

USE OF AGENT ORANGE

THE AIR FORCE HEALTH STUDY: A SUMMARY OF RESULTS

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Introduction

To address concerns of veterans and the public regarding the consequences of exposure to Agent Orange and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), the Air Force began planning the Air Force Health Study in 1978 to evaluate the health, survival and reproductive experience of veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides in Vietnam from 1962 to 1971. The study seeks to determine whether Ranch Hand veterans have experienced adverse health and whether those effects, if they exist, can be attributed to exposure to herbicides or dioxin. Ranch Hand veterans were exposed to herbicides during loading, flight operations and maintenance of the aircraft and spray equipment. A Comparison group of other Air Force veterans involved in C-130 aircraft missions in Southeast Asia during the same period that the Ranch Hand unit was active was included in the study. Comparison veterans were not involved with spraying herbicides. The study includes periodic analyses of post-service mortality, physical examinations, in-person interviews, medical record retrievals, and psychological testing. The study protocol was written and reviewed during the period June 1979 through January 1982. Physical examinations were administered in 1982, 1985, 1987, 1992, and 1997. A final examination is planned for 2002.

Methods and Materials

In 1982, 1985, 1987, 1992, and 1997, approximately 1,000 Ranch Hand and 1,300 Comparison veterans were examined and medical records for each veteran, his spouse and his children were retrieved and coded. In 1986, chemists at the Centers for Disease Control and Prevention (CDC) developed an assay for dioxin in serum and demonstrated its suitability as a substitute for the assay of dioxin in adipose tissue obtained by biopsy. Through an interagency agreement, the Air Force has collaborated with CDC since 1986 to measure dioxin in serum samples from these veterans. In 1987, 1992 and 1997 blood from each willing participant was collected and assayed.

In 1987 and thereafter, the serum dioxin measurement has been used as the exposure index in this study. The median current dioxin level in 872 Ranch Hands in 1987 was 12.7 parts per trillion (ppt), range: 0 to 617 ppt. The median level in 1,060 Comparisons was 4.2 ppt, range: 0 to 54.8 ppt. Ninety-nine percent of the Ranch Hand dioxin levels are less than 200 ppt and 99 percent of the Comparison levels are less than 13 ppt.

Some mortality and morbidity results are briefly summarized.

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Results and Discussion

Mortality

Our most recent mortality study¹ was published in 1998. As a group, Ranch Hand veterans were not experiencing an increased risk of death; 118 Ranch Hand deaths were observed, whereas 120 were expected based on the mortality experience of the comparison population. However, we found an increased risk of death caused by cardiovascular diseases in Ranch Hand enlisted ground personnel (24 such deaths were observed, whereas 16.1 were expected). We also found, in all Ranch Hand veterans, an increased risk of death caused by diseases of the digestive system (9 were observed, whereas 5.1 were expected). Half of the increase in the number of deaths caused by diseases of the circulatory system were caused by atherosclerotic heart disease and most of the deaths caused by diseases of the digestive system were caused by chronic liver cirrhosis. The suggested increases in mortality due to cardiovascular and digestive diseases could be caused by our inability to adjust for smoking and drinking. Smoking and drinking histories are available only for the subgroup of veterans who have attended the physical examinations, most of whom are still living.

Morbidity

Diabetes

We have previously reported a study of dioxin and diabetes in Ranch Hand veterans², in which we found that glucose abnormalities, diabetes prevalence and the use of oral medications to control diabetes increased while time to diabetes onset decreased with dioxin. Serum insulin abnormalities increased with dioxin in Ranch Hand veterans without diabetes. These results suggested an adverse relation between dioxin exposure and diabetes mellitus, glucose metabolism and insulin production. To date, this study has provided the strongest available evidence of an adverse relation between dioxin and diabetes.

To investigate the relation between dioxin and diabetes more closely, we examined the association between serum dioxin level and occurrence of diabetes and impaired insulin-glucose metabolism among 1197 Comparison veterans in the Air Force Health Study whose serum dioxin level was within the range of background exposure³. For an increase of 4.0 ng/kg serum lipid, the multivariate-adjusted odds ratio for diabetes mellitus was 1.55 (95% CI 1.09-2.20). The association was attenuated, however, after adjustment for serum triglycerides at the time the dioxin was measured. Whether adjustment for serum triglycerides was appropriate, however, cannot be determined with available data. The association of background-level dioxin exposure with the prevalence of diabetes in these data may well be due to reasons other than causality, though a causal contribution cannot be wholly dismissed.

