

Cancer, Dioxin, and Calendar Period of Herbicide Spraying in Veterans of Operation Ranch Hand

Marian Pavuk¹, Joel E Michalek², Norma S Ketchum²

¹Spec-pro Inc

²Air Force Research Laboratory

Introduction

The Air Force Health Study is a 20-year prospective study of the health, mortality and reproductive outcomes of Ranch Hand veterans, the unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971.¹ Included as referents was a Comparison cohort of other Air Force veterans who served in the Southeast Asia (SEA) region during the same period that the Ranch Hand unit was active but who were not involved with spraying herbicides. This report updates our previous cancer study with the follow up extending to September 30, 2004.² The herbicide Agent Orange was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) from less than 0.05 to almost 50 parts per million.³ A recent study showed⁴ that higher contamination of herbicides overall, and especially during early years of spraying (1961-66), may have occurred, and tours occurring during that period were given special emphasis in this study.

Materials and Methods

The details of study design and subject selection were published previously.¹ The study included periodic comprehensive medical examinations and in-person interviews, conducted in 1982, 1985, 1987, 1992, 1997, and 2002. Information on cancer was derived from physical examinations and medical records. We classified underlying causes of death in accordance with the rules and conventions of the 9th revision of the International Classification of Diseases (ICD 9). We defined "all SEER sites" cancer as a malignancy included in any of the National Cancer Institute Surveillance Epidemiology and End Results (SEER) anatomical category definitions.⁵ "All sites" cancer included basal and squamous cell carcinoma in addition to SEER site cancers. Dioxin levels were measured on a lipid weight basis in serum collected from veterans who attended the 1987 physical examination. Additional measurements were performed in 1992 and 1997. All Comparison veterans with a dioxin measurement were assigned to the 'Comparison' category and Ranch Hands with a dioxin not exceeding 10 parts per trillion (ppt) to the 'Background' category. Ranch Hands with an initial dioxin less than or equal to 118.5 ppt, the median dioxin among those with dioxin exceeding 10 ppt, were assigned to the 'Low' category and those with an initial dioxin greater than 118.5 ppt were assigned to the 'High' category.

Days of spraying herbicides were enumerated for each Ranch Hand veteran using an old version the Herbs tape. Number of spray days and the calendar period of service were considered motivated by the usage of various herbicides in Vietnam between 1961 and 1969,⁴ and findings of increased risk of cancer related to the length of service in SEA in Comparison veterans.⁷ The analyses were restricted to veterans who had participated in at least one physical examination and who had a non-missing dioxin measurement. Veterans with cancer diagnosis prior to baseline (1982) were excluded from all analyses.

Table 1. Sample size reduction in US Air Force veterans.

	Comparison		Ranch Hand		Total
	Yes	No	Yes	No	
Cancer					
Total	498	1355	359	837	3049
Not compliant	(11)	(198)	(10)	(70)	289
Missing dioxin	(27)	(88)	(15)	(69)	199
Pre-baseline cancer	(47)	--	(46)	--	93
Net	413	1069	288	698	2468

We used Cox proportional hazards to calculate risk ratios and corresponding 95% confidence intervals. The date of entry into follow-up was January 1, 1982. Cancer was analyzed by SEER category, 'all SEER site' and 'all site' cancer category. For each category, the end of follow-up was defined as the earliest of the first cancer diagnosis in the category, death, or September 30, 2004. Due to the small number of cancers in African-American and other minority veterans, all cancer analyses were restricted to 'White' veterans. To examine a possible association of spraying more contaminated herbicides during the early years of conflict on cancer incidence, we performed additional analysis with Ranch Hand veterans categorized to two strata: 1. Ranch Hand who sprayed at least 30 days during or prior to 1967 and served in the unit prior or during 1968, and 2. The complement to strata 1; i.e. those who sprayed less than 30 days before 1967 or more than 30 days after that, or served in SEA after 1968.

Results and Discussion

Demographic characteristics of Ranch Hand and Comparison veterans were similar. Serum dioxin concentrations increased with tertiles of spray-days in Ranch Hand veterans (data not shown). Overall, there was no association between cancer and dioxin exposure category for all sites, all SEER sites cancer, prostate cancer (Table 2), or other specific cancer sites (data not shown).

Table 2. Relative risks of cancer by dioxin category in White US Air Force veterans.

