.0 percent in the Comparisons.

Based on pooled group data, the covariate tests of association with thorax and lung abnormalities were significant for age, occupation, current cigarette smoking, and lifetime cigarette smoking history ($p<0.001$ for all). The association between thorax and lung abnormalities and race was borderline significant ($p=0.055$). The percentage of thorax and lungs abnormalities was found to increase with age (2.2% for those born in or after 1942, 8.5% for those born between 1923 and 1941, and 14.3% for those born in or before 1922). A higher percentage of abnormalities was detected in nonblacks than Blacks (6.3% vs. 2.2%). Enlisted flyers had the highest percentage of thorax and lung abnormalities (11.2% for enlisted flyers vs. 4.1% for officers and 5.8% for enlisted groundcrew). The prevalence rate was found to be increasing with the level of smoking, based on both current and lifetime cigarette smoking patterns. For current cigarette smoking, there were 1.3 percent abnormalities for nonsmokers, 5.1 percent for former smokers, 10.3 percent for moderate smokers, and 12.2 percent for heavy smokers. Based on lifetime cigarette smoking history, the percentages of participants with thorax and lung abnormalities were 1.3, 4.6, and 9.9 for nonsmokers, moderate smokers, and heavy smokers, respectively.

The result of the adjusted analysis on thorax and lung abnormalities was borderline significant (Adj. RR: 1.39, 95% C.I.: [0.97,2.00], $p=0.072$). Age, occupation, current cigarette smoking, and lifetime cigarette smoking history were significant covariates in the adjusted model ($p<0.001$, $p<0.001$, $p<0.001$, and $p=0.030$, respectively). The change from significance in the unadjusted analysis to borderline significance in the adjusted analysis is probably due to the association of thorax and lung abnormalities with current cigarette smoking, in conjunction with the association of group status and this smoking variable, as shown in Chapter 2.

Asymmetric Expansion

No difference between the two groups was detected in the unadjusted analysis of asymmetric expansion ($p=0.999$). Among all of the participants, there was only one occurrence of asymmetric expansion, which was in the Comparison group. An adjusted analysis was not conducted due to the sparse occurrence of this condition.

Hyperresonance

Based on the unadjusted analysis, the difference between the two groups on hyperresonance was borderline significant (Est. RR: 1.51, 95% C.I.: [0.96, 2.40], $p=0.100$). The percentages of participants with hyperresonance in the Ranch Hands and the Comparisons were 4.0 and 2.7, respectively.

The significant covariate associations with hyperresonance were age ($p<0.001$), occupation ($p=0.003$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). The prevalence rate increased with age (0.9% for those born in or after 1942, 4.5% for those born between 1923 and 1941, and 11.9% for those born in or before 1922). Hyperresonance

was found to be highest for enlisted flyers (6.0% for enlisted flyers versus 2.3% for officers and 3.1% for enlisted groundcrew). For both current cigarette smoking and lifetime cigarette smoking history, the prevalence rates of hyperresonance increased with smoking intensity. Based on current cigarette smoking, 1.0 percent of the nonsmokers were diagnosed with hyperresonance, as contrasted with 2.3 percent of the former smokers, 5.6 percent of the moderate smokers, and 7.0 percent of the heavy smokers. The rates were 1.0, 1.7, and 5.6 for nonsmokers, moderate smokers, and heavy smokers, respectively, based on lifetime cigarette smoking history.

In the adjusted analysis of hyperresonance, there was a significant group-by-occupation interaction ($p=0.017$). Age and current cigarette smoking were significant covariates ($p<0.001$ for both). Stratifying by occupation, a significant difference was detected between the two groups for the enlisted flyers (Adj. RR: 3.97, 95% C.I.: [1.48,10.64], $p=0.006$). The Ranch Hand enlisted flyers had a significantly higher prevalence rate than the Comparison enlisted flyers (9.9% vs. 2.8%). No differences were identified in the officer and enlisted groundcrew occupational categories ($p=0.302$ and $p=0.746$, respectively). Without the group-by-occupation interaction in the model, no significant difference between the two groups was detected ($p=0.208$).

Dullness

Three participants, two Ranch Hands and one Comparison, were diagnosed with dullness of the lungs at the physical examination of the 1987 followup. No significant difference was detected in the unadjusted analysis ($p=0.802$). An adjusted analysis was not performed due to the low occurrence of dullness.

Wheezes

Based on the unadjusted analysis of wheezes, no difference was detected between the two groups ($p=0.121$).

