SERUM DIOXIN AND PERIPHERAL NEUROPATHY IN VETERANS OF OPERATION RANCH HAND

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Introduction

This report summarizes a study of peripheral neuropathy and exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) in veterans of Operation Ranch Hand who participated in the 1997 physical examination of the ongoing Air Force Health Study, a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans[1].

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) when 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.

At each physical examination, we evaluated the neurological status of each participant through a standardized neurological examination conducted by a board-certified neurologist. The neurological examination included an evaluation of cranial nerves, muscle strength in the upper and lower limbs, sensory perception of pain (pin prick), light touch (cotton puff), vibration (tuning fork), proprioception (position of the digits), activity of deep tendon reflexes (brachial, patellar, Achilles), stance (balance), gait, coordination of hand and foot, and tremor.

The Vibratron II® device was used to measure vibrotactile threshold on both the left and right great toes. The first, third, fifth and seventh trials on each great toe were descending and the second, fourth and sixth trials on each great toe were ascending. Veterans whose great toes could be examined but who sensed no vibration were included in the study at the maximum level of 23.0 vibrational units (VU), a value greater than the highest recorded measurement in this study. The vibrotactile measurement was summarized using the method-of-limits protocol. The VU

measurements were transformed to displacement in microns (D), using the formula $D=0.550\times VU^{2.02217}$. The displacement (D) was transformed to the natural logarithm scale to enhance normality. For each great toe, the average, in log(microns), of four of the seven trials was determined. The four trials averaged were those remaining after eliminating the results of the first of the seven trials and the high and low of the remaining six trials. The minimum of the two averages for the left and right great toes was used as a summary vibrotactile measure for each subject. We defined the vibrotactile measurement as abnormal if the summary vibrotactile measurement exceeded the 90th percentile of the Comparison distribution of summary vibrotactile measurements.

The measurements used for this study were sensitive to detection of distal symmetrical polyneuropathies of the stocking-glove type; the measures were insensitive to other types of peripheral disorders. We defined the Achilles tendon reflex as abnormal if it was absent and as normal if it was sluggish, active, or very active. We defined polyneuropathy as confirmed if at least two of the following three outcomes were found bilaterally: 1) absent Achilles reflex, 2) abnormal vibration at the ankle, or 3) abnormal pin prick, and if the vibrotactile measurement was bilaterally abnormal.

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 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 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. Among Ranch Hands with dioxin levels greater than 10 ppt, those with an initial dioxin level less than or equal to 94 ppt were assigned to the Low category and those with an initial dioxin level greater than 94 ppt were assigned to the High category. 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. We further excluded veterans with peripheral neuropathy or other neurological disorders before their service in

Southeast Asia, those with positive serological tests for syphilis, those who tested positive for HIV, those with peripheral edema of the lower extremities, those with transient or sustained clonus of the Achilles reflex, and those with a missing vibrotactile threshold measurement (due to amputations, illness, or noncompliance); the resultant sample sizes were Comparison: N=1,141, Background: N=358, Low: N=224, High: N=223.

We defined percent body fat (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 the analysis for age, race, military occupation (officer, enlisted flyer, enlisted ground), PBF at time of dioxin blood draw, lifetime alcohol history, reported exposure to insecticides, reported exposure to industrial chemicals, reported exposure to degreasing chemicals, and diabetic class. We report peripheral neuropathy by dioxin category. We measured the association between the occurrence of peripheral neuropathy 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 occurrence of peripheral neuropathy 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 Hands in the High dioxin category are younger than Ranch Hands in the Low and Background categories.

Table 2. Distribution of dioxin and demographic characteristics in 1997

			Ranch Hand	
Characteristic	Comparison (N=1,213)	Background (N=381)	Low (N=239)	High (N=243)
Dioxin*	3.8 (0-9.97)	5.8 (0-10)	15 (10.0-25.6)	45.7 (18.0-617.8)
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=1.6) and High (aOR=6.0) dioxin categories having peripheral neuropathy are increased relative to the Comparisons (Table 3).

Table 3. Peripheral Neuropathy by Exposure Category

		Ranch Hand		
Condition	Comparison	Background	Low	High
Number (%)	7 (0.6)	2 (0.6)	3 (1.3)	6 (2.7)
aOR	1.0	1.0	1.6	6.0
95% CI		(0.2, 5.0)	(0.4, 6.4)	(1.6, 22.4)

Our findings are inconsistent with those of Sweeney et al.[2], who found no relation between peripheral neuropathy and dioxin levels in a cohort of industrial workers, but are consistent with those of Barbieri et al[3], who found increases in the number of individuals presenting at least two bilateral clinical signs of peripheral neuropathy among residents of Seveso exposed to dioxin during an industrial accident. Differences between studies could be due to differences with regard to length of follow-up, case definitions, exposure, or a combination of these factors. Ranch Hand exposures appear to have been less than the industrial workers and less than individuals exposed in the Seveso accident. Our definition of confirmed peripheral neuropathy was similar to that of Barbieri et al[3], who required the presence of at least two bilateral and symmetric clinical signs and two electrophysiological abnormalities (including reduced conduction velocities). Sweeney et al[2] defined peripheral neuropathy as the presence of an out-of-range latency, amplitude or conduction velocity, plus an abnormal clinical sign, an out-of-range sensory test, or at least two positive symptoms. The data of Barbieri et al[3] was collected within 6 years of the Seveso accident, and the data of Sweeney et al[2] was collected in 1987-1988 from men who were potentially exposed between 1951 and 1972.

The strengths of this study include high participation and low attrition rates, a Comparison population closely matched to the index population, and 15 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.

References

1. Michalek, J.E., Burnham, B.R., Marden, H.E., et al. (2000). The Air Force Health Study. 1997 Follow-up Examination Results. National Technical Information Service: Springfield.
2. Sweeney, M.H., Fingerhut, M.A., Arezzo, J.C., et al. (1993). Am J Ind Med 23, 845-858.
3. Barbieri, S., Priovano, C., Scarlato, G., et al. (1988). Neuroepidemiology 7, 29-37.