



DEPARTMENT OF THE AIR FORCE
AIR FORCE RESEARCH LABORATORY

Gentleman

The Air Force Health Study Team is pleased to announce the release of the Air Force Health Study Report: 2002 Follow-up Physical Examination Report by the Office of the Secretary of Defense. This report summarizes findings of the physical examination conducted at Scripps Clinic between 2002 and 2003. I have attached the Executive Summary for your review.

If you would like to read the complete report, consisting of 21 chapters, please visit our website. To access the website please go to www.brooks.af.mil, under the column 'Information Regarding' select 'Environmental', then select 'Air Force Health Study' from there select 'Reports' and finally '2002 Follow-up Physical Examination Results'.

The Institute of Medicine's Committee on the Disposition of the Air Force Health Study is still meeting and has informed us they are anticipating presenting their recommendation(s) to the Department of Veterans Affairs by the end of this year.

Just to let you know there have been some changes in personnel. I retired from active duty on 31 Mar 2005 and was blessed to be hired back as the civilian branch chief of the Air Force Health Study in June 2005. Dr Joel Michalek, the Principal Investigator of the study for many years, retired in May 2005 from civil service. The new principal investigator is Col (Dr) Karen Fox. Dr Fox is also the study's medical consultant.

I will be sending the annual winter holiday letter but for now those of us at the Air Force Health Study wish you and your loved ones a restful and safe summer.


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Chief, Air Force Health Study

Attachment:
Executive Summary

IOM Review

EXECUTIVE SUMMARY – 2002 FOLLOW-UP EXAMINATION REPORT

Purpose

The Air Force launched the Air Force Health Study (AFHS) in 1980 to address concerns of veterans, Congress, and the public regarding the consequences of exposure to Agent Orange and other herbicides sprayed during the Vietnam War. Agent Orange and other phenoxy herbicides were contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin). The purpose of the AFHS was to determine whether adverse health effects exist in Air Force veterans of Operation Ranch Hand, the unit responsible for spraying Agent Orange and other herbicides in Vietnam from 1962 to 1971, and whether those adverse effects can be attributed to the veterans' occupational exposure to Agent Orange or its dioxin contaminant. This report summarizes the results of the 2002 physical examination.

Study Design

This prospective epidemiologic study included assessments of health, mortality, and reproductive outcomes. Members of the Ranch Hand unit were identified by military records. A comparison group comprising Air Force veterans who flew or serviced C-130 aircraft in Southeast Asia (SEA) during the same time period that the Ranch Hand unit was active, but who were not involved with spraying herbicides, also was formed. The health assessment included six physical examinations. Each physical examination included an in-person interview and laboratory measurements of blood and urine.

The baseline examination was conducted in 1982; follow-up examinations were performed in 1985, 1987, 1992, 1997, and 2002. Participation in this study was voluntary and informed consent was obtained at the examination sites. The protocol and conduct of the study was reviewed and approved by the Institutional Review Boards at the sponsoring and participating organizations.

Prior to the baseline examination and after excluding those killed in action (Ranch Hand: n=22, Comparison: n=109), up to 10 Comparisons were matched to each Ranch Hand based on age, race, and military occupation. Each Ranch Hand, and a randomly selected Comparison from those matched to him, were invited to participate in the baseline examination in 1982. In accordance with the protocol, the Comparisons selected for the baseline examination were called Original Comparisons. All Ranch Hands and Original Comparisons were invited to participate in follow-up examinations. If an Original Comparison declined to attend an examination, he was replaced by a Comparison with a similar self-perception of health as the refusing Original Comparison among those matched to the same Ranch Hand; these were termed Replacement Comparisons. A total of 1,951 veterans (777 Ranch Hands, 737 Original Comparisons, and 437 Replacement Comparisons) participated in the 2002 physical examination, representing 74.5 percent, 67.4 percent, and 46.0 percent compliance, respectively. Physical examination findings, laboratory measurements, and disease histories were studied. Study group (Ranch Hand, Comparison) and serum dioxin measurements were used to assess herbicide exposure. The dioxin measurements were conducted by the Centers for Disease Control and Prevention. The majority of dioxin measurements used in the study were accomplished at the 1987 physical examination. These measurements are referred to as 1987 dioxin. Within Ranch Hands, median dioxin varied with occupation, least among officers, greatest among enlisted groundcrew, and intermediate in enlisted flyers.

Statistical Methods

Four statistical models were used to assess the statistical significance of associations between health and herbicide exposure. Model 1 simply contrasted the two groups as exposed (Ranch Hand) and unexposed (Comparison) to herbicides. The contrasts were conducted both overall and by occupational stratum (officer, enlisted flyer, enlisted groundcrew). Model 1 contrasts did not use serum dioxin measurements. Models 2, 3, and 4 used the serum dioxin measurements. The initial dioxin body burdens in Ranch Hands were estimated using a first-order pharmacokinetic model. Model 2 assessed the significance of the relation between health and the estimated initial dioxin in Ranch Hand veterans. To implement Model 3, the Ranch Hand cohort was stratified according to three dioxin exposure categories: background, low, and high. The background category comprised Ranch Hands with 1987 dioxin of 10 parts per trillion (ppt) or less. The remaining Ranch Hands (above 10 ppt) were separated into low and high categories by the median of their estimated initial dioxin levels. Model 3 contrasted each of the three Ranch Hand dioxin exposure categories with Comparisons. Model 4 assessed the significance of the relation between health and 1987 dioxin in Ranch Hand veterans.

