

PROJECT RANCH HAND II
AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH
EFFECTS IN AIR FORCE PERSONNEL FOLLOWING
EXPOSURE TO HERBICIDES

MORTALITY UPDATE - 1985

29 NOVEMBER 1985

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occur, additional time is necessary for other conditions to develop which may possibly be attributable to herbicide exposure. At this time, however, there is no evidence of increased mortality as a result of herbicide exposure in individuals who performed the Ranch Hand spray operations in Vietnam.

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Air Force Health Study Mortality Update - 1985

EXECUTIVE SUMMARY

BACKGROUND

The purpose of the Air Force Health Study is to determine whether those individuals involved in the aerial spraying of herbicides in Vietnam during the Ranch Hand operation have experienced any adverse health effects as a result of their participation in that program. The study evaluates both mortality (death) and morbidity (disease) in these individuals over a 20-year period after the studies were initiated.

The Baseline Mortality Report was released in June 1983, the Baseline Morbidity Report in February 1984, and the first follow-up mortality study in December 1984. Neither study demonstrated health effects which could be conclusively attributed to herbicide or dioxin exposure. The reader is referred to reports of the studies for further details (1, 2, 3).

METHOD

The present report describes the third mortality analyses. Deaths in the 1257 Ranch Hand and 6171 Comparison subjects were determined, using the data sources of the Air Force, Veterans Administration, Social Security Administration, Internal Revenue Service, and personal contacts. As of 31 December 1984, 55 Ranch Handers and 285 Comparison subjects had died. Death certificates were obtained on all subjects.

Extensive statistical analyses were accomplished, as detailed in the report, to compare the death experience in the Ranch Hand population with the Comparison group. In addition, death experience in these groups was compared to the 1978 U.S. White male mortality experience, the 1978 Department of Defense Nondisability Retired Life Table, and the active U.S. civil service population as discussed in the 1984 mortality report (3). The West Point class of 1956 and the active duty USAF population are not appropriate groups for comparing to the study population and, consequently, they have not been used in the analyses in this report.

RESULTS

As was the case in the last mortality report, the current mortality analyses did not reveal any statistically significant differences in mortality between the exposed and Comparison groups. The percentages dead in each major category are summarized below. Within categories of rank and occupation none of the differences between the Ranch Hand and Comparison groups are statistically significant.

| Rank | Percent Deaths | |
|-------------------|----------------|------------|
| | Ranch Hand | Comparison |
| Officers | 3.4 | 4.3 |
| Enlisted | 4.9 | 4.8 |
| <u>Occupation</u> | | |
| Flying | 3.7 | 5.1 |
| Ground | 5.1 | 4.1 |
| | | |
| Ranch Hand | | Comparison |
| Total | | |
| Overall | 4.4 | 4.6 |

As was reported in the 1984 mortality study, the Ranch Hand officers had a nonstatistically significant though slightly lower death rate than their Comparisons. There is an interaction in these data, however. Ranch Hand officers born between 1905 and 1935 have experienced fewer deaths than Comparison officers born during the same era. On the other hand, Ranch Hand officers born after 1935 have experienced more deaths than their Comparisons. Although these differences within birth-year strata are not statistically significant, this change in the group by survival status relationship with birth year is statistically significant. Additionally, Ranch Hand officers experienced fewer deaths after age 35 years than did Comparison officers, while Ranch Hand officers experienced more deaths before age 35 years than did Comparisons. The relevance of these observations is unclear at this time.

Ranch Hand flyers had a nonstatistically significant though slightly lower death rate than Comparisons, and Ranch Hand ground personnel had a slightly higher but nonstatistically significant death rate than the Comparisons.

The herbicide/dioxin exposure index described in the morbidity report was applied to the data, and no relationship between exposure and mortality experience was identified.

As was also noted in the 1984 mortality study, analyses consistently demonstrated significantly better survival in the Ranch Hand officers than Ranch Hand enlisted members, as was the case with Comparison officers and Comparison enlisted personnel. Cause-specific analyses did not demonstrate any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy or circulatory system disease. No unusual patterns of malignancy were observed in either the Ranch Hand or Comparison groups, a finding which would be expected from the small number of deaths to date. When compared to the 1978 U.S. White male population, all subgroups are living longer than expected. All groups had a mortality experience similar to the civil service population.

CONCLUSION AND RECOMMENDATION

Continued mortality surveillance is recommended, since the study groups are still relatively young and healthy. While sufficient time may have elapsed for some clinically significant conditions to occur, additional time is necessary for other conditions, which may possibly be attributable to herbicide exposure, to develop. At this time, however, there is no evidence of increased mortality as a result of herbicide exposure in those individuals who accomplished the Ranch Hand spray operations in Vietnam.

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Air Force Health Study Mortality Update - 1985

1. Introduction

This report updates the findings of the last mortality report (3) released on 10 December 1984. The reader is referred to the baseline mortality report (1), released on 30 June 1983, for information regarding the study design, statistical procedures and the mortality determination process. One newly identified non-Black enlisted-ground Ranch Hand has been added to the data file since the last report. This individual was previously known, but confirmation of his eligibility was delayed. Summary counts of the population at risk and the number of deaths in each of the two groups (Ranch Hand and Comparison) stratified by rank and occupation are shown in Table 1. The analyses in this report are based on this data and the data in Table 4. Table 2 contains the counts of new deaths in the population since the last report. Table 3 in this report corresponds to Table 3 in the baseline report and contains summary counts and death rates by occupation, race and group. In the December 1984 report, the mortality experience of the study population was contrasted with data from West Point graduates and the active duty Air Force population. As noted in that report, the West Point group consists only of current and former officers, and with respect to the active duty Air Force population, individuals with serious illness are generally not allowed to remain on active duty. Therefore, contrasts with these groups are not appropriate in the context of this study and have not been used. All tables in this report correspond to similar tables in the last annual report. These counts reflect cumulative mortality as of 31 December 1984 (certified as of 15 April 1985).

Careful interpretation of the findings in this and previous reports in this series requires consideration of the large sample approximations and assumptions associated with the statistical procedures. Current knowledge regarding these statistical aspects is presented in Section 7 of this report.

Table 1
Summary Counts of Death by Rank and Occupation

| Rank | Ranch Hand | | | Comparison | | |
|-------------------|------------|------|-------------|------------|------|-------------|
| | At Risk | Dead | Rate (%) | At Risk | Dead | Rate (%) |
| Officers | 466 | 16 | 0.034 (3.4) | 2278 | 98 | 0.043 (4.3) |
| Enlisted | 791 | 39 | 0.049 (4.9) | 3893 | 187 | 0.048 (4.8) |
| <u>Occupation</u> | | | | | | |
| Flying | 646 | 24 | 0.037 (3.7) | 3163 | 161 | 0.051 (5.1) |
| Ground | 611 | 31 | 0.051 (5.1) | 3008 | 124 | 0.041 (4.1) |
| <u>Total</u> | 1257 | 55 | 0.044 (4.4) | 6171 | 285 | 0.046 (4.6) |

In Table 2, the number "at risk" is the number alive on 1 January 1984.

Table 2
Deaths During 1984 by Rank and Occupation

| Rank | Ranch Hand | | | Comparison | | |
|-------------------|------------|-------------|--------------|------------|-------------|--------------|
| | At Risk | 1984 Deaths | Rate Per 100 | At Risk | 1984 Deaths | Rate Per 100 |
| Officer | 451 | 1 | 0.2 | 2187 | 7 | 0.3 |
| Enlisted | 752 | 0 | - | 3719 | 13 | 0.3 |
| <u>Occupation</u> | | | | | | |
| Flying | 623 | 1 | 0.2 | 3014 | 12 | 0.4 |
| Ground | 580 | 0 | - | 2892 | 8 | 0.3 |
| Total | 1203 | 1 | 0.1 | 5906 | 20 | 0.3 |

Since so few deaths have occurred during 1984, the statistical findings and interpretations presented in this report are very similar to those in the 1984 mortality update (3).

Table 3
Occupational and Race-Specific Mortality

| Race | Occupation | At Risk | Ranch Hand | | Comparisons | | |
|-----------|------------------|---------|------------|--------------|-------------|------|--------------|
| | | | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 |
| Non-Black | Officer-Pilot | 350 | 12 | 3.4 | 1740 | 79 | 4.5 |
| | Officer-Nav | 82 | 3 | 3.7 | 390 | 15 | 3.8 |
| | Officer-Other | 25 | 1 | 4.0 | 123 | 4 | 3.3 |
| | Enlisted-Fit Eng | 191 | 7 | 3.7 | 935 | 57 | 6.1 |
| | Enlisted-Other | 533 | 28 | 5.3 | 2628 | 108 | 4.1 |
| | Officer-Pilot | 6 | 0 | 0.0 | 13 | 0 | 0.0 |
| | Officer-Nav | 2 | 0 | 0.0 | 10 | 0 | 0.0 |
| | Officer-Other | 1 | 0 | 0.0 | 2 | 0 | 0.0 |
| | Enlisted-Fit Eng | 15 | 2 | 13.3 | 75 | 10 | 13.3 |
| | Enlisted-Other | 52 | 2 | 3.8 | 255 | 12 | 4.7 |
| Total | | 1257 | 55 | 4.4 | 6171 | 285 | 4.6 |

2. Ranch Hand Versus Comparison Group Analyses.

Survival contrasts were made using linear rank procedures, survival curves, relative risk estimation and standardized mortality ratios. Survival curves were estimated by the product-limit estimate of Kaplan and Meier (4). Linear rank testing was carried out using the logrank test and Prentice's censored data extension of the Wilcoxon test (5). All linear rank tests were carried out with matched sets merged when Ranch Handers differed by less than one year relative to date of

birth. Within each stratum of job and race, these merged matched sets were used as separate strata for testing purposes. The matched data relative risk procedure, due to Ejigou and McHugh (6), is applied only to the 1241 Ranch Handers with matched Comparisons, and the stratified relative risk or SMR estimate is applied to all 1257 Ranch Handers.

Group contrasts were made on officers, enlisted personnel, flying personnel, ground personnel and the total group. Summary counts are shown in Table 4.

Table 4
Summary Counts by Rank, Occupation and Group

| <u>Flying Personnel</u> | | | | | | | | | | |
|-------------------------|----------------|------|-----------------|-----------------|------|-----------------|--------------|------|--|-----------------|
| Groups | <u>Officer</u> | | | <u>Enlisted</u> | | | <u>Total</u> | | | Rate Per 100 |
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 | At Risk | Dead | | |
| Ranch Hand | 440 | 15 | 3.4 | 206 | 9 | 4.4 | 646 | 24 | | 3.7 |
| Comparisons | 2153 | 94 | 4.4 | 1010 | 67 | 6.6 | 3163 | 161 | | 5.1 |

| <u>Ground Personnel</u> | | | | | | | | | | |
|-------------------------|----------------|------|-----------------|-----------------|------|-----------------|--------------|------|--|-----------------|
| Groups | <u>Officer</u> | | | <u>Enlisted</u> | | | <u>Total</u> | | | Rate Per 100 |
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 | At Risk | Dead | | |
| Ranch Hand | 26 | 1 | 3.8 | 585 | 30 | 5.1 | 611 | 31 | | 5.1 |
| Comparisons | 125 | 4 | 3.2 | 2883 | 120 | 4.2 | 3008 | 124 | | 4.1 |

Survival curves were estimated only for officers, enlisted, flying, ground personnel and all personnel in Ranch Hand and Comparison groups. There is a substantial degree of overlap between these subgroups, with 96% of both the Ranch Hand and Comparison ground personnel being enlisted. The enlisted category includes both ground support and flying enlisted personnel. Survival curves for the overall Ranch Hand and Comparison groups are shown in Figure 1. The curves for officers, enlisted, flyers and ground personnel are shown in Figures 2 through 5.

