Health Status of Army Chemical Corps Vietnam Veterans Who Sprayed Defoliant in Vietnam

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Background *U.S. Army Chemical Corps veterans handled and sprayed herbicides in Vietnam resulting in exposure to Agent Orange and its contaminant 2,3,7, 8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). This study examined the long-term health effects associated with herbicide exposure among these Vietnam veterans.*

Methods *A health survey of these 1,499 Vietnam veterans and a group of 1,428 non-Vietnam veterans assigned to chemical operations jobs was conducted using a computer-assisted telephone interview (CATI) system. Exposure to herbicides was assessed by analyzing serum specimens from a sample of 897 veterans for dioxin. Logistic regression analyses were used to estimate the risk of selected medical outcomes associated with herbicide exposure.*

Results *Odds ratios for diabetes, heart disease, hypertension, and chronic respiratory disease were elevated, but not significantly ($P > 0.05$) for those who served in Vietnam. However, they were significantly elevated among those Vietnam veterans who sprayed herbicides: diabetes, odds ratio (OR) = 1.50 (95% confidence interval [95%CI] = 1.15–1.95); heart disease, OR = 1.52 (1.18–1.94); hypertension, OR = 1.32 (1.08–1.61); and chronic respiratory condition, OR = 1.62 (1.28–2.05). Hepatitis was associated with Vietnam service, but not with herbicide application.*

Conclusions *Vietnam veterans who were occupationally exposed to herbicide experienced a higher risk of several chronic medical conditions relative to other non-Vietnam veterans. A potential selection bias is of concern. However, there were relatively high participation rates in both the Vietnam and non-Vietnam veteran groups, and the prevalence rates of some of these medical conditions among non-Vietnam veterans were comparable to general populations. Therefore, self-selection factors are considered unlikely to have biased the study results.* Am. J. Ind. Med. 49:875–884, 2006. *Published 2006 Wiley-Liss, Inc.*[†]

KEY WORDS: Agent Orange; diabetes; dioxin; herbicide; veterans; Vietnam

INTRODUCTION

Agent Orange, an herbicide widely used as a defoliant in Vietnam, was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) which contained dioxin contaminants. In 1994, with growing concerns for the possible long-term health consequences of exposure to Agent Orange contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a National Academy of Sciences (NAS) committee recommended continued

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follow-up of the Air Force Ranch Hand cohort as well as a study of the health of members of the Army Chemical Corps who served in Vietnam [IOM, 1994]. Air Force Ranch Hand personnel were responsible for aerial spraying of herbicides from fixed wing aircraft in Vietnam from 1962 to 1971, while members of the Army Chemical Corps were responsible for spraying of herbicides around the perimeters of base camps and aerial spraying from helicopters in Vietnam. Approximately two-thirds of all herbicides used in Vietnam were Agent Orange and other phenoxyherbicides which contained trace amounts of dioxin. The extent of herbicide exposure of the Army Chemical Corps personnel who served in Vietnam was thought to be similar to those of the Ranch Hand cohort who were involved with the fixed wing aircraft spraying [Kahn et al., 1988; IOM, 1994].

The primary objective of the health survey was to determine the long-term health consequences of Agent Orange exposure among Army Vietnam veterans who were occupationally exposed to the herbicide.

MATERIALS AND METHODS

Selection of Study Subjects

Potential study subjects for the Army Chemical Corps Study were identified from three separate sources: (1) morning reports of Army Chemical Corps detachments assigned to Vietnam between 1966 and 1971, (2) military personnel records maintained by the Defense Manpower Data Center of Army personnel who were on active duty between 1971 and 1974 with a military occupation specialty code (MOSC) indicating chemical operations, and (3) class rosters of those Army personnel who attended the Army Chemical School, Fort McClellan, Alabama, during the Vietnam era, 1965–1973 [Dalager and Kang, 1997; Kang et al., 2001]. Military personnel records of all potential study subjects were retrieved from the National Personnel Records Center in St. Louis, MO and reviewed to identify men from that group who served on active duty in the US Army for a minimum of 18 months during the Vietnam era. The study group was selected to include those men whose permanent tour of duty included service in Vietnam reflecting any chemical operation duties between July 4, 1965 and March 28, 1973. The non-Vietnam veteran comparison group consisted of men who had similar characteristics as the Vietnam group with respect to branch of service, time period of service, and military occupation with the exception that their permanent tours of duty did not include service in Vietnam. A total of 2,872 Vietnam veterans and 2,737 non-Vietnam veterans were identified as potential study participants. Of these, veterans who were known to be deceased as of December 1998 and those who participated in an earlier pilot study were excluded from this study, which resulted in 2,247 Vietnam and 2,242 non-Vietnam veterans who were targeted for the study.

