SERUM DIOXIN AND DIABETES MELLITUS IN VETERANS OF OPERATION RANCH HAND

Norma S. Ketchum and Joel Michalek[1]

[1]Air Force Research Laboratory, Brooks Air Force Base, Texas 78235 USA

Introduction

This report summarizes a study of adult onset diabetes mellitus and exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) in veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971. These results were accumulated during the post-service period from each veteran's departure from Southeast Asia to January 6, 1999 in men participating in the 1997 physical examination in the ongoing Air Force Health Study, a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans.

Diabetes is a disorder of the pancreas which results in a number of significant effects on the body, including macroangiopathy, neuropathy and cataracts. Primary risk factors for diabetes are family history, obesity (over 80% of all diabetics are overweight when they are diagnosed) and physical or emotional stress[1]. Little has been reported on diabetes prevalence in Vietnam veterans. We summarize diabetes prevalence and exposure to dioxin in veterans of Operation Ranch Hand. These data have been gathered during 15 years of follow-up in the ongoing Air Force Health Study from veterans whose exposure in Vietnam occurred from 27 to 36 years ago. This report is derived from a more extensive summary of the relation between diabetes, glucose abnormalities, insulin abnormalities and time to onset in men who participated in the latest physical examination of the Air Force Health Study[2].

Methods

The study seeks to determine whether veterans of Operation Ranch Hand (the personnel tasked with spraying operations during the Vietnam conflict) have experienced adverse health and whether those health effects, if they exist, can be attributed to exposure to herbicides or their dioxin contaminant. Ranch Hand veterans were exposed to herbicides during flight operations and maintenance of the aircraft and herbicide spray equipment. The study compares the current health and cumulative mortality experience of Ranch Hand veterans with a comparison group of other Air Force veterans who served in Southeast Asia during the same period (1962 to 1971) that the Ranch Hand unit was active and who were not involved with spraying herbicides. Comparisons were matched to Ranch Hands on age, race and military occupation. The study includes periodic analyses of noncombat mortality, in-person interviews and physical examinations. Physical examinations were conducted in 1982, 1985, 1987, 1992 and 1997; an additional examination is planned for 2002.

In 1987, blood from willing participants was collected and assayed for dioxin. Participation was voluntary and consent forms were signed at the examination site. Veterans with no quantifiable dioxin result in 1987, those who refused in 1987 and subjects new to the study were also asked to give blood for the assay at the 1992 and 1997 examinations.

Diabetes cases included for analysis were diagnosed during the post-Vietnam period from the end of the veteran's last tour of duty to January 6, 1999. We report cumulative post-service diabetes and diabetes severity. Each case was verified from medical records and may represent a diagnosis at any of the five physical examinations. This analysis includes all veterans who participated in the most recent physical examination in 1997.

We reviewed medical records and laboratory results to determine diabetic status. Veterans who had a verified history of diabetes by medical diagnosis or exhibited a 2-hour postprandial glucose laboratory value of 200 mg/dl or greater were classified as diabetic. Veterans not meeting these criteria were defined as nondiabetic.

We excluded from all statistical analyses veterans with no dioxin measurement, those with a nonquantifiable dioxin result and Comparisons with a dioxin result greater than 10 parts per trillion (ppt), the value we regard as a threshold for background dioxin exposure. Table 1 shows sample size reductions by group (Ranch Hand, Comparison).

Table 1 Sample Size Reduction by Group

	Ranch Hand	Comparison	Total
Fully Compliant in 1997	870	1,251	2,121
Missing or nonquantifiable Dioxin	(7)	(19)	(26)
Comparison Dioxin > 10 ppt		(19)	(19)
Net	863	1,213	2,076

We estimated the initial dioxin dose at the end of the tour of duty in Vietnam in Ranch Hands having measured dioxin levels above background using a constant half-life of 8.7 years[3] and assigned each veteran to one of four exposure categories, named "Comparison", "Background", "Low" and "High", according to his group, measured dioxin level and initial dioxin level. The Comparison category was comprised of Comparisons with dioxin levels less than or equal to 10 ppt. The Background category was comprised of Ranch Hands with dioxin levels less than or equal to 10 ppt. Ranch Hands with dioxin levels greater than 10 ppt were assigned to the Low or High categories depending on their estimated initial dioxin level. The cut point separating the Low and High categories (94 ppt) is the median initial dioxin level among all Ranch Hands having measured dioxin levels greater than 10 ppt. The resultant sample sizes were Comparison: N=1,213, Background: N=381, Low: N=239, High: N=243. In all statistical analyses we further excluded veterans with diabetes before their service in Southeast Asia (Ranch Hand: N=2, Comparison: N=1). Due to missing data, the resultant sample sizes were Comparison: N=1,195, Background: N=379, Low: N=235, High: N=240.