Figure 1

Survival Curve Estimates for All Ranch Handers and All Comparisons

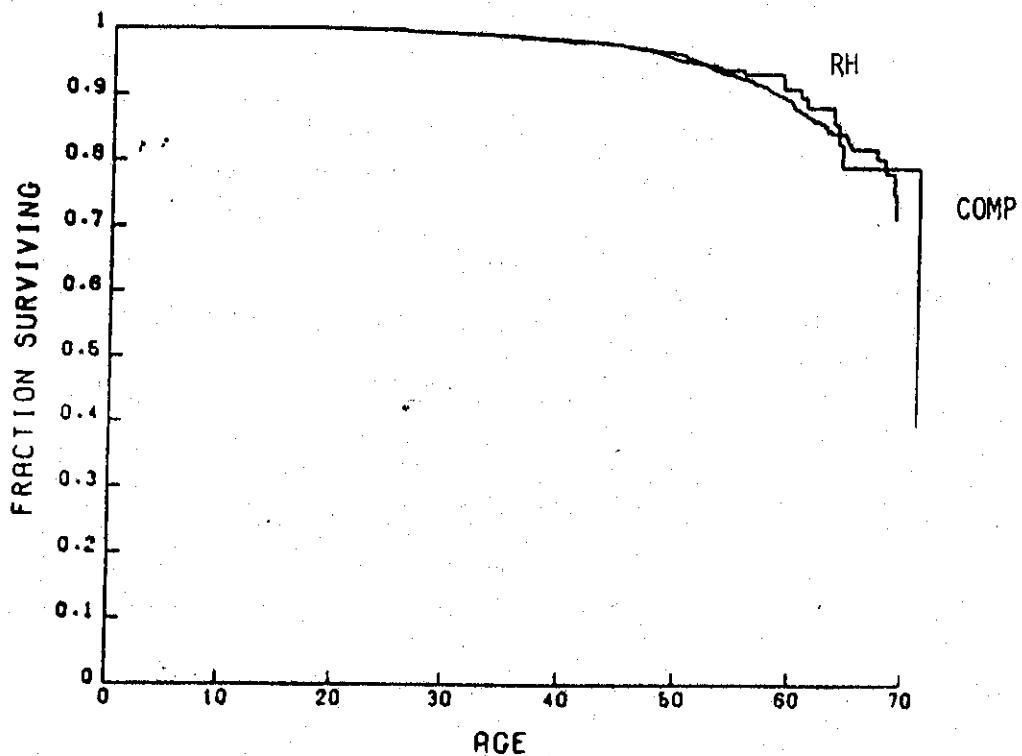


Figure 2

Survival Curve Estimates for Ranch Hand and Comparison Officers

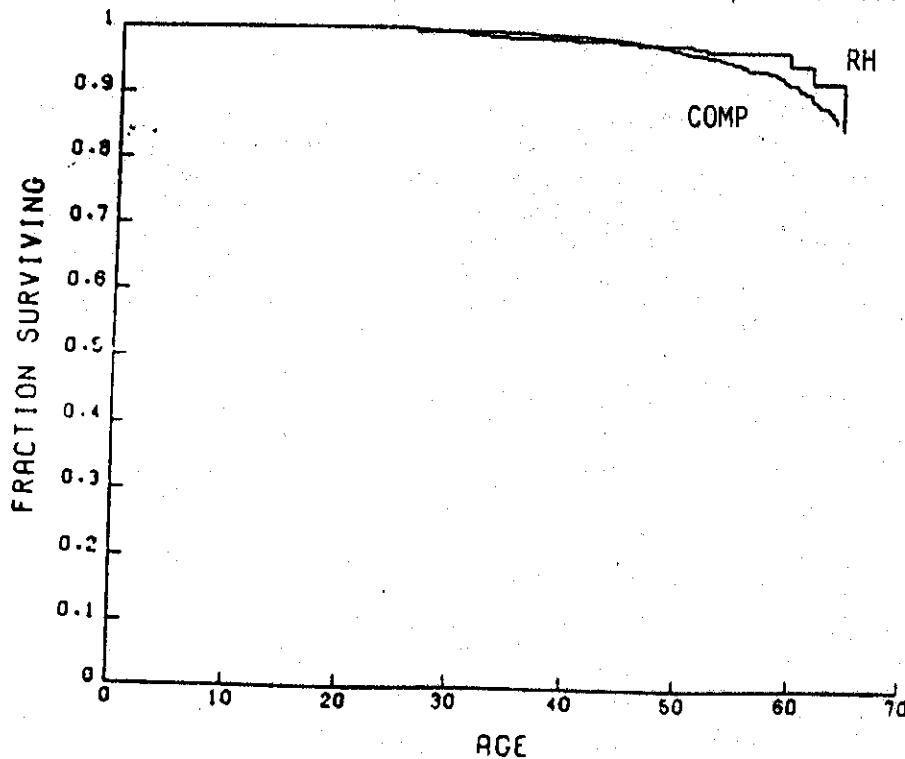


Figure 3

Survival Curve Estimates for Enlisted Ranch Handers and Comparisons

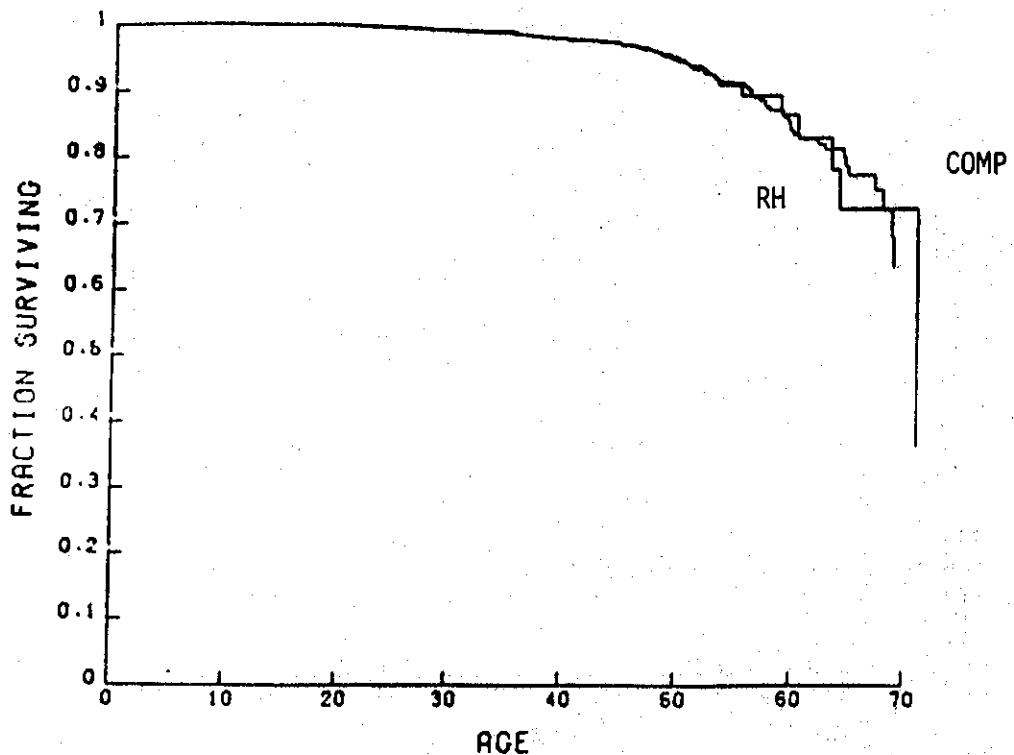


Figure 4

Survival Curve Estimates for Ranch Hand and Comparison Flyers

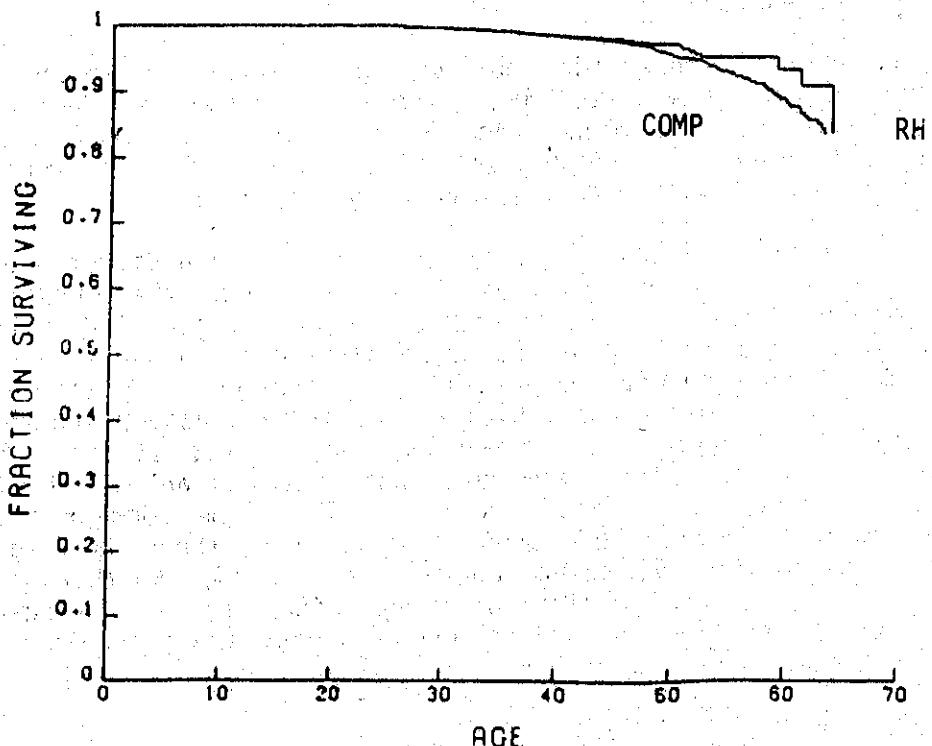
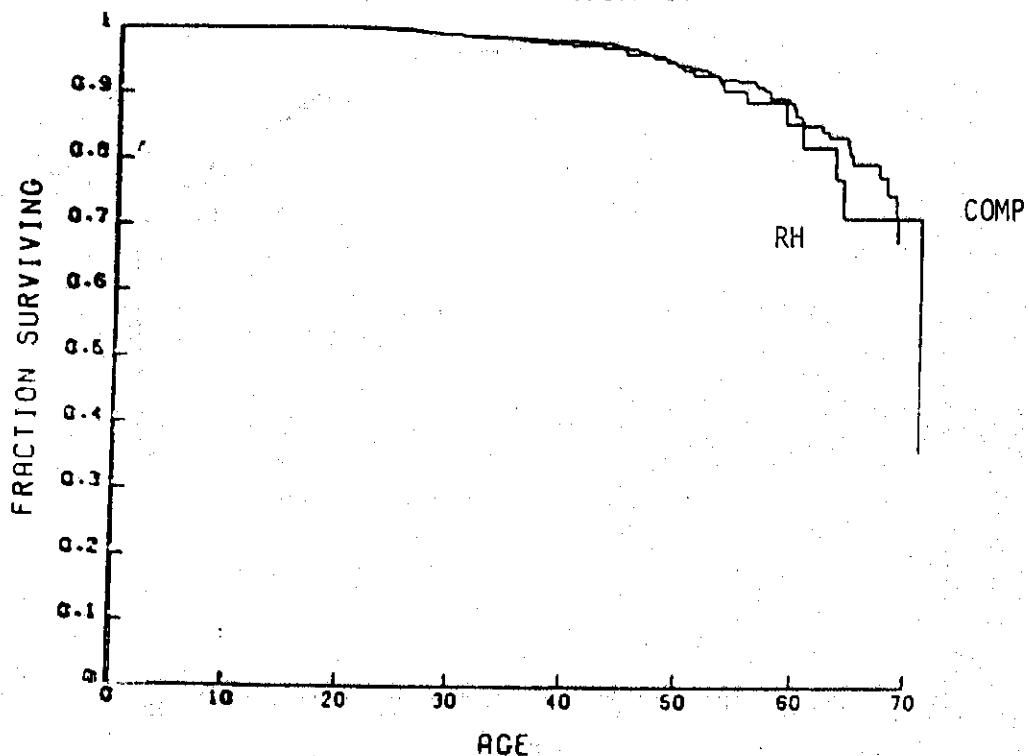


Figure 5

Survival Curve Estimates for Ranch Hand and Comparison Ground Personnel



The patterns qualitatively evident in these graphs are seen quantitatively in subsequent statistical analyses.