Data Collection

A computer-assisted telephone interview (CATI) system was used for the data collection because of its efficiency. Information on the veterans' military and civilian occupational exposures, chronic health conditions, and measures of functional impairment and limitation of activity was collected during the telephone interviews in 1999–2000. Military personnel records were used to supplement and validate self-reported interview data to the extent feasible. For a selected health outcome (diabetes), medical and hospital records were collected to document further the self-reported data.

In order to assess exposure to herbicides, serum dioxin concentration was measured for 795 of 1,084 (73%) Vietnam veterans and 102 of 157 (65%) non-Vietnam veterans who were invited to participate in the serum dioxin study. An unequal number of blood specimens were analyzed for the Vietnam veterans and non-Vietnam veterans for two main reasons: (1) because of the high cost of the laboratory test (approximately $1,000 per specimen), only 1,000 specimens could be budgeted for analysis and (2) given the much smaller variance of TCDD values among non-Vietnam veterans compared to Vietnam veterans observed in the previous study [Kang et al., 2001], it was concluded that adequate statistical power could be obtained even with substantially different sample sizes in the two groups. This approach allowed us to maximize the limited resources and to analyze as many as a half of survey participants who were potentially exposed to TCDD in Vietnam. Blood specimens were collected in 1999–2000 at individuals' homes by trained medical technicians using a collection device and storage containers provided by the participating CDC laboratory. Serum specimens were shipped to the CDC laboratory by overnight delivery service in accordance with the CDC protocol. The CDC lab analyzed the serum specimens for 2,3,7,8-TCDD using the analytical protocol published elsewhere [Patterson et al., 1987]. All laboratory analyses were blinded to the Vietnam service experience and the reported herbicide exposures of the blood donors. The study protocol was approved by the Washington DC VA Medical Center Institutional Review Board and each individual gave signed informed consent for blood specimens.

Health Outcomes

The health interview study collected self-reported data on selected chronic medical conditions diagnosed by medical doctors. These conditions included diabetes, hepatitis (all types combined since veterans could provide few specifics), any type of heart condition (including coronary heart disease,

hardening of the arteries, angina pectoris, myocardial infarction, or heart attack), all cancer and leukemia (excluding non-melanoma skin cancers), all chronic respiratory diseases (such as chronic bronchitis, asthma, emphysema, pleurisy, or tuberculosis), and hypertension for which a doctor prescribed medication. The measures of general health and functional status were obtained using two items from the Medical Outcomes Study 36-Item Short Form (SF-36), which is a well-standardized and widely used instrument to assess health-related quality of life [Ware, 1993]: (1) self-assessed general health status and (2) limitations of work due to health problems. The possibility of over-reporting of a chronic condition by the exposed veterans was evaluated by a review of medical records for diabetes, and by a comparison of reported prevalence rates of selected chronic conditions in relation to serum TCDD levels among the exposed veterans.

Statistical Analysis

As a measure of association between exposure and the risk of selected diseases, the odds ratio (OR) and 95% confidence interval (95%CI) were calculated using a multivariate logistic regression model with adjustment for covariates [SAS, 1999]. The regression coefficients obtained through logistic regression indicated the effect of an individual variable on the log odds of the outcome event with all the remaining variables held constant. For a cohort study, this is often referred to as the incidence odds ratio. Because the risk of disease is relatively small over the period of observation, the values of the odds ratio should approximate that of the risk ratio [Kelsey et al., 1986].

Interview data were used to examine selected disease outcomes and to provide demographic and military data used as covariates in the logistic modeling. Final logistic models included the following covariates: Vietnam service (yes = 1, no = 0), race (white = 0, non-white = 1), body mass index (BMI) (normal, <25.0; overweight, 25.0–29.9; obese, ≥30.0), military rank (enlisted or officer), current cigarette smoking (yes = 1, no = 0), age at time of interview, and a history of spraying herbicides in the military (yes = 1, no = 0). Frequency and duration of herbicide exposure were also examined in the logistic models for major health outcomes. Since the inclusion of frequency and/or duration of herbicide exposure in the logistic models did not significantly change the results, they were not included in the final model.

