Mortality of Air Force veterans exposed to herbicides during the Vietnam War

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Introduction

The long-term effects of herbicide exposure on human health are not fully known and remain controversial. Herbicides were used by US forces for defoliation and crop destruction during the Vietnam War. The toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), the contaminant found in Agent Orange and other herbicides sprayed during the war, continue to be of concern more than thirty years after the war. Studies of the post-service mortality experience of Vietnam veterans[1-7] have given mixed results. The US Army Chemical Corps Study[1] reported an increased risk of death due to digestive diseases and a non-significant increase in the risk of death from cancer. A study of Australian Army veterans[4] reported an increased risk of death due to digestive diseases but no increases due to cancer. However, a study of women veterans[3] found an increased risk of death due to pancreatic cancer and a study of Vietnam veterans from Michigan[6] reported an excess of deaths due to non-Hodgkin's lymphoma.

The Air Force Health Study is a prospective epidemiological study of the health, mortality[8,9], and reproductive outcomes of veterans of Operation Ranch Hand, the unit responsible for aerially spraying herbicides in Vietnam from 1962 to 1971. The study, now in its 22nd year, began in 1982 and will conclude in 2006. Here we update our second report by summarizing current all-cause and cause-specific post-service mortality in veterans of Operation Ranch Hand.

Materials And Methods

Population definition and the process by which mortality was determined were discussed in detail in our first mortality report[8]. We contrast cumulative Ranch Hand (N=1,262) post-service mortality through December 31, 1999 with that of a Comparison population of 19,078 Air Force veterans who flew or serviced C-130 cargo aircraft in Southeast Asia between 1962 and 1971, the same calendar period that the Ranch Hand unit was active in Vietnam. Comparison veterans were stationed throughout Southeast Asia, were not involved with spraying herbicides, and were demographically similar to Ranch Hand veterans. Veterans killed in action during the Vietnam War were excluded because Ranch Hand combat deaths were not caused by herbicide exposure. Twenty-two Ranch Hand and 109 Comparison veterans were killed in action in Vietnam. Since our last mortality report[9], continued record review found one Comparison whose military records

indicated that he was in fact a Ranch Hand and another who was not a member of either cohort. We reassigned the first of these to the Ranch Hand cohort and excluded the second from the study, yielding 1262 Ranch Hand veterans, one more than previously reported, and 19,078 Comparison veterans, two less than previously reported. All of the 20,340 veterans studied were male.

The numbers of veterans at risk are summarized in Table 1 by military occupation (pilots and navigators, administrative officers, enlisted flight engineers, enlisted ground crew). All pilots and navigators were officers. We used military occupation as a surrogate to adjust for both socioeconomic status and inferred herbicide exposure. Most enlisted personnel were not college educated and most officers were college graduates. Dioxin assay results suggest that, among Ranch Hand veterans, enlisted personnel were more heavily exposed than officers and, among enlisted veterans, ground crew were more heavily exposed than flight engineers.

Table 1. Number of veterans at risk by exposure group and military occupation among US Air Force veterans who served in Southeast Asia from 1962 to 1971.

Military Occupation	Ranch Hand	Comparison
Pilots and navigators	441	5,242
Administrative officers	26	284
Enlisted flight engineers	208	2,828
Enlisted ground crew	587	10,724
All personnel	1262	19,078

Cohort contrasts not involving serum dioxin measurements: All 20,340 veterans were included. Veterans who survived to December 31, 1999, the cutoff date for these analyses, contributed the time, in years, between the dates of entry into follow-up (the date of the start of service in Southeast Asia) and the cutoff date, and those known to have died before the cutoff date contributed the time, in years, between the dates of entry into follow-up and death. We computed the relative risk (RR), a 95% confidence interval (CI) for the RR, and the p-value of a test of hypothesis that RR=1 using a proportional hazards model with adjustment for birth year and military occupation. We did not adjust for race because there were too few Blacks (6.2% of the Ranch Hand cohort) to permit adjustment. 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). Among the 20,340 veterans included in this mortality assessment, we were unable to adjust for smoking, a risk factor for cardiovascular disease, or for drinking, a risk factor for liver disease, because risk factor information was available only for the subgroup of veterans who attended at least one physical examination.