Linear rank procedures were carried out on the same four subgroups and on all personnel to assess death patterns by time. These procedures are designed so that the statistic will be positive when Ranch Handers are dying before Comparison subjects and negative when Comparisons are dying prior to Ranch Handers. The results are shown in Table 5 (Table 6 in the baseline report).

The linear rank statistic used is a valid measure of group difference only when this difference occurs consistently across strata. Since the strata in these analyses were formed by date-of-birth, occupation and race, the linear rank statistic is valid only when the direction of the group difference in death times does not change with date-of-birth, race and occupation. As discussed in Section 7, there is currently no statistical procedure available for testing the assumption that differences in group survival distributions remain constant across strata. As will be shown later, there is an indication, however, that there is an effect of date-of-birth on relative risks in the officer subgroup. Thus, the logrank and Wilcoxon tests on officers must be interpreted carefully. However, these data suggest that the summary statistics for the remaining subgroups are valid. Further, since there is an indication that mortality contrasts change with rank and occupation, the overall (total) logrank and Wilcoxon values and p-values, shown in Table 5 are not valid summary statistics.

Table 5
Test Results and P-Values for Noncause-Specific Survival

| Group | Logrank | | Wilcoxon | |
|----------|----------|---------|----------|---------|
| | (Value) | P-Value | (Value) | P-Value |
| Officer | (-0.835) | 0.40 | (-0.903) | 0.37 |
| Enlisted | (0.187) | 0.85 | (0.161) | 0.87 |
| Flying | (-1.34) | 0.18 | (-1.42) | 0.16 |
| Ground | (0.976) | 0.33 | (0.093) | 0.34 |
| Total | (-0.305) | 0.76 | (-0.344) | 0.73 |

Table 5 suggests that ground personnel in the Ranch Hand group are dying sooner than their matched Comparisons (logrank = 0.976), but again the difference is not statistically significant ($p=0.33$). The negative values of the logrank and Wilcoxon statistics for officers (logrank = -0.835) and flying personnel (logrank = -1.34) suggest that Ranch Handers in this group may be living longer than their matched Comparisons, but not to a statistically significant degree.

Similar analyses on the same subgroups (officer, enlisted, flying, ground and total) were carried out on data from non-Black subjects only. The results are shown in Table 6.

Table 6
Test Results and P-Values for Noncause-Specific Survival
Non-Black Ranch Handers and Non-Black Comparisons

| Group | Logrank | | Wilcoxon | |
|----------|----------|---------|----------|---------|
| | (Value) | P-Value | (Value) | P-Value |
| Officer | (-0.819) | 0.41 | (-0.885) | 0.38 |
| Enlisted | (0.211) | 0.83 | (0.192) | 0.85 |
| Flying | (-1.43) | 0.15 | (-1.50) | 0.13 |
| Ground | (1.10) | 0.27 | (1.08) | 0.28 |
| Total | (-0.286) | 0.78 | (-0.320) | 0.75 |

The findings in Table 6 clearly parallel those of Table 5, as would be expected from the small size of the Black cohort in this study.

Relative risk estimates, the associated 95% confidence intervals, two-sided p-values for testing the null hypothesis of relative risk equal to unity, and power for detecting a relative risk of 2 in these data are shown in Table 7. These estimates are based on a matched data algorithm and summarize the relative prevalence of death in the Ranch Hand and Comparison groups. The estimated relative risks are valid summary statistics only when relative risk can be assumed to be constant across date of birth strata. Again, there is indication that this assumption is not met in the officer cohort so their estimated relative risks must be viewed with caution. On the other hand, the assumption appears to be

met in the flying, ground and enlisted subgroups so these relative risk estimates do appear to be valid. Similarly, since there is an indication that relative risk changes with rank and occupation, the overall relative risk, 0.915, is not a valid summary statistic.

Table 7

Relative Risks, 95% Confidence Intervals, P-Values and
Power for Noncause-Specific Deaths to Date
(1241 Ranch Handers Versus 6171 Matched Comparisons)

| <u>Group</u> | <u>Rel Risk</u> | <u>Conf Int</u> | <u>P-Value</u> | <u>Power</u> |
|--------------|-----------------|-----------------|----------------|--------------|
| Officer | 0.715 | (0.311, 1.12) | 0.26 | 0.90 |
| Enlisted | 0.987 | (0.622, 1.35) | 0.94 | 0.99 |
| Flying | 0.692 | (0.377, 1.01) | 0.12 | 0.98 |
| Ground | 1.21 | (0.708, 1.72) | 0.35 | 0.94 |
| Total | 0.915 | (0.636, 1.20) | 0.57 | 1.0 |

Table 7 shows that Ranch Hand flyers are experiencing fewer deaths than their matched Comparisons (relative risk = 0.692), but this group difference is not statistically significant ($p=0.12$). The Ranch Hand ground personnel experienced more deaths (relative risk = 1.21) than their matched ground Comparisons, but again, this excess is also not statistically significant ($p=0.35$). The statistical power to detect a relative risk of two is quite strong (equal to or greater than 90%).

Year-of-birth specific mortality rates are given in Tables 8 through 12, with the corresponding standardized mortality ratios (SMR) and associated p-values (7). In each analysis, the Comparison group is the internal standard. The SMR will accurately estimate the relative risks within each stratum in these analyses if the year-of-birth specific relative risks are equal. A likelihood ratio test for the hypothesis of equal year-of-birth specific relative risks was carried out for each analysis, and its p-value is denoted by P_1 . In addition, the hypothesis that the relative risk is unity, given that relative risk is constant across strata, was tested; its p-value is denoted by P_2 . The SMR and both p-values are given for each contrast. Additional analyses were conducted and are presented at the end of this section. They indicate that the hypothesis of equal year-of-birth specific relative risks may not be met in the officer cohort.

Table 8

Year-Of-Birth Specific Mortality Rates
 (1257 Ranch Handers Versus 6171 Comparisons)
 (SMR = 0.954, P1 = 0.22, P2 = 0.73)

| Birth Year | Ranch Hand | | | Comparison | | | Rate Per 100 |
|------------|------------|------|--------------|------------|------|--|--------------|
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | | |
| 1905-1914 | 5 | 2 | 40.0 | 14 | 3 | | 21.4 |
| 1915-1919 | 17 | 5 | 29.4 | 96 | 14 | | 14.6 |
| 1920-1924 | 48 | 3 | 6.3 | 241 | 30 | | 12.4 |
| 1925-1929 | 84 | 2 | 2.4 | 501 | 46 | | 9.2 |
| 1930-1934 | 305 | 18 | 5.9 | 1389 | 79 | | 5.7 |
| 1935-1939 | 211 | 7 | 3.3 | 1020 | 39 | | 3.8 |
| 1940-1944 | 210 | 5 | 2.4 | 1096 | 24 | | 2.2 |
| 1945-1954 | 377 | 13 | 3.4 | 1814 | 50 | | 2.8 |
| Total | 1257 | 55 | | 6171 | 285 | | |

Table 9

Officer-Specific Mortality Rates by Year-Of-Birth
 (SMR = 0.791, P1 = 0.41, P2 = 0.37)

| Birth Year | Ranch Hand | | | Comparison | | | Rate Per 100 |
|------------|------------|------|--------------|------------|------|--|--------------|
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | | |
| 1910-1924 | 41 | 3 | 7.3 | 205 | 21 | | 10.2 |
| 1925-1934 | 194 | 5 | 2.6 | 930 | 52 | | 5.6 |
| 1935-1939 | 95 | 4 | 4.2 | 458 | 13 | | 2.8 |
| 1940-1944 | 91 | 2 | 2.2 | 495 | 7 | | 1.4 |
| 1945-1949 | 45 | 2 | 4.4 | 190 | 5 | | 2.6 |
| Total | 466 | 16 | | 2278 | 98 | | |

Table 10

Enlisted-Specific Mortality Rates by Year-Of-Birth
(SMR = 1.03, P1 = 0.67, P2 = 0.89)

| Birth Year | Ranch Hand | | | Comparison | | |
|------------|------------|------|--------------|------------|------|--------------|
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 |
| 1905-1914 | 4 | 2 | 50.0 | 12 | 3 | 25.0 |
| 1915-1919 | 9 | 2 | 22.2 | 54 | 10 | 18.5 |
| 1920-1924 | 16 | 3 | 18.8 | 80 | 13 | 16.2 |
| 1925-1929 | 41 | 2 | 4.9 | 211 | 26 | 12.3 |
| 1930-1934 | 154 | 13 | 8.4 | 749 | 47 | 6.3 |
| 1935-1939 | 116 | 3 | 2.6 | 562 | 26 | 4.6 |
| 1940-1944 | 119 | 3 | 2.5 | 601 | 17 | 2.8 |
| 1945-1954 | 332 | 11 | 3.3 | 1624 | 45 | 2.8 |
| Total | 791 | 39 | | 3893 | 187 | |

Table 11

Flying-Specific Mortality Rates by Year-Of-Birth
(SMR = 0.726, P1 = 0.85, P2 = 0.13)

| Birth Year | Ranch Hand | | | Comparison | | |
|------------|------------|------|--------------|------------|------|--------------|
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 |
| 1915-1924 | 44 | 4 | 9.1 | 220 | 26 | 11.8 |
| 1925-1934 | 272 | 10 | 3.7 | 1316 | 84 | 6.4 |
| 1935-1939 | 145 | 6 | 4.1 | 698 | 26 | 3.7 |
| 1940-1944 | 121 | 2 | 1.7 | 653 | 15 | 2.3 |
| 1945-1949 | 64 | 2 | 3.1 | 276 | 10 | 3.6 |
| Total | 646 | 24 | | 3163 | 161 | |

Table 12

Ground-Specific Mortality Rates by Year-of-Birth
(SMR = 1.23, P1 = 0.59, P2 = 0.33)

| Birth Year | Ranch Hand | | | Comparison | | |
|------------|------------|------|--------------|------------|------|--------------|
| | At Risk | Dead | Rate Per 100 | At Risk | Dead | Rate Per 100 |
| 1905-1914 | 5 | 2 | 40.0 | 14 | 3 | 21.4 |
| 1915-1919 | 8 | 1 | 12.5 | 51 | 8 | 15.7 |
| 1920-1924 | 13 | 3 | 23.1 | 66 | 10 | 15.2 |
| 1925-1929 | 31 | 2 | 6.5 | 151 | 20 | 13.2 |
| 1930-1934 | 86 | 8 | 9.3 | 423 | 21 | 5.0 |
| 1935-1939 | 66 | 1 | 1.5 | 322 | 13 | 4.0 |
| 1940-1944 | 89 | 3 | 3.4 | 443 | 9 | 2.0 |
| 1945-1954 | 313 | 11 | 3.5 | 1538 | 40 | 2.6 |
| Total | 611 | 31 | | 3008 | 124 | |

Additional log-linear analyses of the data in Tables 9 through 12 were carried out. These analyses are directed at the hypothesis already tested and reported, via the p-value (P1), but have an advantage in that they are more powerful. They have a disadvantage in that, since they were carried out after the data had already been tested, the overall level of significance is higher than the nominal 5%. The extent of the increases in power and significance level is not known. When year-of-birth is dichotomized (1905-1934, 1935-1954) and survival status (alive, dead) is analyzed by group (Ranch Hand, Comparison) and rank (officer, enlisted), a borderline significant four-way interaction is evident ($p=0.054$). The officer and enlisted relative risks are 0.53 and 1.10 in the 1905-1934 year-of-birth stratum and 1.58 and 0.95 in the 1935-1954 birth-year stratum. There were no three-way interactions in this analysis. When rank is replaced by flying status (flying, ground) in this four-factor analysis, no four-way interaction is seen ($p=0.085$), and no significant group by flying status by birth-year interaction ($p=0.92$) is observed.