RESULTS

Demographic and Military Characteristics

Of the 4,119 veterans whose current residences could be determined for the study, 1,499 Vietnam veterans and 1,428 non-Vietnam veterans completed the telephone interview resulting in an interview rate of 72.9% and 69.2%, respectively. Table I provides the military and demographic characteristics of the 2,927 veterans who completed the telephone interview by their Vietnam service status. There were small but statistically significant differences ($P < 0.05$) between the Vietnam and non-Vietnam veterans who completed the interview with respect to selected characteristics. Because of these differences, adjustment for these covariates was made in the multivariate analyses.

Vietnam Service and Chronic Health Conditions

Table II shows the prevalence of selected chronic health conditions among 1,499 Vietnam veterans and 1,428 non-Vietnam veterans who participated in the study. The odds ratios, adjusted for age, race, BMI, and current smoking status, were significantly elevated for hepatitis, all cancer, respiratory problems, ''poor'' current health status, and work limitation among Vietnam veterans as compared to non-Vietnam veterans. The other outcomes such as diabetes, heart conditions, and hypertension were also elevated, but were not statistically significant ($P > 0.05$).

Serum TCDD Concentrations and a History of Spraying Herbicides

As shown in Table III, analyses of serum samples for TCDD concentrations among the Vietnam veterans revealed a significant difference in mean serum TCDD concentrations by a self-reported history of spraying herbicides while in Vietnam ($P < 0.001$). Because a history of Agent Orange exposure reported by a veteran was supported by a serum TCDD level, a veteran's reported history of spraying Agent Orange in Vietnam was used for the purpose of classifying veterans into an exposure status.

Herbicide Exposure and Chronic Health Conditions Among Vietnam Veterans

Table IV shows the prevalence and adjusted odds ratios for selected health conditions among Vietnam veterans who reported a history of spraying herbicides (n = 662) relative to Vietnam veterans who did not report a history of spraying herbicides (n = 811). The prevalence of each of the outcomes presented was greater among the Vietnam veteran sprayers than among the Vietnam veteran non-sprayers. Adjustment for age, race, BMI, military rank, and smoking status in a multiple logistic model showed a significantly increased risk for diabetes, heart conditions, chronic respiratory conditions, hypertension requiring medication, and self-reported poor health status. Adjusted relative risks for all cancers and for hepatitis, which were significantly elevated with Vietnam

TABLE I. Selected Characteristics of the U.S. Army Chemical Corps Veterans Who Completed the Telephone Interview by Vietnam Service Status*

	Vietnam (n = 1,499)		Non-Vietnam (n = 1,428)	
Characteristic	**Number**	**%**	**Number**	**%**
Rank				
Officer	105	7.0	203	14.2
Enlisted	1,394	93.0	1,225	85.8
Race				
White	1,217	81.2	1,235	86.5
Non-white	282	18.8	193	13.5
Age at interview (years)				
<46	0	—	36	2.5
46–50	249	16.6	559	39.2
51–55	793	52.9	658	46.1
>55	457	30.5	175	12.3
Median age at interview	53 years		51 years	
Regular smoker				
Yes	1,071	71.4	858	60.1
No	428	28.6	570	39.9
Body mass index				
<25.0	341	22.8	390	27.3
25.0–29.9	710	47.4	695	48.7
≥30.0	448	29.9	343	24.0
Herbicide spraying				
Yes	662	44.2	146	10.2
No	811	54.1	1,234	86.4
Unknown	26	1.7	48	3.4

*Distribution of military and demographic characteristics were significantly different, $P < 0.05$ by the Mantel-Haenszel Chi-square test.