We defined percent body fat[4] (PBF) as PBF=1.26×BMI-13.305, where BMI is the body mass index [weight (kg) divided by the square of height (m)] and adjusted all analyses for age, military occupation (officer, enlisted flyer, enlisted ground), personality type, PBF at time of dioxin blood draw, and family history of diabetes[2]. We report cumulative incidence, or prevalence, of diabetes by dioxin category. We measured the association between diabetes prevalence and dioxin category with the adjusted odds ratio (aOR) and assessed the precision of the estimate with a 95% confidence interval (95% CI) for the aOR. We derived the aOR and its confidence interval from a main effects logistic regression model containing dioxin category and all covariates. We compared the diabetes prevalence among Ranch Hand veterans in the Background, Low and High categories with Comparison veterans. We used no stepwise reduction.

Results and Discussion

Demographic characteristics of all veterans in 1997 are presented in Table 2. Ranch Hand: in the High dioxin category are younger than Ranch Hands in the Low and Background categorie s.

Table 2. Distribution of dioxin and demographic characteristics in 1997

Characteristic	Comparison (N=1,213)	Background (N=381)	Ranch Hand Low (N=239)	High (N=24:)
Dioxin*	3.81 (0-9.97)	5.8 (0-10)	15 (10.0-25.6)	45.7 (18.0 617)
Initial dioxin*			51.8 (27.7-93.8)	194.7 (94.0 3290)
Age in 1997*	57.6 (46.7-82.5)	59.6 (46.9-77.5)	60.7 (47.0-79.3)	52.4 (47.2- 76.6)
PBF in 1997*	22.6 (7.1-52.6)	20.7 (9.4-44.6)	22.9 (7.1-47.8)	23.3 (12.9- 45.9)
Race (Black)†	5.8	5.0	9.6	5.3
Officer†	39.4	61.4	40.2	2.9
Enlisted flyer†	15.3	12.6	21.3	21.4
Enlisted Ground†	45.3	26.0	38.5	75.7

*Median (Range) † Percent.

The percentages of Ranch Hands in the Low (aOR=1.2) and High (aOR=1.5) dioxin categories having diabetes are increased relative to the Comparisons (Table 3). The percentage of Ranch Hands in the Background category with diabetes is less than the Comparison percentage (aOR=0.7).

Table 3. Diabetes by Dioxin Exposure Category

	Comparison	Ranch Hand Background	Low	High
Number (%)	199 (16.7)	37 (9.8)	49 (20.9)	57 (23.8)
aOR	1.0	0.7	1.2	1.5
95% CI		(0.5, 1.0)	(0.8, 1.8)	(1.0, 2.2)

Results in other epidemiological studies are mixed. A follow-up study of German industrial workers exposed to dioxin found diabetes less often in the exposed group than among refe rents[5]. In another study of the same cohort, mean fasting glucose levels in the exposed group appeared to increase with measured dioxin, but not back-extrapolated initial dioxin[6]. A study of dioxin-exposed US industrial workers found an increased mean dioxin level in diabetic workers compared with nondiabetic workers and increased mean fasting serum glucose in workers as compared with referents[7]. In the Vietnam Experience Study[8], diabetes prevalence in the Vietnam veteran cohort was similar to that in the non-Vietnam veteran cohort (relative risk=1.1).

The strengths of this study include high participation and low attrition rates, a Comparison population closely matched to the index population, and 10 years of follow-up. Repetitive examinations and active quality control incorporating double blind entry of data with discordances referred for third-party review reduced errors that would bias the study toward the null result.

Our ability to detect associations is limited by the fixed size of the Ranch Hand cohort. Since all Ranch Hands have been identified and invited to participate in the study, their number cannot be increased. Thus, the rarity of some abnormalities led to imprecise measures of association, as indicated by wide confidence intervals, and small numbers prevented us from strong inferences on the most heavily exposed Ranch Hands.

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