Further, when the officer, enlisted, flying and ground subgroups are analyzed separately on survival status, group and birth-year, there is no three-way interaction for enlisted ($p=0.67$), flying ($p=0.30$) or ground personnel ($p=0.28$) but there is a significant three-way interaction for the officers ($p=0.044$). That is, the survival status by group relationship changes with year-of-birth in the officer cohort. Two-factor p-values are 0.87 for enlisted, 0.12 for flying, and 0.077 for ground personnel. These findings are consistent with previous analyses.

Taken together, these log-linear analyses suggest that relative risk changes with year-of-birth in the officer cohort. Specifically, the overall death experience of the Ranch Hand officers appears to compare favorably with the Comparisons. However, these diminished death rates appear to be found in the Ranch Hand officers born before 1935, while Ranch Hand officers with later birth dates evidence a rate equal to or exceeding that of the Comparisons (as seen in Table 14).

These findings cast doubt upon the validity of the SMR and, possibly, the linear rank procedures, as summary statistics for the officer cohort. The SMR appears to be a valid summary statistic for Ranch Hand and Comparison contrasts within the enlisted, flying and ground cohorts.

A summary of Logrank, relative risk and SMR results obtained is shown in Table 13.

Table 13
Noncause-Specific Statistical Summary

| <u>Age at Death</u> | | <u>Logrank</u> | | |
|-----------------------|--------------|----------------|----------------|------|
| <u>Group</u> | <u>Value</u> | <u>P-Value</u> | | |
| Officer | -0.835 | 0.40 | | |
| Enlisted | 0.187 | 0.85 | | |
| Flying | -1.34 | 0.18 | | |
| Ground | 0.976 | 0.33 | | |
| Total | 0.305 | 0.76 | | |
| <u>Deaths to Date</u> | | | | |
| <u>Group</u> | <u>RR</u> | <u>P-Value</u> | <u>SMR</u> | |
| | | | <u>P-Value</u> | |
| Officer | 0.715 | 0.26 | 0.791 | 0.37 |
| Enlisted | 0.987 | 0.94 | 1.03 | 0.89 |
| Flying | 0.692 | 0.12 | 0.726 | 0.13 |
| Ground | 1.21 | 0.35 | 1.23 | 0.33 |
| Total | 0.915 | 0.57 | 0.954 | 0.73 |

The data in Table 13 show reasonable consistency. The ground cohort displays excess death in the Ranch Hand group in contrast to the Comparison group, and the Ranch Hand flying cohort exhibits fewer deaths, but again these group differences are not statistically significant. The officer cohort evidences less death in the Ranch Hand group in contrast to the Comparison group but, again, this group difference is not statistically significant. However, as discussed above and shown in Table 14, these data appear to suggest that favorable mortality experience occurs in those officers born before 1935, while Ranch Hand officers born after 1935 appear to have experienced the same or greater death rate than their Comparisons.

Table 14
Death Rates by Group, Rank, Occupation and Year-of-Birth

| <u>Rank</u> | <u>Year-of-Birth</u> | Death Rate per 100 | | <u>Relative Risk</u> |
|---------------------|----------------------|--------------------|-------------------|----------------------|
| | | <u>Ranch Hand</u> | <u>Comparison</u> | |
| Officer | 1905-1934 | 3.4 | 6.4 | 0.53 |
| | 1935-1954 | 3.5 | 2.2 | 1.58 |
| Enlisted | 1905-1934 | 9.8 | 9.0 | 1.10 |
| | 1935-1954 | 3.0 | 3.2 | 0.95 |
| <u>Occupational</u> | <u>Year-of-Birth</u> | Death Rate per 100 | | <u>Relative Risk</u> |
| | | <u>Ranch Hand</u> | <u>Comparison</u> | |
| Flying | 1905-1934 | 4.4 | 7.2 | 0.62 |
| | 1935-1954 | 3.0 | 3.1 | 0.97 |
| Ground | 1905-1934 | 11.2 | 8.8 | 1.27 |
| | 1935-1954 | 3.2 | 2.7 | 1.19 |

The favorable, though not statistically significant, survival experience of Ranch Hand flying personnel, relative to the matched Comparison flyers is shown in Figure 4, where the survival curves for Ranch Hand and Comparison flyers are drawn on the same scale and coordinate system. In contrast, the relatively poorer, but not statistically significant, survival experience of the Ranch Hand ground personnel is illustrated in Figure 5, wherein the Ranch Hand and Comparison ground personnel survival curves are drawn on the same coordinate system.

3. Within-Group Analyses of Mortality

Within-group year-of-birth adjusted contrasts by occupation and rank via SMR's are summarized in Table 15. The data supporting these SMR analyses are shown in Appendix Tables 1 through 4.

Table 15
Summary of Within-Group SMR Analyses

| <u>Subgroups</u> | <u>SMR</u> | <u>P1</u> | <u>P2</u> |
|--------------------------|------------|-----------|-----------|
| Officers versus Enlisted | | | |
| Ranch Hand | 0.515 | 0.27 | 0.047 |
| Comparison | 0.648 | 0.88 | 0.001 |
| Flying versus Ground | | | |
| Ranch Hand | 0.572 | 0.41 | 0.067 |
| Comparison | 0.909 | 0.46 | 0.65 |

Table 15 shows that Ranch Hand officers are having significantly fewer deaths (SMR=0.515, p=0.047) than Ranch Hand enlisted personnel, after adjustment for year-of-birth. This officer versus enlisted differential is also significant and in the same direction in the Comparison group (SMR=0.648, p=0.001). The table also suggests a favorable mortality experience of Ranch Hand flyers relative to that of the Ranch Hand ground personnel (SMR=0.572, p=0.067), although this difference is not statistically significant. A flyer versus ground differential is not apparent in the Comparison group (SMR=0.909, p=0.65).

4. Cause-Specific Analyses

Table 16 shows death counts by cause and subgroup (flying officer, ground officer, flying enlisted and ground enlisted). Counts are shown for all 1257 Ranch Handers and the 6171 Comparisons. The distribution of new deaths in the Ranch Hand and Comparison groups are presented in Table 17, and age-adjusted relative risks for these data are shown in Table 18. Relative risks are calculated using a matched data algorithm; hence, only the 1241 Ranch Handers having matched Comparisons are used. Of the 16 unmatched Ranch Handers, two have died; a flying officer died of an accident and a ground airman died of circulatory system disease. Since these data are sparse, relative risks are only calculated on officer, enlisted, flying and ground subgroups, as well as on the total population.

One cell in Table 18, the analysis of malignancy deaths in flying personnel, contains two p-values for the significance of the relative risk estimate. The first is calculated using a null variance of the estimated relative risk and the second, within parentheses, is calculated using the non-null variance estimate. A null variance is defined as a variance derived upon the assumption that the true relative risk is unity. A non-null variance is derived without any assumption about the true value of the relative risk. The choice of which variance estimate to use in the standardization of the test statistic is currently a point of research in theoretical statistics. We have chosen to use the null variance when computing p-value because of analogies with other testing situations and because our power studies have shown the resulting test to be more powerful than the test using the general non-null estimate. Unfortunately, the non-null variance must be used in computing 95% confidence intervals for the relative risk, making the p-value and confidence interval sometimes incompatible.

Table 16

Deaths by Cause and Subgroup

| <u>Cause</u> | Officer | | | | Enlisted | | | | <u>Total</u> | |
|----------------------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|--------------|----------|
| | <u>Flying</u> | | <u>Ground</u> | | <u>Flying</u> | | <u>Ground</u> | | | |
| | <u>RH</u> | <u>C</u> | <u>RH</u> | <u>C</u> | <u>RH</u> | <u>C</u> | <u>RH</u> | <u>C</u> | <u>RH</u> | <u>C</u> |
| Accident | 8 | 33 | 0 | 1 | 4 | 27 | 7 | 35 | 19 | 96 |
| Suicide | 0 | 5 | 1 | 1 | 1 | 3 | 1 | 9 | 3 | 18 |
| Homicide | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 2 | 5 |
| Parasitic infection | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 4 |
| Malignant neoplasm | 0 | 15 | 0 | 1 | 1 | 14 | 5 | 21 | 6 | 51 |
| Uncertain neoplasm | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| Endocrine | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| Mental disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Nervous System | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| Circulatory System | 5 | 28 | 0 | 0 | 1 | 14 | 12 | 38 | 18 | 80 |
| Respiratory System | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 2 | 0 | 7 |
| Digestive System | 2 | 4 | 0 | 1 | 1 | 3 | 2 | 5 | 5 | 13 |
| Genitourinary System | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 3 |
| Congenital anomalies | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ill defined | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 2 |
| Total | 15 | 94 | 1 | 4 | 9 | 67 | 30 | 120 | 55 | 285 |

Table 17

New Deaths by Cause

| <u>Cause</u> | <u>Ranch Hand</u> | <u>Comparison</u> |
|-----------------------|-------------------|-------------------|
| Accident | 0 | 2 |
| Suicide | 0 | 2 |
| Homicide | 0 | 1 |
| Malignant Neoplasm | 0 | 8 |
| Circulatory System | 1 | 5 |
| Respiratory System | 0 | 2 |
| Totals | 1 | 20 |

Table 18

Cause-Specific Age Adjusted Relative Risks by Group
(1241 Ranch Handers versus 6171 Comparisons)

| <u>Group</u> | <u>Statistic</u> | <u>Cause</u> | | | | <u>Malignancy</u> | <u>Circulatory</u> | <u>Digestive</u> |
|--------------|------------------|-----------------|----------------|-----------------|---------|-------------------|--------------------|------------------|
| | | <u>Accident</u> | <u>Suicide</u> | <u>Homicide</u> | <u></u> | | | |
| Officer | Rel Risk | 0.968 | 0.833 | | | | 0.577 | 2.00 |
| | Conf Int | (0.160, 1.78) | (0.000, 2.60) | | | | (0.000, 1.27) | (0.000, 5.280) |
| | P-Value | 0.94 | 0.87 | | | | 0.38 | 0.36 |
| | Power | 0.61 | 0.29 | | | | 0.54 | 0.28 |
| Enlisted | Rel Risk | 0.830 | 0.833 | 2.00 | | 0.834 | 1.08 | 1.88 |
| | Conf Int | (0.275, 1.38) | (0.000, 2.08) | (0.000, 5.28) | | (0.104, 1.57) | (0.361, 1.78) | (0.000, 4.36) |
| | P-Value | 0.59 | 0.81 | 0.36 | | 0.69 | 0.82 | 0.31 |
| | Power | 0.79 | 0.37 | 0.28 | | 0.62 | 0.72 | 0.32 |
| Flying | Rel Risk | 0.905 | 0.625 | | | 0.172 | 0.500 | 2.14 |
| | Conf Int | (0.316, 1.49) | (0.000, 1.92) | | | (0.000, 0.516) | (0.000, 1.01) | (0.000, 5.04) |
| | P-Value | 0.77 | 0.67 | | | 0.069(0.000) | 0.20 | 0.22 |
| | Power | 0.78 | 0.32 | | | 0.57 | 0.66 | 0.31 |
| Ground | Rel Risk | 0.803 | 1.00 | 3.333 | | 1.08 | 1.34 | 1.67 |
| | Conf Int | (0.090, 1.52) | (0.000, 2.52) | (0.000, 9.30) | | (0.009, 2.15) | (0.367, 2.31) | (0.000, 4.33) |
| | P-Value | 0.63 | 1.0 | 0.099 | | 0.88 | 0.42 | 0.51 |
| | Power | 0.62 | 0.35 | 0.25 | | 0.49 | 0.62 | 0.29 |
| Total | Rel Risk | 0.917 | 0.833 | 2.00 | | 0.579 | 1.02 | 1.92 |
| | Conf Int | (0.447, 1.39) | (0.000, 1.85) | (0.000, 5.28) | | (0.087, 1.07) | (0.459, 1.58) | (0.000, 3.91) |
| | P-Value | 0.74 | 0.77 | 0.36 | | 0.22 | 0.95 | 0.17 |
| | Power | 0.90 | 0.45 | 0.28 | | 0.73 | 0.85 | 0.39 |

*P-value compatible with the confidence interval.