TABLE II. Prevalence and Adjusted Odds Ratios for Selected Health Conditions Among U.S. Army Chemical Corps Veterans Associated With Vietnam Service

	Vietnam (n = 1,499)		Non-Vietnam (n = 1,428)		
Conditions	**Number**	**%**	**Number**	**%**	**Adj odds ratio (95%CI)[a]**
Diabetes	226	15.08	136	9.52	1.16 (0.91–1.49)
Hepatitis	101	6.74	65	4.55	1.85 (1.30–2.64)
Heart conditions	243	16.21	158	11.06	1.09 (0.87–1.38)
All cancer[b]	108	7.20	53	3.71	1.46 (1.02–2.10)
All respiratory problems[c]	267	17.81	174	12.18	1.41 (1.13–1.76)
Hypertension with medication	496	33.09	355	24.86	1.06 (0.89–1.27)
Current health is poor	189	12.61	91	6.37	1.68 (1.27–2.22)
Health limits kind and amount of work	245	16.34	135	9.45	1.53 (1.21–1.95)

[a]Adjusted odds ratio and 95% confidence interval for each disease condition associated with Vietnam service was derived from a logistic regression model with adjustment for age, race, body mass index, rank, and regular smoking.
[b]The condition category "All cancer" excludes non-melanoma skin cancers.
[c]The condition category "All respiratory problems" includes all non-malignant respiratory conditions.

TABLE III. Mean Serum 2,3,7,8-TCDD Concentration (Range)* by Service in Vietnam and History of Herbicide Spraying

	Self-reported herbicide spraying		
Vietnam service	**Yes**	**No**	***P*-values[a]**
Yes	4.3 (0.5–85.8) $n_1 = 357$[b]	2.70 (0.6–27.7) $n_2 = 413$	$P < 0.001$
No	3.1 (0.8–9.6) $n_3 = 9$	2.1 (0.4–12.5) $n_4 = 87$	$P < 0.15$

*Measured in parts per trillion (ppt), lipid corrected (ng/g serum lipid).
[a]Student's *t*-test was used to compare the geometric means of two exposure groups.
[b]The number of serum samples analyzed for 2,3,7,8-TCDD. Veterans who did not report on the history of herbicide spraying (n = 17) or who provided inadequate blood samples were not included in the table.

service compared to non-Vietnam service, were not statistically elevated when comparing herbicide spray status among veterans serving in Vietnam.

Logistic Regression Analysis of Chronic Health Conditions

To evaluate the effects of both Vietnam service and a history of spraying herbicides while in the military, these covariates were examined in a multiple logistic regression model that also included the other covariates from the earlier models. Table V shows the adjusted odds ratios for each covariate for each selected disease condition. The upper part of Table V shows the relative risks associated with the covariates from the logistic models for diabetes, heart disease, hypertension, and respiratory diseases. There was no statistically significant effect due to Vietnam service in general for each of these four conditions when adjustments were made for the other covariates. However, each of these four conditions was significantly associated with a history of spraying herbicide: diabetes OR = 1.50 (95%CI = 1.15–1.95); heart disease OR = 1.52 (95%CI = 1.18–1.94); hypertension OR = 1.32 (95%CI = 1.08–1.61); and chronic respiratory disease OR = 1.62 (95%CI = 1.28–2.05). There was a significant association of non-white race with diabetes and hypertension. BMI was significantly associated with diabetes, heart disease, and hypertension, but not with respiratory disease. Cigarette smoking was significantly associated with heart disease and respiratory disease. Being an officer was inversely associated with each of these four conditions. Of those study participants who had diabetes, 56% had hypertension and 28% had heart disease.

The lower part of Table V shows the results of the logistic analyses for cancer, hepatitis, poor health status, and health problems that limit the kind and amount of work that can be done. When controlling for all the covariates, the category of all cancer was only significantly associated with increasing age (OR = 1.11, 95%CI = 1.08–1.13). The risk for all cancers associated with Vietnam service or a history of spraying herbicide was slightly elevated but not statistically significant. Hepatitis was significantly associated with

TABLE IV. Prevalence and Adjusted Odds Ratios for Selected Health Conditions Among U.S. Army Chemical Corps Vietnam Veterans Associated With Spraying Herbicides