The results of the covariate associations did not detect a significant association for race; however, there were significant associations for age ($p=0.004$), occupation ($p=0.010$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). The prevalence rate for wheezes increased with age (1.1% for those born in or after 1942, 3.3% for those born between 1923 and 1941, and 3.6% for those born in or before 1922). The rate in the enlisted flyers was 4.4 percent, as contrasted to 1.6 percent in the officers and 2.3 percent in the enlisted groundcrew. Based on current cigarette smoking, the nonsmokers had the lowest rate of wheezes, 0.3 percent, followed by 1.4 percent for the former smokers, 3.9 percent for the moderate smokers, and 6.8 percent for heavy smokers. For lifetime cigarette smoking, the prevalence rates for the nonsmokers, moderate smokers, and heavy smokers were 0.3 percent, 2.2 percent, and 3.8 percent, respectively.

In the adjusted analysis of wheezes, no significant difference between groups was detected ($p=0.267$). Age ($p=0.004$), lifetime cigarette smoking ($p=0.035$), and current cigarette smoking ($p<0.001$) were significant covariates.

Rales

No significant difference between the Ranch Hands and the Comparisons was identified in the unadjusted analysis of rales ($p=0.850$).

The covariate tests of association with rales revealed that age ($p<0.001$), occupation ($p=0.048$), current cigarette smoking ($p=0.009$), and lifetime cigarette smoking history ($p<0.001$) were significant. The prevalence rate of rales increased with age: 0.1 percent of the participants born in or after 1942 were diagnosed with rales, as contrasted to 1.9 percent of those born between 1923 and 1941 and 6.0 percent of those born in or before 1922. The highest rate was in the enlisted flyer occupational category (2.6% for enlisted flyers vs. 1.0% for officers and 1.1% for enlisted groundcrew). For current cigarette smoking, the highest percentage of rales was in the moderate smokers (2.6%), followed by the former smokers (1.5%), the heavy smokers (1.4%), and the nonsmokers (0.2%). Based on lifetime cigarette smoking history, the prevalence rate increased with the level of smoking (0.2% for nonsmokers, 0.5% for moderate smokers, and 2.5% for heavy smokers).

In the adjusted analysis of rales, no significant group difference was detected ($p=0.895$). Age and current cigarette smoking were significant covariates in the adjusted model ($p<0.001$ and $p=0.001$, respectively).

X-Ray Interpretation

Based on the unadjusted analysis, no significant difference between the two groups was detected in the unadjusted analysis of chest x-ray interpretation ($p=0.560$).

Using combined Ranch Hand and Comparison data, the covariate tests detected significant associations between x-ray abnormalities and age ($p<0.001$), occupation ($p=0.020$), current cigarette smoking ($p=0.006$), and lifetime cigarette smoking history ($p=0.003$). The association between x-ray abnormalities and race was borderline significant ($p=0.098$). The percentage of x-ray abnormalities increased with age. Only 3.0 percent of the participants born in or after 1942 had x-ray abnormalities, as contrasted to 6.6 percent of those born between 1923 and 1941 and 9.5 percent of those born in or before 1922. Blacks had a marginally higher percentage of abnormalities than nonblacks (8.8% vs. 5.0%). The highest percentage of abnormalities was in the enlisted flyers (8.1% for enlisted flyers vs. 4.6% for officers and 4.7% for enlisted groundcrew). Based on current cigarette smoking patterns, the moderate and heavy smokers had the highest percentages of abnormalities (8.0% and 6.0%, respectively). The current nonsmokers and former smokers had 3.0 percent and 5.2 percent abnormalities, respectively. For lifetime cigarette smoking history, the percentage of abnormalities increased with the level of smoking (2.9% for nonsmokers, 4.9% for moderate smokers, and 6.5% for heavy smokers).

In the adjusted analysis of chest x-ray interpretation, there was a significant group-by-race interaction ($p=0.023$). Age and current cigarette smoking were significant covariates in the model ($p<0.001$ and $p=0.002$, respectively). After stratifying by race, it was determined that there were more x-ray abnormalities among the Black Ranch Hands than the Black

Comparisons (14.0% vs. 5.0%); this result was borderline significant (Adj. RR: 3.27, 95% C.I.: [0.91, 11.68], p=0.068). No difference between the nonblack Ranch Hands and Comparisons was detected (p=0.119). The adjusted analysis without the group-by-race interaction did not reveal a significant difference (p=0.367).

Laboratory Examination Variables

Tables 20-7 and 20-8 contain the results of the unadjusted and adjusted analyses of the physiology laboratory variables for the pulmonary assessment. Covariate associations and group-by-covariate interactions are presented in Tables Q-1 and Q-2 of Appendix Q, respectively.

