



DEPARTMENT OF THE AIR FORCE
WASHINGTON DC 20330-1000

OFFICE OF THE SECRETARY

05 AUG 2003

SAF/LL
1160 Air Force Pentagon
Washington, DC 20330-1160

The Honorable Duncan Hunter
Chairman, Committee on Armed Services
House of Representatives
Washington, DC 20515

Dear Mr. Chairman

The Air Force is submitting the annual progress report on the activities of the Air Force Health Study on Operation Ranch Hand, as stipulated in the Fiscal Year 1991 National Defense Authorization Act.

The report highlights the study's findings to date, as well as significant activities over the past year. Of note is the end of the 2002, and final, physical examination phase.

This report has also been provided to the Ranking Minority Member of your Committee and the Chairmen and Ranking Minority Members of the Senate and House Veterans' Affairs Committees and the Senate Armed Services Committee.

We trust you will find this report informative.

Very Respectfully

A handwritten signature in black ink, appearing to read "Scott S. Custer".

SCOTT S. CUSTER
Major General, USAF
Director, Legislative Liaison

Attachment:
2002 Progress Report

2003 ANNUAL PROGRESS REPORT ON THE AIR FORCE HEALTH STUDY

Executive Summary

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. Study results up to 31 December 2001, and activities during calendar year 2002 are summarized.

Mortality: As previously reported, our most recent mortality study was published in 1998 covering deaths up to December 31, 1993. 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). This increase in risk may be caused by our inability to adjust for known risk factors, such as smoking, body fat, and family history of heart disease. A new mortality assessment of deaths up to December 31, 1999, not yet published, found a 70 percent increase in the risk of death from cardiovascular diseases in Ranch Hand enlisted ground personnel.

Morbidity: We previously reported a study of dioxin and diabetes in Ranch Hand veterans, which showed that glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased while time-to-onset decreased with dioxin. To address the idea that variation in dioxin half-life may contribute to the association between dioxin and diabetes, we started a new study of diabetes and dioxin elimination. Detailed statistical analyses found no relation between diabetes prevalence or time-to-onset and the rate at which veterans eliminate dioxin from their bodies. To date, no consistent or meaningful relation between cancer and any measure of herbicide or dioxin exposure was found. We found no evidence of a consistent relation between dioxin exposure and immune system alteration. Although we found no global effect of dioxin exposure on cognitive functioning, we did find that several measures of memory functioning were decreased among Ranch Hand veterans with the highest dioxin exposure. Laboratory findings of mean corpuscular volume, mean corpuscular hemoglobin, and platelet count increased with dioxin level; it is not known at this time whether these increases are indicative of adverse health in Ranch Hand veterans. We found few consistent psychological abnormalities associated with serum dioxin levels. After adjustment for diabetes, we found a consistent pattern of increased risk of diagnosed peripheral neuropathy with increased dioxin body burden. We completed a

new study of thyroid function and dioxin levels. Cross-sectional analyses found statistically significantly increased thyroid stimulating hormone means at the 1985 and 1987 examinations in the “High” exposure category and a significant increasing trend across the three Ranch Hand dioxin exposure categories (Background, Low, High) in 1982, 1985, 1987, and 1992. We found no significant relation between the occurrence of thyroid disease and dioxin category. These findings suggest that in the highest exposure category of Ranch Hand veterans, dioxin affects thyroid hormone metabolism and function. Further follow-up will be necessary to understand the relation, if any, between thyroid disease and dioxin levels.

Reproductive outcomes: We continued work on a study of fertility and paternal exposure to herbicides and dioxin.

***Strengths and Limitations:** The strengths of the study include medical record verification of health outcomes, 100% quality control, high participant compliance, measurement of serum dioxin levels, and multiple levels of peer review. Limitations of the study are recognized. The results cannot be generalized to other groups (such as all Vietnam veterans or Vietnamese civilians) who have been exposed in different ways and to different levels of herbicide. We do not know what effect dioxin has at levels other than those found in our study group. We are unable to study health effects of dioxin exposure from other sources, such as contaminated food. Groups with higher exposures may well have effects not seen in our study. The size of the study makes it difficult to detect increases in the prevalence of rare diseases. Hence, small increases in the risk of rare diseases may be missed by the study. For example, because liver cancer is rare, even a tenfold increase in risk may not be detected.*

Other activities: Prompted by concern from the Ranch Hand Advisory Committee that our data releases may violate existing privacy laws, we requested and received a legal review of our data release activities. Air Force lawyers recommended that data not be released to the public without prior consent from study subjects. Because such consent had not been requested, we removed all released data from our web page and requested that the Government Printing Office stop selling study data to the public. We presented study methodology and results to numerous academic audiences and to congressional staff.