Tables 16 and 18 must be interpreted with care since the data are very sparse in some categories. The behavior of the Ejjigou-McHugh estimate, like that of other relative risk estimates, has not been investigated when the death probabilities are very small, as is the case for the causes analyzed in Table 18. The analyses of malignant neoplasm and circulatory system deaths are more reliable than the other cause-specific analyses because these two categories contain more deaths than the others.

Digestive system mortality by ICD code is shown in Table 19, site-specific malignant neoplasm mortality is shown in Table 20 and the morphology of neoplasms is shown in Table 21. There was one case of soft tissue sarcoma in a Comparison individual, but none in the Ranch Hand group. There have been no cancer deaths in the Ranch Hand group and eight in the Comparison group during 1984.

Table 19
Digestive System Mortality

| ICD Code | Deaths | |
|---------------------------------|------------|------------|
| | Ranch Hand | Comparison |
| Pancreatitis (5770) | 1 | 2 |
| Alcoholic cirrhosis (5712) | 0 | 4 |
| Nonalcoholic cirrhosis (5715) | 3 | 3 |
| Nonalcoholic fatty liver (5718) | 0 | 1 |
| Chronic liver disease (5728) | 0 | 2 |
| Alcoholic liver disease (5711) | 1 | 0 |
| Duodenal ulcer (5325) | 0 | 1 |
| Peptic ulcer (5334) | 0 | 0 |
| Hepatocellular disease (573a) | 0 | 0 |
| Total | 5 | 13 |

These codes were based on death certificate data; more detailed etiologic information has been requested but not yet received for the nonalcoholic cirrhosis and fatty liver deaths. It is of interest that during 1984, there were no new deaths attributable to the digestive system in either group.

Table 20
Site-Specific Malignant Neoplasm Mortality

| <u>Site ICD Code</u> | <u>Ranch Hand</u> | <u>Comparison</u> |
|--|-------------------|-------------------|
| Lip, oral cavity, pharynx (140-149) | 0 | 4 |
| Digestive organs, peritoneum (150-159) | 1 | 12 |
| Respiratory, intrathoracic (160-165) | 3 | 21 |
| Bone, connective tissue, skin, breast (170-175) | 0 | 1 |
| Genitourinary organs (179-189) | 1 | 3 |
| Brain (191-192) | 0 | 3 |
| Other and ill-defined sites (195) | 0 | 1 |
| Lymphatic and hematopoietic tissue (200-208) | 0 | 5 |
| No site specification (199) | <u>1</u> | <u>1</u> |
| Total | 6 | 51 |

Table 21

Morphology of Neoplasms

| ICD Code 9th Ed. | Nomenclature | Ranch | Deaths Hand | Deaths Comp |
|---------------------|---|-------|----------------|----------------|
| M800 | Neoplasms not otherwise specified (NOS) | | | |
| | Brain | 0 | 1 | |
| | Bronchus and Lung | 1 | 6 | |
| | Colon | 0 | 2 | |
| | Pancreas | 0 | 2 | |
| | Intestinal Tract | 0 | 1 | |
| | Head and Neck | 0 | 1 | |
| M801-804 | Epithelial neoplasms (NOS) | | | |
| | Bronchus and Lung | 1 | 10 | |
| | Esophagus | 0 | 1 | |
| | Kidney | 1 | 1 | |
| | Nasopharynx | 0 | 1 | |
| | Pancreas | 0 | 2 | |
| | Stomach | 1 | 0 | |
| | Unspecified site | 1 | 1 | |
| M805-808 | Papillary and Squamous Cell | | | |
| | Nasal Sinus | 0 | 1 | |
| | Lip | 0 | 1 | |
| | Tongue | 0 | 1 | |
| | Lung | 0 | 1 | |
| | Tonsil | 0 | 1 | |
| M814-838 | Adenomas and Adenocarcinomas | | | |
| | Appendix | 0 | 1 | |
| | Bronchus and Lung | 0 | 2 | |
| | Colon | 0 | 1 | |
| | Kidney | 0 | 2 | |
| | Stomach | 0 | 1 | |
| | Rectum | 0 | 1 | |
| M872-879 | Nevi and Melanomas | | | |
| | Skin (NOS) | 0 | 1 | |
| | Mediastinal | 1 | 0 | |
| M905 | Mesothelioma | | | |
| | Bronchus and Lung | 0 | 1 | |
| M938-948 | Gliomas | | | |
| | Frontal Lobe | 0 | 1 | |
| | Brain (NOS) | 0 | 1 | |
| M959-963 | Lymphomas NOS and Diffuse | | | |
| | Lymphomas (NOS) | 0 | 1 | |
| M964 | Reticulosarcoma | | | |
| | Malignant lymphoma histiocytic, (NOS) | 0 | 1 | |
| M965-966 | Hodgkin's disease | | | |
| | Hodgkin's (NOS) | 0 | 2 | |
| M986 | Myeloid Leukemias | | | |
| | Acute Myelocytic Leukemia | 0 | 1 | |
| | Total | 6 | 51 | |

5. Noncause-Specific Comparisons with External Populations

It is important to know not only how Ranch Handers and their matched Comparisons relate to each other, but also how their mortality rates compare with other military and civilian populations in the United States. These contrasts are used in an attempt to place the study groups in perspective with the overall mortality experience of known populations. Given the selection factors involved for entry to and retention in the military service, it is anticipated that the study groups would exhibit lower mortality than the U.S. White male population. Similarly, they might be expected to be more equivalent to the DOD retired personnel or occupational cohorts such as the U.S. civil service. In this report, the mortality experience of Ranch Handers and their matched Comparisons is compared with the expected death rates with reference to the 1978 U.S. White Male Life Table (8), the 1978 Department of Defense period life tables for nondisability retired military officer and enlisted personnel (9), and a 1974 U.S. active male civil service life table (10). All analyses in this section depend on the assumption, that relative risk is constant across age strata (Section 7). This assumption is not currently testable.

5.1 Comparisons with 1978 DOD Life Tables

In Tables 22 and 23, Ranch Hand officers and Comparison group officers are contrasted to a 1978 DOD nondisability retired officer life table and in Tables 24 and 25, Ranch Hand and Comparison group enlisted personnel are compared with a 1978 DOD nondisability retired enlisted life table. In each table, the column labeled "At Risk" lists the number of subjects entering each five-year age interval, the column labeled "Deaths" tabulates the number of deaths in the age intervals and the column labeled "Expected Deaths" gives the expected number of deaths in the age intervals of the study subjects if they had experienced the same death rates as those specified by the DOD table. The value of the test statistic for testing the null hypothesis of equality of the study and referenced life table is denoted by T ; its two-sided p-value is denoted by P . While each table summarizes the findings with five-year age intervals for ease of presentation, one-year age intervals were used for the actual computation of the statistic T . A negative value of T means that the study cohort has lived longer than expected relative to the reference population. The magnitude of the statistic T is sample-size dependent. All contrasts are unadjusted for race since the DOD tables are not race-specific. All analyses are conditioned on survival to age 35, since active duty personnel are not eligible for retirement prior to that age and, therefore, the DOD tables do not begin until that age. The totals in Tables 22 through 25 do not, therefore, agree with Table 1.

Table 22

Ranch Hand Officer Versus DOD Nondisability Retired Officer Life Table
($T=-4.43$, $P < 0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|--------------|----------------|---------------|------------------------|
| 37-39 | 459 | 2 | 2.8 |
| 40-44 | 414 | 1 | 4.7 |
| 45-49 | 324 | 1 | 5.4 |
| 50-54 | 232 | 2 | 4.7 |
| 55-59 | 84 | 1 | 2.7 |
| 60-64 | 40 | 2 | 1.7 |
| 65-69 | 6 | 0 | 0.2 |
| 70-70 | 1 | 0 | 0.0 |
| Total | | 9 | 22.2 |

Table 23

Comparison Officers Versus DOD Nondisability Retired Officer Life Table
($T=-3.71$, $P < 0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|--------------|----------------|---------------|------------------------|
| 35-39 | 2264 | 12 | 22.2 |
| 40-44 | 2067 | 14 | 23.1 |
| 45-49 | 1565 | 25 | 25.5 |
| 50-54 | 1095 | 15 | 23.0 |
| 55-59 | 472 | 10 | 13.9 |
| 60-64 | 192 | 8 | 8.2 |
| 65-69 | 40 | 0 | 1.9 |
| 70-70 | 2 | 0 | 0.0 |
| Total | | 84 | 117.9 |

Table 24

Ranch Hand Enlisted Personnel Versus DOD Nondisability
Retired Enlisted Life Table
($T=-1.01$, $P=0.31$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|--------------|----------------|---------------|------------------------|
| 35-39 | 771 | 7 | 8.4 |
| 40-44 | 454 | 5 | 6.4 |
| 45-49 | 333 | 6 | 7.9 |
| 50-54 | 214 | 6 | 6.5 |
| 55-59 | 67 | 2 | 3.0 |
| 60-64 | 26 | 3 | 2.0 |
| 65-69 | 10 | 0 | 1.0 |
| 70-71 | 3 | 1 | 0.2 |
| Total | | 30 | 35.5 |

Table 25

Comparison Enlisted Personnel Versus DOD Nondisability Retired
 Enlisted Life Table
 $(T=-4.29, P < 0.001)$

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 35-39 | 3777 | 21 | 41.2 |
| 40-44 | 2233 | 21 | 31.3 |
| 45-49 | 1628 | 38 | 38.7 |
| 50-54 | 1054 | 21 | 32.1 |
| 55-59 | 331 | 16 | 14.8 |
| 60-64 | 130 | 6 | 10.5 |
| 65-69 | 57 | 4 | 5.0 |
| 70-74 | 9 | 0 | 1.2 |
| 75-76 | 2 | 0 | 0.2 |
| Total | | 127 | 175.1 |

Tables 22 and 23 show highly favorable mortality experiences for Ranch Hand and Comparison officers. Conditioned on survival to age 35, they are living significantly longer than expected using the DOD death rates ($p < 0.001$ for both groups). Tables 24 and 25 show that Ranch Hand enlisted personnel are experiencing mortality patterns similar to the DOD retired enlisted population ($p=0.31$), and the Comparison enlisted personnel are living significantly longer ($p < 0.001$) than the DOD nondisability retired enlisted population. This, together with the nonsignificant logrank value for Ranch Hand versus Comparison enlisted personnel shown in Table 5 ($p=0.85$), suggests that the Ranch Hand versus Comparison contrasts may change with age at death. A view of this is seen in Table 26, which shows linear rank test results, comparing Ranch Handers and Comparisons conditioned on survival to age 35 (analogous to Table 5). Comparing the conditional analyses in Table 26 with the unconditional analyses in Table 5, it appears that group contrasts change with age at death within the officer cohort.

Table 26

Ranch Hand Versus Comparison
 Test Results and P-Values for Noncause-Specific Survival
 Conditioned on Survival to Age 35

| <u>Group</u> | <u>Logrank</u> | | <u>Wilcoxon</u> | |
|--------------|----------------|----------------|-----------------|----------------|
| | <u>(Value)</u> | <u>P-Value</u> | <u>(Value)</u> | <u>P-Value</u> |
| Officer | (-1.87) | 0.061 | (-1.99) | 0.047 |
| Enlisted | (0.802) | 0.42 | (0.810) | 0.42 |
| Flying | (-1.55) | 0.12 | (-1.66) | 0.097 |
| Ground | (1.12) | 0.27 | (1.12) | 0.26 |
| Total | (-0.481) | 0.63 | (-0.529) | 0.60 |

Additional categorical analyses described below reveal the interaction suggested by the previous conditioned analyses. These are shown in Tables 27 and 28 where survival status (alive, dead) is analyzed as a function of group (Ranch Hand, Comparison) and rank (officer, enlisted) on deaths under 35-years of age and separately on deaths over 35-years of age.