Technical quality of the pulmonary function testing was a major focus of quality control during the physical examination. The primary factors in achieving technical quality are the skill of the technician, the equipment, and the ability of the participants to give reproducible patterns over two or three runs. For each participant, technical quality was recorded as adequate or inadequate; measurements for two Ranch Hands were missing. The technical quality for seven Ranch Hands and two Comparisons was classified as inadequate (0.7% for Ranch Hands and 0.2% for Comparisons). The combined percentage was judged to be very low. The difference in technical quality between the Ranch Hands and Comparisons was marginally significant (p=0.075), although the technician was blind to the group membership of the participants and the same procedures and equipment were used throughout the 1987 followup.

FVC

No difference was found between the Ranch Hands and the Comparisons based on the unadjusted analysis of FVC (p=0.368).

Using the pooled Ranch Hand and Comparison data, the covariate tests with FVC showed significant associations for all five covariates: age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history (p<0.001 for all). The analysis showed that FVC was negatively correlated with age (r=-0.094). The mean FVC for Blacks was significantly lower than for nonblacks (85.7% vs. 97.5%). The lowest mean FVC was observed in the enlisted groundcrew occupational category (95.6%). The mean FVC for the officers end the enlisted flyers was 98.6 percent and 96.0 percent, respectively. FVC was negatively correlated with both current cigarette smoking and lifetime cigarette smoking history (r=-0.139 and r=-0.200, respectively).

The adjusted analysis of FVC did not detect a significant difference between the two groups (p=0.580). Race (p<0.001), occupation (p<0.001), lifetime cigarette smoking history (p<0.001), and an age-by-current cigarette smoking interaction (p=0.049) were significant terms in the adjusted model.

FEV_1

Based on the unadjusted analysis of FEV_1, no group difference was detected (p=0.329).

TABLE 20-7.

Unadjusted Analysis for Pulmonary Laboratory Examination Variables by Group

Variable	Statistic	Group		Contrast	Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand	Comparison			
FVC	n	993	1,299			
	Mean	96.5	97.0		--	0.368
	95% C.I.	(95.7,97.3)	(96.3,97.7)			
FEV_1	n	993	1,299			
	Mean	97.3	97.9		--	0.329
	95% C.I.	(96.3,98.3)	(97.1,98.8)			
FEV_2	n	993	1,299			
	Mean	95.4	96.0		--	0.330
	95% C.I.	(94.5,96.3)	(95.2,96.8)			
FEV_3	n	993	1,299			
	Mean	95.3	95.9		--	0.336
	95% C.I.	(94.5,96.2)	(95.1,96.7)			
FEFmax	n	993	1,299			
	Mean	136.6	137.5		--	0.344
	95% C.I.	(135.0,138.1)	(136.2,138.8)			
Ratio of Observed FEV_1 to Observed FVC	n	993	1,299			
	Mean[a]	0.813	0.814		--	0.816
	95% C.I.[a]	(0.809,0.818)	(0.811,0.818)			

TABLE 20-7. (continued)

Unadjusted Analysis for Pulmonary Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Loss of Vital Capacity	n	993		1,299				
	Number/%							
	None	887	89.3%	1,173	90.3%	Overall		0.670
	Mild	85	8.6%	104	8.0%	Mild vs. None	1.08 (0.80,1.46)	0.664
	Mod./Sev.	21	2.1%	22	1.7%	Mod./Sev. vs. None	1.26 (0.69,2.31)	0.544
Obstructive Abnormality	n	993		1,299				
	Number/%							
	None	691	69.6%	942	72.5%	Overall		0.299
	Mild	255	25.7%	299	23.0%	Mild vs. None	1.16 (0.96,1.41)	0.140
	Mod./Sev.	47	4.7%	58	4.5%	Mod./Sev. vs. None	1.11 (0.74,1.64)	0.694

--Estimated relative risk not applicable for continuous analysis of a variable.

*Transformed from natural logarithm (1-X) scale.

TABLE 20-8.

Adjusted Analysis for Pulmonary Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
FVC	n Adj. Mean 95% C.I.	993 91.4 (90.1,92.7)	1,299 91.7 (90.5,92.9)		—	0.580	RACE (p<0.001) OCC (p<0.001) PACKYR (p<0.001) AGE*CSMOK (p=0.049)
FEV_1	n Adj. Mean** 95% C.I.**	993 92.9 (91.5,94.4)	1,299 93.2 (91.7,94.6)		—	0.721**	GRP*AGE (p=0.037) RACE (p<0.001) OCC (p=0.005) AGE*CSMOK (p=0.001) CSMOK*PACKYR (p<0.001)
FEV_2	n Adj. Mean** 95% C.I.**	993 90.7 (89.3,92.0)	1,299 90.9 (89.6,92.2)		—	0.652**	GRP*AGE (p=0.042) RACE (p<0.001) OCC (p<0.001) AGE*CSMOK (p<0.001) CSMOK*PACKYR (p=0.002)
FEV_3	n Adj. Mean 95% C.I.	993 90.4 (89.1,91.7)	1,299 90.6 (89.4,91.9)		—	0.621	RACE (p<0.001) OCC (p<0.001) AGE*CSMOK (p=0.001) CSMOK*PACKYR (p=0.006)
FEFmax	n Adj. Mean 95% C.I.	993 137.4 (135.9,138.9)	1,299 137.7 (136.4,139.0)		—	0.778	AGE*PACKYR (p=0.008) OCC*PACKYR (p=0.027) CSMOK*PACKYR (p=0.006)