Program management: The last round of examinations began in May 2002 and concluded in April 2003. We expect 2000 veterans to participate in the study. The final report of examination results will be released to the public in the first quarter of calendar year 2005. The analysis of data and writing of the final report will be accomplished by Science Applications International Corporation.

2003 ANNUAL PROGRESS REPORT OF THE AIR FORCE HEALTH STUDY

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 began in May 2002 and concluded in April 2003.

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, 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. In 1987, 1992, and 1997 blood from each willing participant was collected and assayed.

Through an interagency agreement, the Air Force has collaborated with CDC since 1986 to measure dioxin in serum samples from these veterans. 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.

The strengths of the study include medical record verification of health outcomes, 100 percent quality control, high participant compliance, measurement of serum dioxin levels, and multiple levels of peer review. Limitations of the study are recognized. The results cannot be generalized to other groups (such as all Vietnam veterans or Vietnamese civilians) who have been exposed in different ways and to different levels of herbicide. We do not know what effect dioxin has at levels other than those found in our study

group. We are unable to study health effects of dioxin exposure from other sources, such as contaminated food. Groups with higher exposures may well have effects not seen in our study. The size of the study makes it difficult to detect increases in the prevalence of rare diseases. Hence, small increases in the risk of rare diseases may be missed by the study. For example, because liver cancer is rare, even a tenfold increase in risk may not be detected.

The current state of knowledge derived from study peer-reviewed articles and reports is summarized below.

Mortality

Our most recent mortality study was published in 1998 in the American Journal of Epidemiology, covering deaths up to December 31, 1993. 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 was caused by diseases of the circulatory system and by atherosclerotic heart disease; most of the deaths caused by diseases of the digestive system were caused by chronic liver cirrhosis.

A new mortality analysis, completed in 2002 but not yet published, covering deaths up to 31 December 1999, found similar results. The study compared the risk of death among 1,262 Ranch Hand and 19,078 Comparison veterans, adjusted for age, race, and military occupation. As a group, Ranch Hand veterans were experiencing a 15 percent increase in the risk of death from any cause, based on 186 Ranch Hand and 2,330 Comparison deaths. We found a significant 70 percent increase in the risk of death from cardiovascular diseases among Ranch Hand enlisted ground personnel, based on 40 Ranch Hand and 393 Comparison deaths. The risk of death from diseases of the digestive system was no longer significantly increased among Ranch Hand veterans.

The increases in mortality due to cardiovascular diseases in both studies, and digestive diseases in the earlier study, could be caused by our inability to adjust for known risk factors, such as smoking, alcohol consumption, body fat, and family history of heart disease. Risk factors are available only for the subgroup of veterans who have attended the physical examinations, most of whom are still living.

Morbidity

Diabetes

Our study of dioxin and diabetes in Ranch Hand veterans, published in 1997 in Epidemiology, found glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased while time-to-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 in humans.

To further elucidate an association between dioxin and diabetes, we conducted a study of diabetes and the rate at which Ranch Hand veterans eliminate dioxin from their bodies. It is known that veterans with more body fat eliminate dioxin more slowly than veterans with less body fat and, that, among Ranch Hand veterans, diabetes risk increases with body fat. These relations have led some reviewers to suggest that the relation between diabetes and dioxin levels may be an artifact of this variation in dioxin elimination. To study this, diabetes prevalence and time-to-onset were statistically modeled in terms of the dioxin elimination rate and known risk factors for diabetes, including body fat, age, and family history of diabetes in first-order relatives. No significant or meaningful relation was found between diabetes and the dioxin elimination rate in these veterans. The results are summarized in an article published in the Journal of Toxicology and Environmental Health in February.

Cancer

We have studied cancer prevalence and dioxin exposure. 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. These findings were published in the American Journal of Epidemiology in 1999.

To address concerns expressed by our Advisory Committee that we may have missed a “Vietnam” effect because Comparison veterans were also Vietnam veterans, we continued a study of cancer versus national cancer rates in collaboration with Dr. David Garabrant at the University of Michigan. A paper has been submitted for possible publication in the Journal of Occupational and Environmental Medicine.

Cognitive Function

Cognitive function was measured in 1982 by the Halstead Reitan Battery, Wechsler Adult Intelligence Scale-Revised, Wide Range Achievement Test, and the Wechsler Memory Scale. Dioxin levels were measured in 1987 and 1992 in Ranch Hand and Comparison veterans. 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 with reported skin exposure to herbicides. Although statistically significant, these differences were relatively small and of uncertain clinical significance. The results were published in Neurotoxicology in 2001.