Table 27

Death Before Age 35, Ranch Hand Versus Comparisons
(Group By Rank By Status Interaction: $P=0.044$)

| | | <u>Status</u> | | | |
|-------------|--------------|---------------|-------------|--------------|----------------------|
| <u>Rank</u> | <u>Group</u> | <u>Alive</u> | <u>Dead</u> | <u>Total</u> | <u>Relative Risk</u> |
| Officer | Ranch Hand | 459 | 7 | 466 | 2.44 |
| | Comparison | <u>2264</u> | <u>14</u> | <u>2278</u> | |
| | Totals | 2723 | 21 | 2744 | |
| Enlisted | Ranch Hand | 782 | 9 | 791 | 0.738 |
| | Comparison | <u>3833</u> | <u>60</u> | <u>3893</u> | |
| | Totals | 4615 | 69 | 4684 | |

Table 28

Death After Age 35, Ranch Hand Versus Comparisons
(Group By Rank By Status Interaction: $P=0.039$)

| | | <u>Status</u> | | | |
|-------------|--------------|---------------|-------------|--------------|----------------------|
| <u>Rank</u> | <u>Group</u> | <u>Alive</u> | <u>Dead</u> | <u>Total</u> | <u>Relative Risk</u> |
| Officer | Ranch Hand | 450 | 9 | 459 | 0.528 |
| | Comparison | <u>2180</u> | <u>84</u> | <u>2264</u> | |
| | Totals | 2630 | 93 | 2723 | |
| Enlisted | Ranch Hand | 752 | 30 | 782 | 1.16 |
| | Comparison | <u>3706</u> | <u>127</u> | <u>3833</u> | |
| | Totals | 4458 | 157 | 4615 | |

In Table 27 and 28, the Ranch Hand versus Comparison contrast in the officer category is significantly different from the corresponding contrast in the enlisted category. This suggests that, among those surviving to age 35, Ranch Hand officers are experiencing fewer deaths (relative risk = 0.528) than their matched Comparisons while the Ranch Hand enlisted are experiencing more deaths than their matched Comparisons (relative risk = 1.16). This situation is reversed in those men dying prior to age 35. The relevance of these observations is unclear at this time. These death rates are summarized in Table 29. The rate that is most apparently different is the low Ranch Hand officer death rate for those officers who survived to age 35. This low rate may parallel the favorable mortality experienced by those Ranch Hand officers born before 1935, as will be shown later in this report. Further analyses in future reports will attempt to clarify these patterns.

Table 29
Death Rates by Age at Death, Group, and Rank

Death Rates per 100

| Age at Death | Ranch Hand | | Comparison | |
|---------------|-------------|-------------|--------------|--------------|
| | Officers | Enlisted | Officers | Enlisted |
| Before Age 35 | 1.5 (N=466) | 1.1 (N=791) | 0.6 (N=2278) | 1.5 (N=3893) |
| After Age 35 | 2.0 (N=459) | 3.8 (N=782) | 3.7 (N=2264) | 3.3 (N=3833) |

5.2 Comparisons with the U.S. Active Male Civil Service Life Table

To further place the Ranch Handers and their matched Comparisons in perspective, Ranch Handers, Comparisons, and officer and enlisted personnel are contrasted with the 1974 male active U.S. civil service life table (10). These contrasts are shown in Tables 30 through 35. There was no adjustment for civil service grade in these analyses. Therefore, socioeconomic factors may not be fully equivalent, especially in the analyses of the officer and enlisted subgroups. In future mortality updates, attempts will be made to account for the grade structure of the civil service population.

Table 30
All Ranch Handers Versus U.S. Male Civil Service
(T=-0.313, P=0.75)

| Age | At Risk | Deaths | Expected Deaths |
|-------|---------|--------|-----------------|
| 21-24 | 1257 | 2 | 6.8 |
| 25-29 | 1255 | 7 | 6.0 |
| 30-34 | 1248 | 7 | 5.7 |
| 35-39 | 1230 | 9 | 7.0 |
| 40-44 | 868 | 6 | 8.3 |
| 45-49 | 657 | 7 | 9.6 |
| 50-54 | 446 | 8 | 7.3 |
| 55-59 | 151 | 3 | 3.7 |
| 60-64 | 66 | 5 | 2.2 |
| 65-69 | 16 | 0 | 0.6 |
| 70-71 | 4 | 1 | 0.1 |
| Total | | 55 | 57.3 |

Table 31

Comparison Versus U.S. Male Civil Service
($T=-1.04$, $P=0.30$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 19-19 | 6171 | 2 | 10.5 |
| 20-24 | 6169 | 18 | 43.1 |
| 25-29 | 6151 | 29 | 29.5 |
| 30-34 | 6122 | 25 | 28.1 |
| 35-39 | 6041 | 33 | 34.3 |
| 40-44 | 4300 | 35 | 40.6 |
| 45-49 | 3193 | 63 | 46.4 |
| 50-54 | 2149 | 36 | 35.7 |
| 55-59 | 803 | 26 | 18.8 |
| 60-64 | 322 | 14 | 11.1 |
| 65-69 | 87 | 4 | 3.7 |
| 70-74 | 11 | 0 | 0.6 |
| Total | | 285 | 302.5 |

Table 32

Ranch Hand Officers Versus U.S. Male Civil Service
($T=-1.92$, $P=0.054$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 25-29 | 466 | 3 | 2.2 |
| 30-34 | 463 | 4 | 2.1 |
| 35-39 | 459 | 2 | 3.0 |
| 40-44 | 414 | 1 | 4.0 |
| 45-49 | 324 | 1 | 4.8 |
| 50-54 | 232 | 2 | 4.0 |
| 55-59 | 84 | 1 | 2.2 |
| 60-64 | 40 | 2 | 1.2 |
| 65-69 | 6 | 0 | 0.2 |
| 70-74 | 1 | 0 | 0.0 |
| Total | | 16 | 23.7 |

Table 33

Comparison Officers Versus U.S. Male Civil Service
(Comparisons: $T=-1.88$, $P=0.060$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|--------------|----------------|---------------|------------------------|
| 25-29 | 2278 | 9 | 10.9 |
| 30-34 | 2269 | 5 | 10.4 |
| 35-39 | 2264 | 12 | 14.6 |
| 40-44 | 2067 | 14 | 19.8 |
| 45-49 | 1565 | 25 | 22.7 |
| 50-54 | 1095 | 15 | 19.3 |
| 55-59 | 472 | 10 | 11.3 |
| 60-64 | 192 | 8 | 6.1 |
| 65-69 | 40 | 0 | 1.4 |
| 70-70 | 2 | 0 | 0.0 |
| Total | | 98 | 116.6 |

Table 34

Ranch Hand Enlisted Personnel Versus U.S. Male Civil Service
($T=1.28$, $P=0.20$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|--------------|----------------|---------------|------------------------|
| 21-24 | 791 | 2 | 4.3 |
| 25-29 | 789 | 4 | 3.8 |
| 30-34 | 785 | 3 | 3.6 |
| 35-39 | 771 | 7 | 4.0 |
| 40-44 | 454 | 5 | 4.3 |
| 45-49 | 333 | 6 | 4.8 |
| 50-54 | 214 | 6 | 3.3 |
| 55-59 | 67 | 2 | 1.5 |
| 60-64 | 26 | 3 | 1.0 |
| 65-69 | 10 | 0 | 0.5 |
| 70-71 | 3 | 1 | 0.1 |
| Total | | 39 | 31.1 |

Table 35

Comparison Enlisted Personnel Versus U.S. Male Civil Service
(T=1.54, P=0.12)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 19-19 | 3893 | 2 | 6.6 |
| 20-24 | 3891 | 18 | 27.2 |
| 25-29 | 3873 | 20 | 18.5 |
| 30-34 | 3853 | 20 | 17.6 |
| 35-39 | 3777 | 21 | 19.7 |
| 40-44 | 2233 | 21 | 20.9 |
| 45-49 | 1628 | 38 | 23.7 |
| 50-54 | 1054 | 21 | 16.4 |
| 55-59 | 331 | 16 | 7.5 |
| 60-64 | 130 | 6 | 5.0 |
| 65-69 | 57 | 4 | 2.3 |
| 70-74 | 9 | 0 | 0.6 |
| Total | 187 | | 166.1 |

The Ranch Handers and their matched Comparisons are statistically quite close to the male civil service population. In these contrasts, the healthy worker effect is roughly equivalent although there is no adjustment for socioeconomic status. The contrasts of officer personnel in the Ranch Hand and Comparison cohorts with the male civil service reveal that the Ranch Hand and Comparison officers are experiencing a slightly, but not significantly better mortality than the civil service. Ranch Hand and Comparison enlisted personnel are experiencing more mortality than the civil service, but these differences are not statistically significant. All of these findings are consistent with the linear rank testing shown in Table 5, the relative risks in Table 6 and the SMR's in Tables 8, 9, and 10.

5.3 Comparisons with the U.S. 1978 White Male Life Table

Finally, the mortality experience of the non-Black Ranch Handers and their matched Comparisons is contrasted with the 1978 U.S. White Male Life Table.

Table 36

Non-Black Ranch Handers Versus the 1978 U.S. White Male Life Table
($T=-5.63$, $P<0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 21-24 | 1181 | 2 | 9.1 |
| 25-29 | 1179 | 6 | 9.9 |
| 30-34 | 1173 | 7 | 9.6 |
| 35-39 | 1155 | 8 | 10.7 |
| 40-44 | 824 | 5 | 11.6 |
| 45-49 | 627 | 7 | 14.5 |
| 50-54 | 432 | 7 | 12.4 |
| 55-59 | 150 | 3 | 6.7 |
| 60-64 | 66 | 5 | 4.7 |
| 65-69 | 16 | 0 | 1.3 |
| 70-71 | 4 | 1 | 0.2 |
| Total | | 51 | 90.8 |

Table 37

Non-Black Comparisons Versus the 1978 U.S. White Male Life Table
($T=-12.8$, $P<0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Deaths</u> | <u>Expected Deaths</u> |
|------------|----------------|---------------|------------------------|
| 19-19 | 5816 | 1 | 10.3 |
| 20-24 | 5815 | 16 | 55.5 |
| 25-29 | 5799 | 27 | 48.6 |
| 30-34 | 5772 | 23 | 47.6 |
| 35-39 | 5693 | 31 | 53.1 |
| 40-44 | 4095 | 31 | 57.3 |
| 45-49 | 3047 | 56 | 70.1 |
| 50-54 | 2069 | 36 | 60.7 |
| 55-59 | 793 | 24 | 34.0 |
| 60-64 | 322 | 14 | 23.5 |
| 65-69 | 97 | 4 | 7.7 |
| 70-74 | 11 | 0 | 1.2 |
| 75-76 | 2 | 0 | 0.2 |
| Total | | 263 | 469.7 |

Table 38

Non-Black Ranch Hand Officers Versus the 1978 U.S. White Male Life Table
($T=-5.89$, $P<0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Dead</u> | <u>Expected Deaths</u> |
|------------|----------------|-------------|------------------------|
| 25-29 | 457 | 3 | 3.8 |
| 30-34 | 454 | 4 | 3.7 |
| 35-39 | 450 | 2 | 4.7 |
| 40-44 | 407 | 1 | 5.8 |
| 45-49 | 321 | 1 | 7.5 |
| 50-54 | 231 | 2 | 6.9 |
| 55-59 | 84 | 1 | 3.9 |
| 60-64 | 40 | 2 | 2.6 |
| 65-69 | 6 | 0 | 0.4 |
| 70-70 | 1 | 0 | 0.0 |
| Total | | 16 | 39.5 |

Table 39

Non-Black Comparison Officers Versus the 1978 U.S. White Male Life Table
($T=-9.85$, $P<0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Dead</u> | <u>Expected Deaths</u> |
|------------|----------------|-------------|------------------------|
| 25-29 | 2253 | 9 | 18.9 |
| 30-34 | 2244 | 5 | 18.5 |
| 35-39 | 2239 | 12 | 23.6 |
| 40-44 | 2042 | 14 | 28.8 |
| 45-49 | 1548 | 25 | 35.5 |
| 50-54 | 1086 | 15 | 33.6 |
| 55-59 | 472 | 10 | 20.6 |
| 60-64 | 192 | 8 | 12.9 |
| 65-69 | 40 | 0 | 2.8 |
| 70-70 | 2 | 0 | 0.0 |
| Total | | 98 | 195.3 |