TABLE 20-8. (continued)

Adjusted Analysis for Pulmonary Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Ratio of Observed FEV_1 to Observed FVC	n	993	1,299				AGE*OCC (p=0.013)
	Adj. Mean[a]	0.818	0.817		—	0.645	RACE*PACKYR (p=0.047)
	95% C.I.[a]	(0.811,0.825)	(0.810,0.824)				CSMOK*PACKYR (p=0.001)
Loss of Vital Capacity	n	993	1,299	Overall		0.679	AGE (p<0.001)
				Mild vs. None	1.08 (0.80,1.46)	0.623	RACE (p<0.001)
				Mod./Sev. vs. None	1.26 (0.70,2.27)	0.445	PACKYR (p<0.001)
Obstructive Abnormality	n	993	1,299	Overall		0.389	AGE (p<0.001)
				Mild vs. None	1.15 (0.94,1.42)	0.175	OCC (p=0.011)
				Mod./Sev. vs. None	1.11 (0.74,1.65)	0.610	PACKYR (p<0.001)

—Adjusted relative risk not applicable for continuous analysis of a variable.

**Group-by-covariate interaction ($0.01<p\leq0.05$)—adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

[a]Transformed from natural logarithm (1-X) scale.

The covariate tests for FEV_1 revealed significant relationships with all five covariates ($p<0.001$ for age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history). The analysis identified a negative correlation between FEV_1 and age ($r=-0.170$). The Blacks had a lower mean FEV_1 than nonblacks (89.1% vs. 98.2%). The lowest mean FEV_1 was observed in the enlisted flyers (95.1%) followed by the enlisted groundcrew (97.1%) and officers (99.4%). The analysis showed negative correlations for current cigarette smoking and lifetime cigarette smoking history ($r=-0.230$ and $r=-0.298$, respectively).

In the adjusted analysis of FEV_1, there was a significant group-by-age interaction ($p=0.037$). Race ($p<0.001$), occupation ($p=0.005$), an age-by-current cigarette smoking interaction ($p=0.001$), and a current cigarette smoking-by-lifetime cigarette smoking history interaction ($p<0.001$) were also significant terms in the model. As shown in Table Q-2 of Appendix Q, stratifying by age showed a significant difference between the two groups for those who were born between 1923 and 1941 ($p=0.022$) and a borderline significant difference for those born in or before 1922 ($p=0.081$). The adjusted mean of the Ranch Hands was significantly lower than the adjusted mean of the Comparisons for those born between 1923 and 1941 (90.0% vs. 91.9%); however, for those born in or before 1922, the adjusted mean of the Comparisons was marginally lower than the adjusted mean of the Ranch Hands (86.8% vs. 92.4%). No difference between the two groups was shown for those born in or after 1942 ($p=0.126$). Without the group-by-age interaction in the model, no difference between the two groups was detected ($p=0.721$).

$\underline{FEV_2}$

The results of the unadjusted analysis of FEV_2 showed no significant difference between the two groups ($p=0.330$).

Based on pooled group data, all covariate tests of association with FEV_2 were found to be statistically significant ($p<0.001$ for age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history). FEV_2 was negatively correlated with age, current cigarette smoking, and lifetime cigarette smoking history ($r=-0.140$, $r=-0.204$, and $r=-0.271$, respectively). The means of the Blacks and nonblacks were 85.9 percent and 96.4 percent, respectively. The lowest FEV_2 was found in the enlisted flyers (93.8% for enlisted flyers vs. 94.9% in the enlisted groundcrew and 97.6% in the officers).

In the adjusted analysis, there was a significant group-by-age interaction ($p=0.042$). The other significant effects in the model were race ($p<0.001$), occupation ($p<0.001$), age-by-current cigarette smoking interaction ($p<0.001$), and current cigarette smoking-by-lifetime cigarette smoking history interaction ($p=0.002$). Stratification by age revealed a significant difference between the two groups for those born between 1923 and 1941 (88.1% for Ranch Hands vs. 90.0% for Comparisons; $p=0.017$) and a borderline significant difference for those born in or before 1922 (91.1% for Ranch Hands vs. 85.7% for Comparisons; $p=0.070$). No difference was identified between the Ranch Hands and the Comparisons based on the adjusted analysis of FEV_2 without the group-by-age interaction ($p=0.652$).