Contrasts utilizing serum dioxin measurements: These analyses were restricted to the 2,452 veterans who attended at least one physical examination administered in 1982, 1985, 1987, 1992 or 1997 and received a dioxin assay result (Ranch Hand: N=1,016, Comparison: N=1,436), adjusting for potential risk factors. We defined a pack-year as the equivalent of smoking one pack of cigarettes per day for one year. A drink-year was defined as the equivalent of drinking one 1.5 ounce of 80-proof alcoholic beverage per day for one year. Smoking and drinking data were taken

from 1982, the year in which the first physical examinations were given. All-cause mortality was adjusted for military occupation, year of birth, smoking history (pack-years), drinking history (drink-years) and family history of heart disease. Cancer mortality was adjusted for military occupation, year of birth, smoking history, reaction to sun exposure (low, medium, high) and eye color (brown, hazel/green, gray/blue). We adjusted circulatory disease mortality for military occupation, year of birth, smoking history and family history of heart disease. The protocol was reviewed and approved by the Institutional Review Boards at the medical treatment and sponsoring facilities. Participation was voluntary and signed informed consent was obtained from each veteran at the examination site.

Dioxin levels were measured by CDC in parts per trillion (ppt) on a lipid weight basis in serum collected from veterans who completed the 1987 physical examination. Additional measurements were made in 1992 and 1997. For those veterans whose dioxin level was not measured in 1987, the subsequent measure was extrapolated to 1987 using a first-order kinetics model with a constant half-life of 7.6 years.

We assigned each veteran to one of four dioxin exposure categories based on his cohort (Ranch Hand, Comparison), dioxin concentration, and half-life extrapolated initial dioxin concentration. Comparison veterans with a dioxin measurement were assigned to the "Comparison" category. Ranch Hand veterans with a dioxin measurement not exceeding 10 ppt were assigned to the "Background" category. Ranch Hand veterans with dioxin levels exceeding 10 ppt had their initial dioxin at the end of service in Vietnam estimated using a first-order kinetics model with a constant half-life of 7.6 years. Among Ranch Hand veterans with a dioxin body burden exceeding 10 ppt, those with an initial dioxin less than or equal to 117.6 ppt (the median initial dioxin in this subgroup) were assigned to the "Low" category and those with an initial dioxin greater than 117.6 ppt were assigned to the "High" category.

We report deaths from all causes, cancer and circulatory disease, and the associated RR, 95% CI, and p-value, for contrasting each of the three Ranch Hand dioxin exposure categories with the Comparison category, based on a proportional hazards model. We report the p-value for trend, for the test of the hypothesis that the coefficient of the log-transformed serum dioxin concentration was equal to 1.0 in the combined cohort. All statistical testing was 2-sided with a significance level of 5%.

Results

Cohort contrasts not involving serum dioxin measurements: Ranch Hand and Comparison mortality is summarized in Table 2. One hundred eighty six of 1,262 (14.7%) Ranch Hand veterans and 2,330 of 19,078 (12.2%) Comparison veterans died from all causes during the post-service period through 1999; the all-cause relative risk of death was non-significantly increased (RR=1.15, 95% CI: 1.0, 1.3, p=0.06). The relative risk of death from diseases of the circulatory system was also non-significantly increased (RR=1.3, 95% CI: 1.0, 1.6, p=0.07), based on 66 Ranch Hand and 745 Comparison deaths.

Table 2**.** Cause-specific and all-cause mortality of 20,340 US Air Force veterans who served in Southeast Asia from 1962 to 1971.