	Vietnam sprayers (n = 662)		Vietnam non-sprayers (n = 811)		
Conditions	**Number**	**%**	**Number**	**%**	**Adj odds ratio (95%CI)[a]**
Diabetes	123	18.58	99	12.21	1.49 (1.10–2.02)
Hepatitis	49	7.40	50	6.17	1.40 (0.92–2.12)
Heart disease	129	19.49	110	13.56	1.41 (1.06–1.89)
All cancer[b]	57	8.61	50	6.17	1.36 (0.91–2.04)
All respiratory problems[c]	140	21.15	119	14.67	1.57 (1.20–2.07)
Hypertension with medication	247	37.31	242	29.84	1.26 (1.00–1.58)
Current health is poor	99	14.95	85	10.48	1.57 (1.14–2.15)
Health limits kind and amount of work	119	17.98	121	14.92	1.17 (0.88–1.55)

[a]Adjusted odds ratio and 95% confidence interval for each disease condition associated with spraying herbicide in Vietnam was derived from a logistic regression model with adjustment for age, race, body mass index, rank, and regular smoking.
[b]The condition category "All cancer" excludes non-melanoma skin cancers.
[c]The condition category "All respiratory problems" includes all non-malignant respiratory conditions.

TABLE V. Adjusted Odds Ratios and 95% Confidence Intervals Derived From a Logistic Regression Model, All Veterans

	Health conditions			
Covariates	**Diabetes**	**Heart disease**	**Hypertension**	**Respiratory disease**
Vietnam service	1.04 (0.80–1.37)	0.96 (0.75–1.24)	0.96 (0.80–1.17)	1.22 (0.95–1.55)
Race, Non-white	2.17 (1.66–2.85)	0.94 (0.70–1.26)	2.22 (1.79–2.75)	0.84 (0.63–1.13)
BMI	2.27 (1.91–2.70)	1.27 (1.09–1.48)	1.66 (1.47–1.87)	1.02 (0.88–1.18)
Rank, officer	0.60 (0.37–0.95)	0.63 (0.41–0.96)	0.72 (0.53–0.98)	0.64 (0.42–0.96)
Regular smoker	1.02 (0.79–1.32)	1.78 (1.37–2.31)	1.13 (0.94–1.36)	1.28 (1.01–1.62)
Age in years	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.02 (0.99–1.04)
Herbicide sprayer	1.50 (1.15–1.95)	1.52 (1.18–1.94)	1.32 (1.08–1.61)	1.62 (1.28–2.05)
	All cancer[a]	**Hepatitis**	**Poor health**	**Functional limits**
Vietnam service	1.32 (0.89–1.95)	1.70 (1.17–2.46)	1.48 (1.09–2.00)	1.46 (1.13–1.89)
Race, Non-white	0.93 (0.60–1.45)	1.84 (1.27–2.66)	1.64 (1.21–2.21)	1.13 (0.85–1.51)
BMI	0.80 (0.64–1.01)	0.85 (0.68–1.07)	0.97 (0.81–1.16)	1.09 (0.94–1.28)
Rank, officer	0.81 (0.46–1.41)	0.79 (0.37–1.67)	0.23 (0.10–0.53)	0.72 (0.47–1.10)
Regular smoker	0.83 (0.58–1.19)	2.04 (1.36–3.07)	1.87 (1.36–2.58)	1.21 (0.94–1.55)
Age in years	1.11 (1.08–1.13)	0.91 (0.87–0.95)	1.03 (1.00–1.05)	1.04 (1.02–1.06)
Herbicide sprayer	1.28 (0.89–1.85)	1.29 (0.90–1.85)	1.68 (1.27–2.22)	1.30 (1.01–1.66)

[a]The condition category "All cancer" excludes non-melanoma skin cancers.

Vietnam service, non-whites, and regular smoking but not with a history of spraying herbicide. Self-perceived poor health was significantly associated with Vietnam service, non-whites, regular smoking, and a history of spraying herbicide. Likewise, self-reported functional limits were significantly associated with Vietnam service, age, and a history of spraying herbicide.

Documentation of a Self-Reported Chronic Health Condition

A total of 362 veterans reported having diabetes. Overall, 79.2% (n = 287) of reported conditions were documented in individual medical records (n = 128), Veterans Affairs hospital discharge records (n = 82), and/or use of prescription medications for diabetes (n = 77). The documentation rate was not significantly different between the Vietnam veterans and non-Vietnam veteran controls. Of the 75 non-confirmed conditions, 36 were due to not having the medical records for review for various reasons, and 39 were due to the absence of confirmatory information in the records received from a medical facility. The reasons for not having the records may include: (1) veterans' refusal to mail in a written informed consent form, (2) delay in sending in the signed form in time for the study, (3) records not found by the medical facility, and (4) delay in sending in the record by a medical facility. Reasons for non-confirmation may include an over-reporting by a veteran or not having obtained relevant medical records for review.

