

AIR FORCE HEALTH STUDY

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

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

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

AIR FORCE HEALTH STUDY

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

May 1995

Volume I

1995 Followup Examination Results

**Epidemiologic Research Division
Armstrong Laboratory
Human Systems Center (AFMC)
Brooks Air Force Base, Texas 78235**

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EXECUTIVE SUMMARY

1992 FOLLOWUP EXAMINATION REPORT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The Pulmonary Assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort relative to the Comparison cohort or in relation to body burden of dioxin. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be at an increased risk, relative to Comparisons, with respect to the history of bronchitis and thorax and lung abnormalities, but there was no evidence from the serum dioxin analyses to confirm a dose-response relationship. The ratio of observed FEV₁ to observed FVC in Ranch Hands revealed a significant relationship with initial dioxin that was consistent with a dose-response effect, but the changes in the ratio were slight and of doubtful physiologic significance.

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

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

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

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

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

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

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

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

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

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

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

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

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