Strengths and Weaknesses

Study strengths included record verification of reported health conditions, rigorous quality control, good compliance, long follow-up, and adjustment for confounding factors. The study benefited from a two-tiered management structure based on separate but parallel management and technical teams, an independently appointed and administered Advisory Committee, and periodic review by the National Academy of Sciences.

Study weaknesses included the sample size (which prevented the study of rare diseases), imperfect exposure metrics, and, possibly, incomplete adjustment for confounding factors.

Parameters of the Study and Statistically Significant Findings

More than 300 health-related endpoints in 12 clinical areas were studied. Associations found significant after adjustment for confounders are summarized by clinical area. Interpretations were based on toxicological data, biological plausibility, dose-response relationship, and consistency with results of other epidemiologic studies.

General Health Assessment

Self-perception of health, appearance of illness or distress, relative age, and body mass index were studied. Body mass index was positively associated with 1987 dioxin, possibly reflecting the pharmacokinetics of dioxin elimination. The other measures of general health appeared unrelated to herbicide exposure.

Neoplasia Assessment

During the 2002 interview, each participant was asked whether a doctor had told him that he had cancer. Affirmative responses were confirmed by a medical records review. At each examination, suspicious skin lesions were biopsied and the pathology determined. During the entire follow-up period, AFHS staff made every effort to contact and encourage participants to see their physicians regarding abnormal

x-ray findings, laboratory measurements, and pathology reports. Other than skin biopsies, no invasive procedures were used to detect neoplasms at the physical examination.

With regard to malignancies, a mixed pattern of associations with no suggestion of internal or external consistency was found. For example, the risk of basal cell carcinoma was increased among Ranch Hand officers, but not among enlisted groundcrew, the occupation with the highest median dioxin. Similarly, the risk of basal cell carcinoma was increased in the Ranch Hand low dioxin exposure category, but not in the high category. The risk of all-sites cancer was also increased in the low, but not the high dioxin category. These patterns did not suggest an adverse relation between cancer and herbicide exposure.

Neurology Assessment

The neurology assessment included an evaluation of cranial and peripheral nerve function and an examination of the central nervous system. Associations between dioxin and cranial nerve and central nervous system function did not appear consistent or clinically important. The risk of an abnormal visual field was increased in the Ranch Hand background exposure category, but not the high exposure category. The risk of abnormal balance and coordination increased with initial dioxin, but was not increased in the high exposure category or in any occupational subgroup. The risks of abnormal reaction to pinprick and absent patellar reflex were increased in the high dioxin exposure category, providing some support for a relation between dioxin exposure and peripheral nerve function.

Psychology Assessment

Psychological health was evaluated with subscales of the Symptom Checklist-90-Revised (SCL-90-R) and the Wechsler Memory Scale-Revised (WMS-R). Psychoses, alcohol and drug dependence, anxiety, and other neuroses as determined by a medical records review were also studied. None of these outcome measures was associated with herbicide or dioxin exposure.

Gastrointestinal Assessment

Liver disorders were determined by a medical records review. Laboratory assessments of liver metabolism and function, such as levels of triglycerides, C3 complement, alkaline phosphatase and other liver enzymes, haptoglobin, and prothrombin were also studied. The risk of abnormally high triglycerides was increased among Ranch Hand enlisted groundcrew and among those in the low and high dioxin exposure categories. The risk of abnormally high triglycerides increased with initial dioxin. These results suggested subclinical relation between dioxin and lipid metabolism. None of the other measures in this assessment exhibited a consistent or meaningful association with herbicide or dioxin exposure.

Dermatology Assessment

Chloracne is a skin condition recognized as a consequence of exposure to high levels of dioxin and other cyclic organochlorine compounds. It usually appears without long latency after a short interval of exposure to dioxin and persists for about 2 to 3 years. Primary lesions of chloracne were not expected to persist and be noted upon physical examination in 2002. Chloracne might be suggested if the secondary lesions such as scarring, hyperpigmentation, and depigmentation had been observed in the typical distribution areas of chloracne around eyes, temples, and ears. No evidence of chloracne was found in the Ranch Hand or Comparison group.

The dermatology assessment included the occurrence of self-reported acne and physical examination. The occurrence and duration of acne were reported by the participants at the 2002 physical examination. The frequency and occurrence of reported acne after service in SEA were increased in Ranch Hand enlisted groundcrew, the subgroup with the highest median dioxin levels. The frequency of reported acne since SEA service was increased in the background, low, and high dioxin exposure categories. The frequency of acneiform lesions on physical examination was increased only in the background category. The duration of reported acne after service in SEA increased with 1987 dioxin.

