SERUM DIOXIN AND CANCER IN VETERANS OF OPERATION RANCH HAND

Norma S. Ketchum, Joel E. Michalek and Joseph E. Burton

Air Force Research Laboratory, Brooks AFB TX 78235-5250

Introduction

This report summarizes a study of cancer 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[1]. These results were accumulated during the post-service period from each veteran's departure from Southeast Asia to 10 July 1997 in men participating in the ongoing Air Force Health Study, a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans.

Materials and 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 could have been 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, the index group, 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. The study includes in-person interviews and physical examinations and serum dioxin measurements.

We defined cancer as a malignant neoplasm and considered all occurrences of cancer during the entire post-service period from the end of each veteran's service in Southeast Asia to 10 July 1997 in all veterans who participated in at least one physical examination. Information on the occurrence of cancer was collected in questionnaires and physical examinations in 1982, 1985, 1987 and 1992. During the period between the 1992 physical examination and 10 July 1997, we telephoned each veteran, seeking additional reports of new cases diagnosed since the last examination. All reported conditions were verified by medical record review and double blind medical coding with independent adjudication of discordances by certified medical record specialists. Conditions verified from medical records were coded according to the conventions of the International Classification of Diseases, 9th Revision, Clinical Modification manual. Cancers discovered at death were coded from the underlying causes of death on death certificates in accordance with the rules and conventions of the International Classification of Diseases, 9th Revision.

We excluded veterans with cancer prior to service in Vietnam, those with a missing dioxin measurement, a dioxin measurement we could not quantify or a cancer we could not verify. We also excluded Comparison veterans having a dioxin result greater than 10 parts per trillion (ppt), the value we regard as the threshold for background dioxin exposure. The sample size reduction

is summarized in Table 1. The single unverified case was lung cancer reported by a nonblack Ranch Hand officer.

Table 1. Study size reduction by group

	Ranch Hand	Comparison	Total
Compliant at any examination	1109	1493	2602
Missing dioxin	(100)	(140)	(240)
Nonquantifiable dioxin	(17)	(50)	(67)
Comparison dioxin > 10 ppt	(0)	(25)	(25)
Cancer not verified by medical record	(1)	(0)	(1)
Cancer before service in Southeast Asia:	(6)	(3)	(9)
Skin cancer	(5)	(0)	(5)
Cancer at sites other than the skin	980	1275	2255
Net			

Because exposure to ultraviolet light is a primary cause of basal cell carcinoma, we computed a cumulative sun-exposure index based on lifetime residential history. We estimated an average residential latitude by dividing the total degree-years (the sum of the product of the latitude and the number of years lived at each residence) from all of the residences by the total number of reported residential years spanning the entire life time of each veteran. We defined percent body fat (PBF) as PBF=1.264×BMI-13.305, where BMI is the body mass index [weight (kg) divided by the square of height (m)]. We computed PBF using the weight and height measured at the physical examination during which the veteran gave blood for the dioxin measurement. We defined a pack-year as smoking one pack of cigarettes per day for one year and a drink-year as drinking one shot of 80 proof whiskey per day for one year.

We restricted analyses of skin cancer to nonblack veterans and adjusted for birth year, military occupation (officer, enlisted flyer, enlisted ground personnel), skin color (dark, medium, pale, dark peach, pale peach), hair color (black, dark brown, light brown, blonde, red, bald), eye color (brown, hazel, green, gray, blue), reaction of skin to sun exposure after at least 2 hours (no reaction, becomes red, burns, painfully burns), reaction of skin after repeated exposures (deeply tanned, moderately tanned, mildly tanned, no tan), average lifetime residential latitude, percent body fat at the time of the dioxin blood draw, and exposure to ionizing radiation (yes, no), industrial chemicals (yes, no), herbicides (yes, no), insecticides (yes, no), and degreasing chemicals (yes, no). We included all veterans in analyses of cancer at sites other than the skin and adjusted for birth year, military occupation, race, percent body fat at the time of the dioxin blood draw, lifetime cigarette smoking (pack-years), lifetime alcohol consumption (drink-years), and exposure to asbestos (yes, no), ionizing radiation (yes, no), industrial chemicals (yes, no), herbicides (yes, no), insecticides (yes, no), and degreasing chemicals (yes, no).