Peripheral Neuropathy

We studied whether exposure to Agent Orange and its dioxin contaminant was related to peripheral neuropathy in Ranch Hand veterans. 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. After adjustment for diabetes, we found a statistically increased risk of probable peripheral neuropathy among Ranch Hand veterans in the High exposure category in 1992 and 1997. However, corresponding patterns were not found in 1982. The risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, was significantly increased in the High category in 1992 and 1997. The numbers of affected veterans were small, and the clinical meaning of these findings is uncertain. These findings were published in Neurotoxicology in 2001. At the request of the National Academy of Sciences, we responded in writing to questions regarding our studies of cognitive function and peripheral neuropathy.

Thyroid function

We assessed potential health effects of dioxin on thyroid function. We analyzed thyroxine (total T4), thyroid stimulating hormone (TSH), triiodothyronine percent uptake (T3 percent uptake), the free thyroxine index (FTI), and thyroid diseases against serum dioxin levels. Ranch Hand and Comparison veterans who attended any of the examinations in 1982, 1985, 1987, 1992, and 1997 were included. Each veteran was assigned to one of four exposure categories based on serum dioxin levels named Comparison, Ranch Hand Background, Ranch Hand Low, and Ranch Hand High. Cross-sectional analyses found statistically significantly increased TSH means at the 1985 and 1987 examinations in the High exposure category and a significant increasing trend across the three Ranch Hand dioxin categories in 1982, 1985, 1987, and 1992. A repeated-measures analysis found significantly increased TSH means in the High and

Low dioxin categories. We found no significant relation between the occurrence of thyroid disease and dioxin category. These findings suggest that in the highest exposure category of Ranch Hand veterans, dioxin affects thyroid hormone metabolism and function. A paper summarizing these results was accepted for publication in the Annals of Epidemiology.

Reproductive Outcomes

We continued work on a study of fertility and paternal exposure to herbicides and dioxin. The results will be summarized in a paper to be submitted to a journal for publication.

Ranch Hand Advisory Committee

There were no meetings with the Ranch Hand Advisory Committee during calendar year 2002.

Presentations

On March 4, 2002, Dr. Michalek presented a talk entitled, "Diabetes Mellitus and Dioxin Elimination in Veterans of Operation Ranch Hand," at the Vietnam-United States Scientific Conference on Human Health Effects and Environmental Effects of Agent Orange/Dioxin, in Hanoi, Vietnam.

On March 21, 2002, Dr. Michalek presented a talk entitled, "Diabetes Mellitus and Dioxin Elimination in Veterans of Operation Ranch Hand," to students and faculty of the Department of Epidemiology, Tulane University, New Orleans, Louisiana.

On April 4, 2002, Dr. Michalek presented an overview of the peripheral neuropathy and cognitive papers at the Institute of Medicine, National Academy of Sciences, in Washington, DC. At that meeting, the committee requested further analysis of data relevant to the cognitive paper. The new analyses describe psychotropic medications used and psychological abnormalities versus dioxin exposure category.

On Aug. 14, 2002, Dr. Michalek presented a talk on dioxin and hypertension at Dioxin2002 in Barcelona, Spain.

Program Management

On May 6, 2002, the last round of physical examinations began at Scripps Clinic, La Jolla, California.

GAO and data release

In July 2002, under direction of the Brooks AFB Legal Office, study staff removed all data from the study web page and requested the Government Printing Office to stop selling study data to the public. We informed GAO of these activities.

Congressional briefings

On Nov. 20, 2002, Dr Michalek delivered an annual briefing to House and Senate Veterans' Affairs Committee staff.

Inter-agency collaboration

On July 20, 2002, Dr Albert Kingman of NIDCR, National Institutes of Health, visited with us to discuss his analysis of neurological deficits and mercury exposure from dental amalgam.

Interactions with veterans

We attended the Ranch Hand reunion, in Fort Walton Beach, Florida, Oct. 10-13, 2002.

Activities for 2003

A meeting with the Ranch Hand Advisory Committee took place March 13, 2003.

Papers on dioxin and hypertension, diabetes, cardiovascular disease, cancer, diseases of the gastrointestinal system, fertility, and reported medical symptoms are in progress.

During 2003, we will conclude the current physical examination, prepare the resultant data for analysis, and begin statistical analysis and report writing.

Data analysis and report writing will continue in our ongoing study of dioxin and insulin sensitivity in 30 Ranch Hand and 30 matched Comparison veterans.

We will continue laboratory analysis of adipose tissue specimens collected at the 1997 physical examination. This work is being conducted by the Department of Toxicology, University of California at Davis.

We will begin statistical analysis of data received from Dr. Michael DeVito, U.S. Environmental Protection Agency, describing dioxin elimination in rats and mice. This data will be used to assess the validity of the estimate of the initial dioxin dose in Ranch Hand veterans.