Table 40

Non-Black Ranch Hand Enlisted Personnel Versus the 1978 U.S. White Male Life Table
($T=-2.20$, $P=0.028$)

| <u>Age</u> | <u>At Risk</u> | <u>Dead</u> | <u>Expected Deaths</u> |
|------------|----------------|-------------|------------------------|
| 21-24 | 724 | 2 | 5.6 |
| 25-29 | 722 | 3 | 6.0 |
| 30-34 | 719 | 3 | 5.9 |
| 35-39 | 705 | 6 | 6.0 |
| 40-44 | 417 | 4 | 5.8 |
| 45-49 | 306 | 6 | 7.0 |
| 50-54 | 201 | 5 | 5.5 |
| 55-59 | 66 | 2 | 2.8 |
| 60-64 | 26 | 3 | 2.1 |
| 65-69 | 10 | 0 | 1.0 |
| 70-71 | 3 | 1 | 0.2 |
| Total | | 35 | 47.9 |

Table 41

Non-Black Comparison Enlisted Personnel Versus the 1978 U.S. White Male Life Table
($T=-6.56$, $P<0.001$)

| <u>Age</u> | <u>At Risk</u> | <u>Dead</u> | <u>Expected Deaths</u> |
|------------|----------------|-------------|------------------------|
| 19-19 | 3563 | 1 | 6.3 |
| 20-24 | 3562 | 16 | 34.0 |
| 25-29 | 3546 | 18 | 29.7 |
| 30-34 | 3528 | 18 | 29.0 |
| 35-39 | 3454 | 19 | 29.5 |
| 40-44 | 2053 | 17 | 28.5 |
| 45-49 | 1499 | 31 | 34.7 |
| 50-54 | 983 | 21 | 27.1 |
| 55-59 | 321 | 14 | 13.4 |
| 60-64 | 130 | 6 | 10.6 |
| 65-69 | 57 | 4 | 4.9 |
| 70-74 | 9 | 0 | 1.1 |
| 75-76 | 2 | 0 | 0.2 |
| Total | | 165 | 248.9 |

The healthy worker effect is an expected phenomenon in these data since Air Force veterans have been selected for active duty on the basis of health and technical ability. This effect is clearly evident in the contrasts shown in Tables 36 through 41. Both Ranch Handers and Comparisons are seen to be living far longer than expected relative to the general U.S. White male population. The same effect

is seen in both Ranch Hand and Comparison officers (Tables 38 and 39) and in Ranch Hand and Comparison enlisted personnel. In contrast with previous mortality analyses (1,3), the analysis of the Ranch Hand enlisted cohort has reached statistical significance with the passage of time.

6. Further Covariate Adjustments

Some of the contrasts shown in previous sections in this report were further analyzed using information about the Vietnam experience for Ranch Handers and Comparisons. These analyses are motivated by the need for clarification of previous contrasts and should be viewed as preliminary to more complete analyses which will be presented in future reports. The information used here consists of (1) tour length and (2) a measure of cumulative exposure to dioxin. Tour length is defined as the cumulative time, in months, spent on assignment to Ranch Hand units by a Ranch Hander and to C-130 cargo units in SEA by a Comparison. Cumulative exposure to dioxin, termed the "exposure index," is defined in the Baseline Morbidity Report (2) and is proportional to the dioxin content of the herbicides being sprayed and inversely proportional to the number of persons sharing the workload with the subject to whom it is applied.

6.1 Ranch Hand and Comparison Contrasts on Tour Length

In this report, some descriptive statistics on tour length are presented. Table 42 shows the 5th, 50th, and 95th percentiles of tour length in months for flying and ground personnel, and officers and enlisted personnel in the Ranch Handers and Comparison groups. The effect of tour length on mortality will be more thoroughly investigated in future reports.

Table 42

Tour Length Percentiles (in Months) for Ranch Handers and Comparisons*

| <u>Group</u> | <u>Rank</u> | <u>Flying Status</u> | <u>Percentiles</u> | | | <u>Sample Size</u> | <u>Population Size</u> |
|---------------|-------------|----------------------|--------------------|------------|------------|--------------------|------------------------|
| | | | <u>5%</u> | <u>50%</u> | <u>95%</u> | | |
| Ranch Hand | Officer | Flying Ground | 4 | 12 | 19 | 439 | 440 |
| | | | 5 | 13 | 15 | 26 | 26 |
| | Enlisted | Flying Ground | 4 | 12 | 21 | 206 | 206 |
| | | | 5 | 13 | 20 | 585 | 585 |
| <u>Totals</u> | | | | | | 1256 | 1257 |
| Comparison | Officer | Flying Ground | 11 | 19 | 46 | 2123 | 2153 |
| | | | 11 | 18 | 43 | 123 | 125 |
| | Enlisted | Flying Ground | 10 | 19 | 49 | 995 | 1010 |
| | | | 10 | 18 | 45 | 2859 | 2883 |
| <u>Totals</u> | | | | | | 6100 | 6171 |

* The totals show that one Ranch Hander and 71 Comparisons have no tour data at this time.

In general, the Comparisons had longer tour lengths than did the Ranch Handers. This is the result of longer tours of duty at noncombat zone bases (Comparisons) relative to combat area bases (Ranch Hand).

6.2 Ranch Hand Exposure Analyses

The effect of exposure on mortality was assessed on the 1140 Ranch Handers having exposure information in a log-linear analysis based on survival (dead, alive), rank (officer, enlisted), year-of-birth (1905-1934, 1935-1954), and exposure (light, medium, heavy). These data are shown in Table 43.

Table 43

Ranch Hand Mortality Adjusted for Year-Of-Birth, Rank and Exposure*

| Exposure | Rank | Birth Year | Survival Status | | | Death Rate per 100 |
|---------------|----------|------------|-----------------|-------------|-------------|--------------------|
| | | | Dead | Alive | Total | |
| Light | Officer | 1905-1934 | 1 | 54 | 55 | 1.8 |
| | | 1935-1954 | 2 | 61 | 63 | 3.2 |
| | Enlisted | 1905-1934 | 7 | 50 | 57 | 12.2 |
| | | 1935-1954 | 3 | 121 | 124 | 2.4 |
| Medium | Officer | 1905-1934 | 2 | 79 | 81 | 2.5 |
| | | 1935-1954 | 2 | 66 | 68 | 2.9 |
| | Enlisted | 1905-1934 | 4 | 51 | 55 | 7.3 |
| | | 1935-1954 | 6 | 214 | 220 | 2.7 |
| Heavy | Officer | 1905-1934 | 5 | 84 | 89 | 5.6 |
| | | 1935-1954 | 3 | 73 | 76 | 3.9 |
| | Enlisted | 1905-1934 | 6 | 84 | 90 | 6.7 |
| | | 1935-1954 | 7 | 155 | 162 | 4.3 |
| Totals | | | 48 | 1092 | 1140 | 4.2 |

* 117 Ranch Hand personnel either had a tour AFSC which removed any chance of exposure or were assigned to a Ranch Hand unit at a time when no spraying occurred or both. Tour information is not available for one Ranch Hander.

There is no four-way interaction (exposure/rank/birth year/survival status) in the data shown in Table 43 ($p=0.40$); there are no statistically significant three-way interactions involving survival, and the two-way survival by exposure interaction is not significant ($p=0.54$). These patterns do not indicate a herbicide exposure effect.

7. Statistical Aspects

The purpose of this section is to update the information contained in Chapter VI, Statistical Aspects, of the Baseline Mortality Report (1), regarding the properties of the statistical procedures used in this and all preceding mortality reports in this series. The procedures discussed here are: linear rank tests (5),

log-linear analysis (11), the SMR analysis (7), and the Gail and Ware study group versus reference life table analysis (12) and the Ejigou-McHugh relative risk estimator (6).

7.1 Large Sample P-Value Approximations

P-value calculations for all five of these procedures rely on large sample approximations of the distribution of the statistic under the associated null hypotheses, termed the null distribution. This is because the finite sample null distributions of these procedures have not been formulated. The relevant issue, therefore, is the adequacy of these approximations in the context of this study.

Linear rank tests: The adequacy of the large sample p-value approximation in certain linear rank procedures has been investigated via Monte Carlo simulation by Latta (13) in the two-sample situation and by Michalek, Mihalko and White (14) on one-to-many matched data. The primary goal of both of these studies was to investigate the power of certain linear rank procedures under various failure time distributions, censoring percentages and sample size configurations. In the two-sample case, the Prentice efficient score censored data extension of the Wilcoxon procedure was judged to be best overall, and in the matched data case, the logrank test with the hypergeometric variance was deemed the best overall procedure. These are the two procedures used in this and all previous mortality reports in this series. These simulation studies did not, however, attempt to assess the adequacy of the large sample distributions of these procedures as a function of sample size and percent censoring. In particular, neither study assessed the properties of these procedures with heavy censoring (as seen in these mortality data). Unpublished Monte Carlo studies conducted at the USAF School of Aerospace Medicine have shown, however, that the logrank and Wilcoxon tests achieve nominal 1% and 5% significance levels in two-sided testing on simulated 1:5 matched data with 1200 matched sets and 96% censoring when the survival distributions follow the accelerated failure time model (5) and the censoring variable is uniformly distributed. These results, while encouraging, are not directly applicable to this study since all linear rank testing in these reports were carried out with the data stratified by one-year birth intervals, race and occupation. Other simulations did confirm the validity of the large sample null distributions in this highly stratified case, but not with censoring percentages as high as 96%. Based on these published and unpublished investigations and the smallest sample sizes in this study (466 Ranch Hand officers contrasted with 2278 Comparison officers), the authors of this report believe that the linear rank p-value approximations are adequate when consideration is restricted to sample size and percent censoring.

Log-linear analyses: All p-values derived from log-linear analyses are based on large sample chi-square approximations. The adequacy of these approximations has generally been studied in terms of the magnitudes of the expected cell counts in multiway contingency tables. There is extensive literature on this subject with resultant guidance published in recent statistical texts. Conover (15) states that the chi-square approximation is good if the expected cell counts are fairly large but if some of the expected counts are small, the approximation may be poor. He quotes Cochran (16), who concluded that, if any of the expected counts are less than 1 or if more than 20% are less than 5, the approximation may be poor. Conover views

Cochran's advice as, perhaps, too conservative and renders the opinion that the expected counts may be as small as 1 without endangering the validity of the test. Since most expected counts in this report are greater than 5, the chi-square approximations are considered adequate by the authors of this report.

SMR analyses: Large sample chi-square approximations were used to obtain the p-values in the SMR analyses. The first of these was for a likelihood ratio test for the hypothesis that the data satisfies the product model (7), the second was for a likelihood ratio test that the SMR was equal to unity. The test of fit for the product model is analogous to a test for no three-factor interaction in a log-linear model, the factors being survival states (dead, alive), group (Ranch Hand, Comparison) and year-of-birth. Sample size requirements for this procedure are, therefore, the same as those described above for log-linear analysis; that is, that the expected numbers of dead at each level of year-of-birth be at least 5 or at least 1, depending on the advice of Conover and Cochran. The test for an SMR equal to unity is not analogous to a test on the main effect in the same log-linear model. No guidance has been published regarding the sample size requirements for the adequacy of the chi-square approximation. In our opinion, this approximation is adequate in these data.

Gail and Ware analysis: The test statistic for comparing an observed survival distribution with a reference life table is a standardized sum of deviations between observed and expected numbers of deaths and has, for large samples, an approximate standard normal distribution under the null hypothesis. The minimum sample size and maximum censoring percentage needed for this approximation to be adequate is not known. In our opinion, this approximation is adequate in these data.