	Comparison (n=1,325)	Background (n=412)	Ranch Hand	
			Low (n=247)	High (n=247)
All sites ^a				
Number (%)	411 (31.1)	141 (34.2)	97 (39.3)	54 (21.9)
RR (95% CI)	1.0 (Ref.)	1.0 (0.8-1.2)	1.3 (1.1-1.7)	0.9 (0.6-1.2)
p-value		0.79	0.01	0.34
All SEER sites ^b				
Number (%)	190 (14.4)	67 (16.3)	48 (19.4)	27 (10.9)
RR (95% CI)	1.0 (Ref.)	1.0 (0.8-1.4)	1.3 (0.9-1.7)	1.0 (0.7-1.5)
p-value		0.87	0.16	0.98
Prostate ^b				
Number (%)	75 (5.7)	23 (5.6)	18 (7.3)	10 (4)
RR (95% CI)	1.0 (Ref.)	0.8 (0.5-1.)	1.2 (0.7-1.7)	1.0 (0.5-2.1)
p-value		0.42	0.56	0.89

In the stratified analysis, for the Ranch Hands who sprayed at least 30 days prior to or during 1967 and served in the unit prior to or during 1968, the risk of all SEER site cancer increased statistically significantly in the High dioxin category (RR=1.9, p=0.02) (Table 3). An increase in the risk of prostate cancer was also found in the high exposure category (RR=3.7, p=0.004) but the number of prostate cancers in the dioxin categories was small. There was no association between dioxin exposure and cancer in the stratum complement to that of Table 3 (data not shown).

Results presented here showed no association between dioxin exposure categories and risk of cancer for all sites, all SEER sites, prostate cancer or other specific cancer sites. There was a suggestion of increased risk for all SEER sites cancer and prostate cancer in the subgroup of veterans exposed to higher contaminated herbicides, and possibly other factors, early during the Vietnam conflict (before 1968). Further study and a greater number of cancers at specific cancer sites is needed to determine whether this is due to dioxin or other factors related to service in SEA.

Table 3. Relative risks of cancer by dioxin category, Ranch Hands with at least 30 spray-days prior or during 1967. Last year of service prior or during 1968.

	Comparison (n=379)	Background (n=174)	Ranch Hand	
			Low (n=91)	High (n=143)
All sites ^a				
Number (%)	121 (31.9)	55 (31.6)	34 (37.4)	37 (25.9)
RR (95% CI)	1.0 (Ref.)	0.8 (0.6-1.2)	1.1 (0.8-1.7)	1.0 (0.7-1.5)
p-value		0.3	0.56	0.89
All SEER sites ^b				
Number (%)	46 (12.1)	22 (12.6)	20 (22)	23 (16.1)
RR (95% CI)	1.0 (Ref.)	0.9 (0.5-1.5)	1.6 (0.9-2.8)	1.9 (1.1-3.3)
p-value		0.68	0.08	0.02
Prostate ^b				
Number (%)	15 (4)	9 (5.2)	4 (4.4)	10 (7)
RR (95% CI)	1.0 (Ref.)	1.0 (0.4-2.2)	0.9 (0.3-2.8)	3.7 (1.5-9.2)
p-value		0.92	0.87	0.004

a. Adjusted for age at tour, military occupation, pack-years of smoking, reaction to sun exposure and eye color.

b. Adjusted for age at tour, military occupation, pack-years of smoking.

References

1. Wolfe W.H., Michalek J.E., Miner J.C., Rahe A.J., Silva J., Thomas W.F., Grubbs W.D., Lustik M.B., Karrison T.G., Roegner R.H. and Williams D.E. (1990) *JAMA*. 264: 1824-1831.
2. Akhtar F.Z., Garabrant D.H., Ketchum N.S. and Michalek J.E. (2004) *J Occup Environ Health*. 46: 123-136.
3. Institute of Medicine. (2003) Washington DC, National Academy Press.
4. Stellman J.M., Stellman S.D., Christian R., Weber T. and Tomasallo C. *Science* (2003) 422: 681-687.
5. Surveillance Epidemiology and End Results. (1993) National Cancer Institute. DHHS. Washington, DC.
6. Hornung R.W. and Reed D.R. (1990) *App Occup Environ Hyg*. 5(1): 46-51.
7. Pavuk M., Michalek J.E., Schechter A., Ketchum N.S., Akhtar F.Z., Fox K.A. (2005) *J Occup Environ Med*.47(4): 335-342.