To further elucidate an association between dioxin and diabetes, we studied the relation between insulin, fasting glucose, sex hormone binding globulin (SHBG), diabetes and dioxin⁴. Among nondiabetic Ranch Hand veterans, we found the mean of the logarithm of insulin significantly increased in the High dioxin exposure category. Additionally, in nondiabetic veterans the relation between SHBG and insulin interacted significantly with dioxin exposure on the log scale within

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strata defined by age and percent body fat. Among young (age \leq 53 years), lean (percent body fat \leq 25%) and nondiabetic veterans in the High dioxin exposure category, the slope relating the logarithm of SHBG and the logarithm of insulin was significantly decreased. These results suggest a compensatory metabolic relationship between dioxin and insulin regulation.

Cancer

We studied cancer prevalence and dioxin exposure⁵. We found no consistent or meaningful relation between dioxin body burden and cancer in Ranch Hand veterans. The prevalence of skin cancer, either by cell type or anatomical location, appeared unrelated to dioxin exposure. The risk of systemic cancer was not increased in Ranch Hand veterans in the highest exposure category. We found no excess risk of malignancy of the prostate among Ranch Hands in any exposure category. We also found an overall decreased risk of cancer in Ranch Hand veterans who had experienced 20 years of latency. An analysis of time to cancer onset revealed no meaningful relation with dioxin.

Immune Function

We completed a study of dioxin and the immune system alteration⁶. We studied skin test results, total lymphocytes, lymphocyte subpopulations, immunoglobulin concentrations, the presence of a broad range of autoantibodies and evidence of clonal B cells. Overall, we found no evidence of a consistent relation between dioxin exposure and immune system alteration.

Cognitive Function

We used the Halstead Reitan Battery, Wechsler Adult Intelligence Scale-Revised, Wide Range Achievement Test and the Wechsler Memory Scale to assess cognitive functioning and dioxin in Ranch Hand veterans⁷. Cognitive functioning was assessed in 1982, and dioxin levels were measured in 1987 and 1992. We assigned each Ranch Hand veteran to the background, low, or high dioxin exposure category on the basis of a measurement of dioxin body burden. Although we found no global effect of dioxin exposure on cognitive functioning, we did find that several measures of memory functioning were decreased among veterans with the highest dioxin exposure. These results became more distinct when we restricted the analysis to enlisted personnel, the subgroup with the highest dioxin levels. Although statistically significant, these differences were relatively small and of uncertain clinical significance. Additional studies using more sensitive memory measures may provide more insight on the long-term health impact of Agent Orange, if any, on memory.

Hematological Effects

We completed a study of dioxin and hematologic function⁸ based on data collected in 1982, 1985, 1987 and 1992. We found no important relation between dioxin body burden and red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration and erythrocyte sedimentation rate. Mean corpuscular volume, mean corpuscular hemoglobin and platelet count, however, generally increased with dioxin level at each of the four

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examinations. It is not known at this time whether these increases are indicative of adverse health in Ranch Hand veterans.

Psychological Functioning

Using the Minnesota Multiphasic Personality Inventory (MMPI) and the Millon Clinical Multiaxial Inventory (MCMI), we studied psychological functioning and serum dioxin levels in Ranch Hand veterans⁹. We found few consistent psychological abnormalities associated with serum dioxin levels. Ranch Hand veterans with higher dioxin levels showed some difficulties in anxiety, somatization, depression, and a denial of psychological factors. However, those with background levels also showed indications of emotional distress, primarily in emotional numbing and lability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or behaviors.

Peripheral Neuropathy

We studied whether exposure to Agent Orange and its dioxin contaminant was related to peripheral neuropathy in Ranch Hand veterans¹⁰. We summarized peripheral nerve function assessed in 1982, 1985, 1987, 1992 and 1997, nerve conduction velocities measured in 1982 and vibrotactile thresholds of the great toes measured in 1992 and 1997. We assigned each Ranch Hand veteran to one of three exposure categories, named Background, Low and High, based on his serum dioxin level. We found a consistent pattern of increased risk of probable peripheral neuropathy among Ranch Hand veterans in the High exposure category, with the increase reaching statistical significance in 1997. However, corresponding patterns were not found in 1982. The risk of confirmed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, was significantly increased in the High category in 1997. The numbers of affected veterans were small and the clinical meaning of these findings is uncertain.

References

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