Evaluation of Reporting Bias

The possibility of over-reporting of chronic health conditions was evaluated among 357 Vietnam veterans who reported spraying herbicide and subsequently donated blood samples for dioxin measurement. At the time of the health interview, which preceded the collection of the blood samples by several weeks, the concentration of serum dioxin was not known to either the interviewer or the veteran. Nonetheless, those who were found to have a higher level of serum dioxin (TCDD concentrations at or above median level for the group) reported higher prevalence of these chronic health conditions than those who had lower serum dioxin level (TCDD concentrations below the median for the group) ($P < 0.05$, the Wilcoxon signed-ranks test) [Lehmann, 1975] (Table VI). There was a significant association among selected medical conditions and objective measure of exposure to herbicides (i.e., serum dioxin levels), which is inconsistent with a suggestion of a random over-reporting of a chronic health condition by Vietnam veterans who reported spraying herbicides.

DISCUSSION

The Army Chemical Corps is one of the few groups of Vietnam veterans who were occupationally exposed

TABLE VI. Prevalence (%) of Self-Reported Health Conditions Among 357 Vietnam Herbicide Sprayers Stratified by Two Levels of Serum TCDD Concentration*

	Serum TCDD concentration[a]			
	High (TCDD $\geq$ 2.5 ppt)		Low (TCDD $<$ 2.5 ppt)	
Conditions	**Number (n = 179)**	**%**	**Number (n = 178)**	**%**
Diabetes	39	21.8	21	11.8
Heart conditions	41	22.9	28	15.7
Hypertension with medication	78	43.6	60	33.7
Respiratory problems	33	18.4	32	18.0
Current health is poor	30	16.8	21	11.8
Health limits amount and kind of work	34	19.0	30	16.9

*Significance probability for Wilcoxon Signed Test was $P < .05$ (2-tailed).
[a] Veterans with the serum TCDD levels equal to or above the median value (2.5 ppt) were grouped into the "High" group; those who were below the median value were grouped into the "Low" group.

to phenoxyherbicide and its contaminant TCDD. It is considered, therefore, an appropriate group for the study of long-term health effects of phenoxyherbicide exposure [IOM, 1994, 2001, 2003]. In the current study, we could not measure serum dioxin concentrations for all 2,927 study participants because of the expense of the laboratory tests. Alternatively, we measured the serum TCDD concentrations in a sample of 795 Vietnam veterans and 102 non-Vietnam veteran controls and demonstrated that those veterans who reported spraying herbicides in Vietnam had a significantly higher concentration of dioxin in their serum than those who did not serve in Vietnam and who never sprayed herbicides. This finding replicated the results from the earlier feasibility study [Kang et al., 2001]. In both the feasibility study and the current study, a self-reported history of herbicide spraying in Vietnam was found to be a good surrogate measure of dioxin exposure that could be applied to all the Army Chemical Corps veterans who completed the health interview survey.

We observed statistically significant associations between a reported history of spraying herbicide while in the military and the self-reported history of physician-diagnosed diabetes, heart disease, hypertension, and chronic respiratory diseases among this cohort of Army Chemical Corps personnel. These findings were independent from any Vietnam service effect. The significant association between diabetes and a history of spraying herbicides is consistent with data from the Air Force Ranch Hand Study [Henriksen et al., 1997]. Among the Air Force Ranch Hand personnel, dioxin exposure increased risk of diabetes and decreased time-to-onset of diabetes. A study of industrial cohorts heavily exposed to dioxin (IARC cohorts) also reported a high risk of diabetes among dioxin-exposed workers, especially those with 10 or more years of latency and duration of exposure [Vena et al., 1998]. However, a recent analysis of the combined NIOSH [Steenland et al., 1999] and Ranch Hand data showed little overall evidence that the exposed individuals were at higher risk of diabetes or abnormal fasting glucose concentration than non-exposed individuals [Steenland et al., 2001]. The study did report that there was an increasing trend in prevalence of diabetes with increased serum TCDD concentrations among the Ranch Hand population.