The interpretation of the increased frequency of reported acne after service in SEA in Ranch Hand enlisted groundcrew is uncertain because secondary lesions that were observed revealed no association with herbicide or dioxin exposure.

Cardiovascular Assessment

Cardiac function and history of heart disease were studied. Central cardiac function was assessed by measuring blood pressure, heart sounds, and a resting electrocardiograph. Peripheral vascular function was assessed by the presence or absence of carotid bruits, various pulse-point readings, a resting blood pressure index, measures of intermittent claudication and vascular insufficiency, and a fundoscopic examination of small vessels. The lifetime history of essential hypertension, myocardial infarction, and stroke or transient ischemic attack was also studied.

Associations between these measures and herbicide exposure were not consistent or clinically interpretable as adverse. One of the findings, the risk of abnormally high diastolic blood pressure, was increased among Ranch Hand enlisted flyers and among Ranch Hands in the high dioxin exposure category. The risk of abnormally high systolic blood pressure, however, was decreased among Ranch Hands in the low and high categories combined; this risk increased with 1987 dioxin in all Ranch Hands. Overall, cardiovascular health did not appear to be adversely associated with herbicide or dioxin exposure.

Hematology Assessment

Red blood cell counts, white blood cell counts, counts of segmented neutrophils, neutrophilic bands, lymphocytes, monocytes, eosinophils, basophils, hematocrit, platelet count, fibrinogen, erythrocyte sedimentation rate (ESR), and red blood cell morphology were studied.

The mean platelet count was increased among Ranch Hand enlisted flyers. The risk of abnormal red blood cell morphology was increased in Ranch Hand enlisted groundcrew and in Ranch Hands in the low and high dioxin exposure categories. The mean ESR was increased in the low and high dioxin exposure categories. White blood cell count decreased as 1987 dioxin increased. These associations did not suggest an adverse relation between herbicide or dioxin exposure and any hematologic diagnosis. They may, however, suggest the future development of inflammatory disorders and monoclonal gammopathies.

Renal Assessment

The history of renal disease and laboratory measures of renal function were studied. The laboratory measurements included urinary protein, urine specific gravity, serum creatinine, blood urea nitrogen, urinary microalbumin, urinary creatinine, and an index of creatinine clearance. The few associations found did not indicate an adverse relation between renal function and herbicide or dioxin exposure.

Endocrine Assessment

Thyroid disease and type 2 diabetes were studied through physical examination, laboratory measurements, and medical records review. The risk of diabetes requiring insulin control was increased in the Ranch Hand high dioxin category. Fasting insulin and the risk of diabetes requiring insulin control increased and time to diabetes onset decreased with initial dioxin. The risk of diabetes requiring oral hypoglycemic or insulin control increased and time to diabetes onset decreased with 1987 dioxin. The risk of abnormally high hemoglobin A1c increased with 1987 dioxin.

The mean thyroid-stimulating hormone was increased in Ranch Hand officers and in all Ranch Hands. The mean luteinizing hormone, the risk of an abnormally high 2-hour postprandial urinary glucose, and abnormally high free testosterone were increased only in Ranch Hand officers.

The adverse associations between type 2 diabetes and dioxin exposure were consistent with findings at previous physical examinations. In contrast, associations between herbicide or dioxin exposure and measures of thyroid function or gonadotropins did not appear consistent or clinically important.

Immunology Assessment

Red cell surface markers, lymphocytes, quantitative immunoglobulins, and a lupus panel were studied. The risk of antinuclear antibody increased with initial dioxin. An examination of individual antibodies revealed no consistent association with dioxin exposure. Overall, there was no consistent or interpretable association between any measure of immune function and herbicide or dioxin exposure.

Pulmonary Assessment

Pulmonary disease history, including history of asthma, bronchitis, and pneumonia, forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), the FEV₁ to FVC ratio, obstructive abnormality, and loss of vital capacity were studied. The frequency of reported pneumonia was increased in Ranch Hand enlisted flyers. The mean FVC was decreased in the low dioxin exposure category. Considering all pulmonary data, these associations did not suggest an adverse relation between respiratory health and exposure to herbicides or dioxin.

Clinically Significant Findings

Consistent with previous AFHS reports, current results indicate a significant and clinically meaningful adverse relation between type 2 diabetes and exposure to dioxin. The risk of diabetes was associated with 1987 dioxin in Ranch Hands. This increase was supported by an increase in disease severity, a decrease in time to onset, and an increase in fasting glucose and hemoglobin A1c with dioxin in Ranch Hand veterans. Similar patterns were observed in 1987, 1992, and 1997.

Ranch Hand enlisted groundcrew and those in the low and high dioxin exposure categories experienced an increased risk of abnormally high triglycerides. The risk of abnormally high triglycerides also increased with initial dioxin. These results suggest a possibility of a subclinical relation between dioxin and lipid metabolism.