Using a first order model for dioxin elimination and a constant half life of 8.7 years, we extrapolated the current dioxin to the initial dioxin level at the end of service in Southeast Asia among Ranch Hand veterans having current dioxin levels greater than 10 ppt. To assess the association between dioxin and cancer, we stratified the data according to group, current dioxin

level and initial dioxin level to four exposure categories named Comparison, Background, Low and High. The Comparison category was comprised of Comparison veterans with current dioxin less than or equal to 10 ppt. The Background category was comprised of Ranch Hand veterans with current dioxin less than or equal to 10 ppt. The Low and High categories are comprised of Ranch Hand veterans having current dioxin greater than 10 ppt, with veterans assigned to the Low category if their initial dioxin was less than or equal to 94 ppt and to the High category if their initial dioxin was greater than 94 ppt, where 94 ppt was the median initial dioxin among those with current dioxin levels greater than 10 ppt. The resultant sample sizes by dioxin category were Comparison: N=1,275, Background: N=421, Low: N=276, High: N=283. The numbers of nonblack veterans included in the skin cancer analyses were Comparison: N=1,202, Background: N=400, Low: N=253, High: N=269.

We report cumulative incidence, or prevalence, of cancer by dioxin category. We measured the association between cancer prevalence and dioxin category with the odds ratio (OR) and assessed the precision of the estimate with a 95% confidence interval (95% CI) for the OR. We derived the OR and its confidence interval from a main effects logistic regression model containing dioxin category and all covariates. We compared the cancer 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 are summarized in Table 2. Initial serum dioxin levels are summarized in the Low and High categories, in ppt. Age was determined at the most recent physical examination. PBF was measured at the time of the dioxin blood draw. Veterans in the High dioxin category were younger on the average and tended to drink less than those in the Comparison category

Table 2. Distribution of dioxin and demographic characteristics

		Ranch Hand		
Characteristic	Comparison	Background	Low	High
Dioxin (ppt) [Median (range)]	4.0 (0-10)	5.7 (0-10)	52.3 (27-94)	195.7 (94-3,290)
Age (years) [Mean (SD)]	53.5 (7.6)	54.6 (7.2)	54.6 (7.6)	50.9 (7.4)
Percent Body Fat [Mean (SD)]	21.9 (5.1)	20.2 (4.5)	22.2 (5.3)	23.4 (5.6)
Lifetime Smoking (median pack-years)	6.9	6.1	9.8	7.0
Lifetime Drinking (median drink-years)	18.9	16.5	19.6	16.0
Black (%)	5.7	5.0	8.3	5.0
Occupation:				
Officer (%)	38.4	61.3	37.7	2.8
Enlisted Flyer (%)	16.0	11.9	21.0	20.9
Enlisted Ground (%)	45.6	26.8	41.3	76.3

No association was found between skin cancer and dioxin category (Table 3). One Black Comparison enlisted flyer with melanoma with a non-detectable dioxin level was excluded from these analyses. No Black Ranch Hand veterans had skin cancer.

Table 3. Skin cancer in nonblack veterans

		Ranch Hand		
	Comparison	Background	Low	High
Number (%)	158 (13.4)	57 (14.4)	44 (17.6)	22 (8.3)
OR	1.0	1.0	1.3	0.8
95% CI		0.7, 1.5	0.8, 2.0	0.5, 1.4

No association was found between the prevalence of cancer at sites other than the skin and dioxin category (Table 4).

Table 4. Cancer at sites other than the skin

		Ranch Hand		
	Comparison	Background	Low	High
Number (%)	81 (6.5)	26 (6.3)	28 (10.3)	11 (4.0)
OR	1.0	0.8	1.3	0.7
95% CI		0.5, 1.3	0.8, 2.2	0.3, 1.4

We found no evidence of a dose-response gradient and no significant increased risk of cancer in the High dioxin category, the subgroup of greatest a priori interest. The prevalence of skin cancer appeared unrelated to dioxin exposure category. The risk of skin cancer among veterans in the High category was not greater than the Comparison risk, whereas we found an increased risk of skin cancer in the Low category. The risk of cancer at sites other than the skin was not increased in the High category, but we noted an increased risk in the Low category. These patterns were not suggestive of an adverse association between dioxin and cancer. Our ability to detect associations was limited by the size of the Ranch Hand group.

References

1. Ketchum NS, Michalek JE and Burton JE: *Am. J. Epidemiol.* **1999** (in press).