The positive finding of an association between phenoxyherbicide exposure and circulatory diseases (including hypertension requiring medication) is also consistent with the results reported in other occupational/community cohorts. An increased risk of death due to heart diseases was reported in the expanded IARC international cohorts (RR = 1.7, 95%CI = 1.2–2.3), the NIOSH occupational cohort (SMR = 1.1, 95%CI = 1.0–1.2), enlisted Ranch Hand personnel, 15-year follow-up (SMR = 1.5, 95%CI = 1.0–2.2), 20-year follow-up (RR = 1.7, 95%CI = 1.2–2.4), and the Seveso community cohort (heart disease RR = 3.0, 95%CI = 1.2–7.3; hypertensive disease RR = 3.6, 95%CI = 1.2–11.4) [Michalek et al., 1998; Pesatori et al., 1998; Vena et al., 1998; Steenland et al., 1999; Ketchum and Michalek, 2005]. In animal studies, dioxin was reported to cause disturbances in lipid metabolism and cardiovascular functions, and morphologic changes in peripheral vessels [Kociba et al., 1978; Schiller et al., 1985; Hermansky et al., 1988]. In a group of 12 former workers heavily exposed to dioxin more than 35 years ago, 9 had elevated levels of triglycerides and/or cholesterol, 6 were treated for hyperlipidemia, 6 with hypertension, 4 with ischemic heart disease, and 2 still presented with chloracne. The dioxin levels of these 12 persons were correlated with the highest level of triglycerides ($P = 0.02$) and cholesterol ($P = 0.01$) [Pelclova et al., 2002]. The results of this study should be considered tentative, however, because of the small sample size (n = 12) and the lack of a comparison group in the study. Another

study of 133 workers at municipal-waste incinerator plants in Taiwan showed significant variation in cholesterol by a dichotomous measure of TCDD. Workers with serum TCDD concentrations above the median had higher average cholesterol and were more likely to have cholesterol above 220 mg/dl ($P < 0.05$). However, the relationship was not statistically significant when TCDD was measured by tertiles, quartiles or as a continuous variable [Hu et al., 2003].

An association between dioxin exposure and the risk of non-malignant lung diseases has been rarely reported. In the 15-year period after the Seveso accident, increased deaths from chronic obstructive pulmonary disease (RR = 3.7, 95%CI = 1.4–9.9) were found in the male residents of the area where dioxin contamination was the highest (Zone A) [Pesatori et al., 1998]. Reporting of poor health and functional limitation by herbicide sprayers is consistent with an observation among the 158 BASF chemical plant workers accidentally exposed to dioxin in 1953. Their overall illness rates were positively correlated with serum dioxin concentrations and the increased illness rates were observed throughout the 36-year period and not just in the early years after the exposure [Zober et al., 1994].

Our findings among the Army Chemical Corps Vietnam veterans who sprayed herbicide are not always supported by other studies. Notably, the NIOSH medical study of workers exposed to chemicals contaminated with dioxin did not find elevated prevalence of chronic bronchitis, COPD, cardiovascular diseases including hypertension, and abnormal pulmonary function parameters [Sweeney et al., 1997]. A mortality update of the same NIOSH cohort, however, reported an increased overall cancer mortality (SMR = 1.13, 95%CI = 1.02–1.25) and ischemic heart disease (SMR = 1.1, 95%CI = 1.0–1.2). While statistically significant trends for cancer (15-year lag time) and heart disease (no lag time) with increasing exposure were also reported, diabetes showed a negative exposure-response trend [Steenland et al., 1999].

The lack of a significant association between cancer and herbicide exposure observed in the study may be due to many reasons including the study design, the statistical power, and the exposure level. A prevalence study may not be the best study design for a rare disease with a short survival time, such as cancer. Also, the number of prevalent cancer cases was too small, which contributed to the low statistical power of the study. When a comparison was made between Vietnam veterans and non-Vietnam veteran controls, the risk for all cancer combined was significantly higher among Vietnam veterans (OR = 1.46, 95%CI = 1.02–2.10). However, when a comparison was among a subgroup of Vietnam veterans, although those who sprayed herbicide demonstrated a higher prevalence of cancer (8.6%) than non-sprayers (6.2%) or non-Vietnam veterans (3.7%), the risk was not statistically significant (OR = 1.36, 95%CI = 0.91–2.04). A site-specific analysis was precluded by the small numbers of specific cancer types. There were only seven lung cancer cases observed in the entire study population of Army Chemical Corps personnel. In addition, the level of dioxin exposure of Vietnam veterans who sprayed Agent Orange is considered only a fraction of the amount experienced by industrial workers who manufactured phenoxyherbicides [Mocarelli et al., 1991]. While no increase in cancer mortality or morbidity was reported among the Ranch Hand personnel after 5 and 15 years of follow-up [Michalek et al., 1990, 1998; Ketchum et al., 1999], a more recent study of 1,482 Air Force veterans who served in Southeast Asia indicated an increasing cancer risk with TCDD (RR = 1.6, 95%CI = 1.2–2.2) [Pavuk et al., 2005].