	Number of Deaths (%)				
Cause of Death[a]	Ranch Hand	Comparison	RR	95% CI	p
All causes	186 (14.7)	2330 (12.2)	1.15	1.0, 1.3	0.06
Infectious diseases	2 (0.2)	28 (0.2)	1.1	0.3, 4.5	0.92
Cancer	51 (4.0)	690 (3.6)	1.0	0.8, 1.4	0.75
Endocrine diseases	3 (0.2)	31 (0.2)	1.4	0.4, 4.7	0.56
Nervous system diseases	1 (0.1)	43 (0.2)	0.3	0.0, 2.3	0.26
Circulatory diseases	66 (5.2)	745 (3.9)	1.3	1.0, 1.6	0.07
Respiratory diseases	8 (0.6)	96 (0.5)	1.2	0.6, 2.5	0.63
Digestive diseases	10 (0.8)	89 (0.5)	1.6	0.8, 3.0	0.17
Ill Defined or Unknown	7 (0.6)	74 (0.4)	1.5	0.7, 3.3	0.29
Accident	30 (2.4)	360 (1.9)	1.2	0.9, 1.8	0.27
Suicide	5 (0.4)	110 (0.6)	0.7	0.3, 1.7	0.43
Homicide	3 (0.2)	27 (0.1)	1.8	0.5, 5.8	0.35

a All causes (ICD 001-969), Infectious or parasitic diseases (001-139), Cancer (140-208, 230-234), Endocrine diseases (240-279), Nervous system diseases (320-389), Circulatory diseases (390-459), Respiratory diseases (460-519), Digestive diseases (520-579), Ill-defined or unknown (780-799), Accident (800-949), Suicide (950-959), Homicide (960-969).

All-cause mortality and mortality due to cancer and circulatory diseases were summarized by military occupation (not shown). The relative risk of death from any cause was significantly increased among enlisted ground crew (RR=1.3, 95% CI: 1.0, 1.6, p=0.02) mostly due to a significant increase in the risk of death caused by diseases of the circulatory system (RR=1.7, 95% CI: 1.2, 2.4, p=0.001).

Contrasts utilizing serum dioxin measurements: All-cause mortality and mortality due to cancer and circulatory diseases, adjusted for risk factors, are summarized in Table 3 by dioxin exposure category; no significant increases in the risk of death were found in any of the three Ranch Hand dioxin exposure categories.

Table 3. Mortality of 2,452 US Air Force Veterans with dioxin assay results who attended at least one physical examination.

	Dioxin	Comparison	Background	Low	High
All causes					
Number Deaths (%)		102 (7.1)	34 (7.7)	23 (8.0)	19 (6.6)
Relative Risk[a]	1.0		1.1	1.1	1.0
95% CI	0.9, 1.2		0.7, 1.6	0.7, 1.7	0.6, 1.7
P-value	0.98		0.79	0.73	0.94
Cancer					
Number Deaths (%)		40 (2.8)	18 (4.1)	4 (1.4)	4 (1.4)
Relative Risk[b]	0.7		1.3	0.3	0.6
95% CI	0.6, 1.0		0.7, 2.3	0.1, 1.0	0.2, 1.6
P-value	0.04		0.36	0.05	0.30
Circulatory diseases					
Number Deaths (%)		31 (2.2)	8 (1.8)	12 (4.2)	9 (3.1)
Relative Risk[c]	1.2		0.8	1.8	1.5
95% CI	1.0, 1.6		0.4, 1.8	0.9, 3.5	0.7, 3.3
P-value	0.07		0.61	0.09	0.29

[a]Adjusted for military occupation, birth year, smoking, drinking and family history of heart disease.
[b]Adjusted for military occupation, birth year, smoking, reaction to sun exposure and eye color.
[c]Adjusted for military occupation, birth year, smoking, and family history of heart disease.

Discussion

An evaluation of all-cause post-service mortality through December 31, 1999 found a non-significantly increased relative risk (RR=1.15, p=0.06) and a significant increase in the risk of death from diseases of the circulatory system in Ranch Hand enlisted ground crew, the subgroup with the highest dioxin levels (RR=1.7, p=0.001). The all-cause result differs from that of previous reports in that it marked the first time in the study that the all-cause relative risk numerically exceeded 1.0. Until now, this and other veteran's studies found either no increase or a deficit of deaths among those veterans presumed exposed. An increased risk of death from diseases of the circulatory system in Ranch Hand enlisted ground crew has been seen before but the relative risk is now increased.

In conclusion, an analysis of all-cause and cause-specific mortality through December 31, 1999 found a significant increase in the risk of death from diseases of the circulatory system in Ranch Hand enlisted ground crew, the subgroup with the highest dioxin levels. Further follow-up of this cohort is necessary to confirm the increased risk suggested by these results.

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