Ejigou-McHugh relative risk analyses: The statistic used in testing relative risk equal to unity has an approximate standard normal distribution under the null hypothesis when the number of matched sets is large. In-house simulations have shown that this approximation is adequate with 1200 match sets. The threshold of adequacy has not been investigated to date. In our judgement, the approximation is good in these analyses.

7.2 Assumptions and Statistical Assessment of their Validity

In all studies, statistical procedures are based upon assumptions regarding the data. Good statistical practice requires that the assumptions be checked before proceeding to the final analysis. In most cases this is done subjectively by examining plots of the data. For some statistical procedures, the assumptions can be tested directly; such tests are termed pretests. When resampling is not possible, pretesting should be accounted for in the overall inference. Unfortunately, pretests and procedures which account for pretests in the overall inference are almost nonexistent in the field of statistics. Of the five procedures used in this report, a pretest of assumptions exists only for the SMR analysis, and it is not currently known, how to take that pretesting into consideration in the overall analysis. Generally, pretesting should be carried out so that the overall significance level of the pretests and the final inferential test should be a prescribed value, such as 5%.

Linear rank tests: The logrank and Wilcoxon procedures are based upon the assumptions that the underlying survival distributions are continuous, that survival and censoring are statistically independent and that the difference in group sur-

survival distributions does not change with levels of the stratification variable. The third assumption would hold if, for example, there were no interaction terms involving group membership in the accelerated failure time model (5). In our opinion, the first two of these assumptions can be safely assumed in these analyses. The third must be checked. There does not exist a statistical procedure for testing the assumption that the difference in group survival distributions does not change with levels of the stratification variable, without making further assumptions. If further assumptions were made and such a test were developed, there would, at this time, be no way to adjust its critical value so that the overall significance level was 5%. In this report, the stratification variables were year-of-birth, race, and occupation. The no-interaction assumption was subjectively checked by comparing the logrank and Wilcoxon values with other analyses, looking for consistency. There is some indication that the assumption is not met in the officer subgroup and, therefore, the logrank and Wilcoxon values are misleading for contrasting Ranch Hand and Comparison officers.

Log-linear analyses: The log-linear analyses are based upon the assumptions that the data are distributed as multinomials or product-multinomials, that all interactions of order higher than the one of interest are nonexistent and that there is no confounding. The multinomial assumption is correct in these analyses because the data were categorized so that the multinomial or product-multinomial model would hold. Tests for the existence of interactions of all orders are available and are carried out in all analyses but, at this time, there is no way to adjust their critical values so that the significance level of the overall procedure is 5%. Statisticians typically use a 5% significance level for each pretest, but this may vary.

SMR analyses: The basic assumption in these analyses is that relative risk is constant across levels of the stratification variable. In these analyses the stratification variable is year-of-birth. A likelihood ratio test was used to check this assumption. It is not known how to prescribe its critical value so that the overall level of significance is 5%. This assumption was also checked using additional log-linear analyses.

Gail and Ware analyses: The basic assumption in these analyses is that the study hazard function is proportional to the reference hazard function. There does not exist a single sample test for the proportional hazards assumption. This assumption was checked subjectively by computing relative risks at different ages within the data sets.

Ejigou-McHugh relative risk analyses: This analysis assumes that relative risk is constant with respect to the matching variables. A procedure for testing this assumption has been recently developed (17) but has not yet been programmed for inclusion in these reports. The new method does not provide for the adjustment of the pretest critical value so that the overall significance level is 5%. This assumption was subjectively checked in this report by comparing the Ejigou-McHugh relative risk with the SMR, looking for consistency.

7.3 Summary

The issues regarding large sample approximations and pretesting assumptions are intrinsic to the field of mathematical statistics and, therefore, are relevant to

applications of statistical theory in any research. In this respect, the statistical content of this report reflects the extent of current theory.

8. Future Commitments

Future work will attempt to evaluate mortality patterns as a function of occupational subgroup in the ground cohort. This effort will require the collection of data to delineate differential exposure between occupational subgroups. Flight line duties and herbicide contact will be ascertained objectively, along with additional medical risk factors, occupational exposures and socioeconomic factors. These analyses will be increasingly meaningful as the population ages and mortality rates permit use of more incisive statistical tools. Joint morbidity-mortality analyses, adjusting for relevant covariates will be carried out. Finally, the small sample properties of the linear rank, relative risk, and SMR tests will be investigated by simulation and analytical methods.

9. Summary and Conclusion

Evaluation of summary counts of death by rank and occupation did not reveal any statistically significant differences between the Ranch Hand and Comparison groups. Other mortality analyses described in this report have revealed some differences in death experience between the herbicide/dioxin exposed group, their matched Comparisons and other external Comparison groups.

Overall mortality of the Ranch Hand group (4.4%) is nearly identical to that of the Comparison group (4.6%). Ranch Hand officers have experienced fewer deaths than the Comparison group officers, but this difference is not statistically significant. There is an interaction in these data, however. Ranch Hand officers born between 1905 and 1935 have experienced fewer deaths than Comparison officers born during the same era. On the other hand, Ranch Hand officers born after 1935 have experienced more deaths than their Comparisons. Although these differences within birth-year strata are not statistically significant, this change in the group by survival status relationship with birth year is statistically significant. Additionally, Ranch Hand officers experienced fewer deaths after age 35 years than did Comparison officers, while Ranch Hand officers experienced more deaths before age 35 years than did Comparisons. Further research will investigate whether there is any association between birth year and age of death and mortality patterns in these officer cohorts.

At this time, Ranch Hand ground and enlisted personnel have experienced more mortality and Ranch Hand flying personnel have experienced lower mortality than their Comparisons, but these differences are not statistically significant. Preliminary analyses using exposure indices have indicated no association between herbicide exposure in either the officer, enlisted, flying or ground Ranch Hand subgroups.

Both Ranch Hand and Comparison officers have experienced less mortality than Ranch Hand or Comparison enlisted personnel. Ranch Hand flying personnel have experienced less mortality than Ranch Hand ground personnel, while Comparison flying and ground personnel have experienced similar mortality patterns.

Examining causes of death, Ranch Hand officer and flying groups have experienced fewer deaths from cardiovascular disease and cancer than have the Comparisons, but this difference is not statistically significant. No apparent specific disease excesses were noted in the Ranch Hand ground or enlisted groups relative to their Comparisons. All Ranch Hand cohorts are elevated in the category of digestive system deaths, but this difference is not statistically significant. There was a single case of soft tissue sarcoma in the Comparison group, and no cases occurred in the Ranch Handers.

The Ranch Hand and Comparison groups were contrasted with five external populations. All study groups are experiencing significantly less mortality than U.S. White males. All study groups except Ranch Hand enlisted personnel are experiencing statistically significantly less mortality than the corresponding nondisability retired DOD population. The Ranch Hand enlisted mortality is not significantly different from the nondisability retired DOD enlisted population. The Ranch Hand and Comparison groups taken together have experienced a mortality pattern not statistically different from civil service employees.

In conclusion, summary counts of death by rank and occupation did not reveal any statistically significant differences, within the power limitations of this study, between the Ranch Hand and Comparison groups. This study has excellent power of detecting a doubling of risk of death, and therefore it is unlikely that an effect of this magnitude could have been missed. Ranch Hand officers born between 1905 and 1935 have experienced favorable mortality relative to their Comparisons while the converse is true for officers born after 1935. Analogous patterns are seen in officers, conditioned on age at death. Although Ranch Hand ground personnel experienced less favorable mortality relative to Comparisons irrespective of date of birth or age at death, this difference is not statistically significant. Exposure index analyses indicate these mortality rate differences cannot be attributed to herbicide exposure. These analyses have identified several findings of interest, which will be further evaluated in future mortality updates. The findings of this report are similar to those of prior mortality analyses with the exception that the non-Black Ranch Hand enlisted personnel now demonstrate statistically significantly better survival than the 1978 U.S. White male population.

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Appendix Table 1

Ranch Hand Officers Versus Ranch Hand Enlisted
 Mortality by Year-Of-Birth
 (SMR = 0.515, P1 = 0.27, P2 = 0.047)

| Birth Year | Ranch Hand Officers | | | Ranch Hand Enlisted | | |
|---------------|---------------------|------|-----------------|---------------------|------|-----------------|
| | At Risk | Dead | Rate per 100 | At Risk | Dead | Rate per 100 |
| 1905-1924 | 41 | 3 | 7.3 | 29 | 7 | 24.1 |
| 1925-1934 | 194 | 5 | 2.6 | 195 | 15 | 7.7 |
| 1935-1939 | 95 | 4 | 4.2 | 116 | 3 | 2.6 |
| 1940-1944 | 91 | 2 | 2.2 | 119 | 3 | 2.5 |
| 1945-1954 | 45 | 2 | 4.4 | 332 | 11 | 3.3 |
| Total | 466 | 16 | | 791 | 39 | |

Appendix Table 2

Comparison Officers Versus Comparison Enlisted Mortality by Year-Of-Birth
 (SMR = 0.648, P1 = 0.88, P2 = 0.001)

| Birth Year | Officers | | | Enlisted | | |
|---------------|----------|------|-----------------|----------|------|-----------------|
| | At Risk | Dead | Rate per 100 | At Risk | Dead | Rate per 100 |
| 1905-1919 | 44 | 4 | 9.1 | 66 | 13 | 19.7 |
| 1920-1924 | 161 | 17 | 10.6 | 80 | 13 | 16.2 |
| 1925-1929 | 290 | 20 | 6.9 | 211 | 26 | 12.3 |
| 1930-1934 | 640 | 32 | 5.0 | 749 | 47 | 6.3 |
| 1935-1939 | 458 | 13 | 2.8 | 562 | 26 | 4.6 |
| 1940-1944 | 495 | 7 | 1.4 | 601 | 17 | 2.8 |
| 1945-1954 | 190 | 5 | 2.6 | 1624 | 45 | 2.8 |
| Total | 2278 | 98 | | 3893 | 187 | |

Appendix Table 3

Ranch Hand Flying Personnel Versus Ranch Hand Ground Personnel
 Mortality by Year-Of-Birth
 (SMR = 0.572, P1 = 0.41, P2 = 0.067)

| Birth Year | Flyers | | | Ground | | |
|---------------|---------|------|-----------------|---------|------|-----------------|
| | At Risk | Dead | Rate per 100 | At Risk | Dead | Rate per 100 |
| 1905-1924 | 44 | 4 | 9.1 | 26 | 6 | 23.1 |
| 1925-1934 | 272 | 10 | 3.7 | 117 | 10 | 8.5 |
| 1935-1939 | 145 | 6 | 4.1 | 66 | 1 | 1.5 |
| 1940-1944 | 121 | 2 | 1.7 | 89 | 3 | 3.4 |
| 1945-1954 | 64 | 2 | 3.1 | 313 | 11 | 3.5 |
| Total | 646 | 24 | | 611 | 31 | |

Appendix Table 4

Comparison Flying Versus Comparison Ground Personnel Mortality by Year-Of-Birth
 Within Comparison Group
 (SMR = 0.909 P1 = 0.46, P2 = 0.65)

| Birth Year | Flyers | | | Ground | | |
|---------------|---------|------|-----------------|---------|------|-----------------|
| | At Risk | Dead | Rate per 100 | At Risk | Dead | Rate per 100 |
| 1905-1919 | 45 | 6 | 13.3 | 65 | 11 | 16.9 |
| 1920-1924 | 175 | 20 | 11.4 | 66 | 10 | 15.2 |
| 1925-1929 | 350 | 26 | 7.4 | 151 | 20 | 13.2 |
| 1930-1934 | 966 | 58 | 6.0 | 423 | 21 | 5.0 |
| 1935-1939 | 698 | 26 | 3.7 | 322 | 13 | 4.0 |
| 1940-1944 | 653 | 15 | 2.3 | 443 | 9 | 2.0 |
| 1945-1954 | 276 | 10 | 3.6 | 1538 | 40 | 2.6 |
| Total | 3163 | 161 | | 3008 | 124 | |