Another limitation of this analysis was the reliance on self-reported data for health outcomes. As in any survey, the possibility of recall bias is of concern. We evaluated this possibility by two different methods: medical records review and analysis of a reported health outcome by dioxin body burden. In reviewing medical records for 362 veterans who reported having physician-diagnosed diabetes, we were able to document 79.2% of reported cases. More importantly, the documentation rate was almost the same between Vietnam veterans and non-Vietnam veterans. Furthermore, among the 357 Vietnam veterans who reported spraying herbicide, there was a consistent pattern of a higher prevalence of certain medical conditions in the ''High'' exposure group than in the ''Low'' exposure group. At the time of the survey, although all reported having sprayed herbicides in Vietnam, neither the interviewer nor the veteran knew the concentration of serum dioxin which was the basis of classifying the respondents into two exposure groups.

A potential selection bias is of concern in this survey. The effects of selection bias on measures of association (e.g., relative risk or odds ratio) depend on both the size of the non-participant group and its specific characteristics. If the participation rates differ only by exposure status (e.g., Vietnam service), or only by outcome status (e.g., presence of a chronic health condition), the value of the relative risk (or odds ratio) will remain unbiased. However, if the participation rates vary by specific combinations of exposure and outcome, it may render a significant impact on the study results. For example, if a group of Vietnam veterans with hypertension is more (or less) likely to participate in the study than a group of non-Vietnam veterans with the same condition, the study results, that is, estimates of odds ratio, are likely to be biased. Given the relatively high participation rates by both groups (Vietnam veterans, 79.2%; non-Vietnam veterans, 69.2%), absence of direct evidence of differential participation rates by a combination of exposure status and disease outcome, and a similarity of the prevalence rate of hypertension or diabetes among non-Vietnam veterans to other comparable general populations, we considered a significant selection bias was unlikely to have contributed to the study results. The CDC Health Data for 1997–2003

indicate that 36% and 10% of US males aged 45–64 have confirmed hypertension and diabetes, respectively (source: NHANES). The corresponding self-reported data for non-Vietnam veterans in our study are 30% and 12%, respectively.

A major strength of the study is in the selection of a study group which included a sample of Vietnam veterans with documented occupational exposure to herbicide. One of many limitations of studying the long-term health consequences of herbicide exposure in Vietnam had been the difficulty in identifying a large number of Vietnam veterans with documented exposure. In this study, the exposure status of veterans was carefully characterized by a combination of military occupational history recorded in personnel documents and measurement of 2,3,7,8-TCDD in serum for 30% of the study participants. Another strength is the study design which included a veteran control group that was similar to the study group except for service in Vietnam. Having the non-Vietnam control group enabled us to identify the health outcomes associated with Vietnam service in general and with the outcomes associated with herbicide exposure in particular.

In summary, almost three decades after Vietnam service, U.S. Army veterans who were occupationally exposed to phenoxyherbicide in Vietnam experienced significantly higher risks of diabetes, heart disease, hypertension, and non-malignant lung diseases than other veterans who were not exposed to herbicides. The risk of all cancers combined among these veterans was increased but it was not statistically significant.

ABBREVIATIONS

BMI	body mass index
CATI	computer-assisted telephone interview
CI	confidence interval
IARC	International Agency for Research on Cancer
MOSC	military occupational specialty code
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
OR	odds ratio
P	probability
ppt	parts per trillion
RR	relative risk
SMR	standardized mortality ratio
TCDD	2,3,7,8-terachlorodibenzo-p-dioxin
VA	Department of Veteran Affairs

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