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Serum Dioxin and Peripheral Neuropathy in Veterans of Operation Ranch Hand

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Abstract

We studied whether exposure to Agent Orange and its contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), during the Vietnam War is related to peripheral neuropathy. The index subjects were veterans of Operation Ranch Hand, the unit responsible for aerial herbicide spraying in Vietnam from 1962 to 1971. We report peripheral nerve function assessed in 1982, 1985, 1987, 1992 and 1997, nerve conduction velocities measured in 1982, and vibrotactile thresholds of the great toes measured in 1992 and 1997. We assigned each Ranch Hand veteran to one of three exposure categories named "background", "low" and "high", based on his serum dioxin level. Other than the bilateral vibrotactile abnormalities, we consistently found a statistically significant increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the high exposure category in 1997, and a statistically significant increased risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, in the high category in 1992. Restricting to the enlisted veterans did not alter these results. Cautious interpretation of these results is appropriate until the relationship between pre-clinical diabetes mellitus and peripheral neuropathy is further evaluated in future examinations. Published by Elsevier Science Inc.

Keywords: Dioxin; Epidemiology; Herbicides; Peripheral neuropathy; TCDD

INTRODUCTION

The herbicide Agent Orange was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid and was contaminated, from <0.05 to almost 50 parts per million, with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin) (Institute of Medicine, 1994). Signs and symptoms consistent with peripheral neuropathy have been reported by veterans in association with exposure to Agent Orange in Vietnam (Lathrop et al., 1984), and by workers and community residents after exposure to dioxin-contaminated substances (Poland et al., 1971; Moses et al., 1984; Pasderova-Vejlupkova et al., 1981; Baader and Bauer, 1951; Kimmig and Schulz, 1957; Goldstein et al., 1959; Todd, 1962; Berkley and Magee, 1963; Jurasek et al., 1974; Oliver, 1975). Few studies of the peripheral nervous system provide comparison group data or adequately control for other common conditions or exposures known to be associated with peripheral neuropathy (Goetz et al., 1994). A study of dioxin exposure in victims of an industrial accident in Seveso, Italy, found an increased frequency of electrophysiological signs of peripheral nervous system involvement among residents with chloracne 6 years after the accident (Barbieri et al., 1988). Vietnam veterans participating in the Vietnam Experience Study (Centers for Disease Control and Prevention, 1988) reported more symptoms of peripheral neuropathy than non-Vietnam veterans, but there was no objective evidence

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of increased peripheral neuropathy. An evaluation of peripheral chronic neuropathy in a study of chemical workers exposed 15 years earlier to dioxin found no relation between peripheral neuropathy and exposure group or between peripheral neuropathy and dioxin levels (Sweeney et al., 1993). A recent review by the National Academy of Sciences concluded that there was limited/suggestive evidence of an association between herbicide exposure and acute or subacute transient peripheral neuropathy and inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and chronic peripheral system disorders (Institute of Medicine, 1999).

We examined indicators of peripheral neuropathy and exposure to 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. These data were accumulated during 15 years of follow-up in the ongoing Air Force Health Study in veterans whose exposure in Vietnam occurred between 26 and 36 years ago.

MATERIALS AND METHODS

The details of study design and subject selection are published elsewhere (Wolfe et al., 1990). The study seeks to determine whether veterans of Operation Ranch Hand 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 health (Henriksen et al., 1997; Michalek et al., 1999a,b, 2001; Ketchum et al., 1999; Burton et al., 1998), mortality experience (Michalek et al., 1990, 1998a), and reproductive outcomes (Wolfe et al., 1995; Henriksen et al., 1996; Michalek et al., 1998b,c) of Ranch Hand veterans with a comparison group of other Air Force veterans who served in Southeast Asia during the same period that the Ranch Hand unit was active and who were not involved with spraying herbicides. Comparisons were matched to Ranch Hands on date of birth, race (Black, non-black) and military occupation (officer pilot, officer navigator, nonflying officer, enlisted flyer, enlisted ground crew). Birth date matching resulted in 70.6% of comparison veterans matched to their respective Ranch Hand veteran to within 1 month, 95.8% to within 1 year and 100% to within 5 years of the Ranch Hand birth date (Lathrop et al., 1984). Each comparison veteran was matched perfectly to his respective Ranch Hand veteran with regard to race and military occupation. The study includes periodic physical examinations and in-person interviews, conducted in 1982, 1985, 1987, 1992 and 1997. An additional examination is planned for 2002.

We report conditions determined at neurological examinations at the 1982, 1985, 1987, 1992 and 1997 physical examinations. The first examination was conducted at Kelsey Seybold Clinic, Houston, Texas, and all subsequent examinations were conducted at Scripps Clinic, La Jolla, California. All examiners, interviewers and staff were masked to the veteran's exposure group. Participation was voluntary, and consent forms were signed at the examination site. The protocol and the manner in which informed consent was obtained from veterans were approved by the institutional review boards of the sponsoring laboratory and the respective medical treatment facilities. In 1987, blood from willing participants was collected and assayed for dioxin. Veterans with no quantifiable dioxin result in 1987, those who refused in 1987 and veterans new to the study were also asked to give blood for the assay at the 1992 examination. Similarly, veterans with no quantifiable dioxin results in 1987 and 1992, those who refused in 1987 and 1992, and veterans new to the study were also asked to give blood for assay at the 1997 examination. Of the 2121 veterans who attended the 1997 physical examination, dioxin measurements were made for 2101 veterans (99.1%). Of the 2101, the 1987 dioxin level was measured for 1644 (78.2%); the 1992 dioxin level was measured for 312 (14.9%) and the 1997 dioxin level was measured for 139 (6.6%). Four (0.2%) received a detectable result less than the limit of quantitation (LOQ), and two (0.1%) received no result (due to a failure of one or more laboratory quality control checks and insufficient sample to repeat the assay), and 143 (6.8%) received results below the limit of detection (LOD). Dioxin results less than the LOD (LOQ) were assigned the value LOD (LOQ) divided by the square root of 2 (Hornung and Reed, 1990). The serum dioxin measurements were done with high-resolution gas chromatography/high resolution mass spectrometry (Patterson et al., 1987). The between assay coefficient of variation at three different concentrations of dioxin ranged from 9.4 to 15.5%.

We estimated the initial dioxin dose at the end of the tour of duty in Vietnam in Ranch Hands having dioxin levels above background using a constant half-life of 8.7 years Michalek et al., 1996); the median initial dose was 94 parts per trillion (ppt). We assigned each veteran to one of the four exposure categories, named

''comparison'', ''background'', ''low'' and ''high''. Comparison veterans were assigned to the comparison category. Ranch Hand veterans with dioxin levels not exceeding 10 ppt were assigned to the background category. Ranch Hand veterans with dioxin levels >10 ppt and initial dioxin levels not exceeding the median (94 ppt) were assigned to the low category and those with dioxin levels >10 ppt and initial dioxin levels greater than median were assigned to the high category.

At each examination, veterans not known to be diabetic were orally administered 100 g of glucose and 2 h later, blood was taken and serum glucose was measured. Glucose was measured with the Paramax Analytical System (Baxter Diagnostics Incorporated, Irvine, California), which employs a coupled enzymatic method using hexokinase and glucose 6-phosphate dehydrogenase. The between-assay coefficient of variation at three different concentrations of glucose ranged from 2.2 to 2.7%.

A lifetime medical history was obtained from each examined participant and medical records were retrieved and coded according to the rules and conventions of the International Classification of Diseases (ICD), 9th Revision, Clinical Modification (US Department of Health and Human Services, 1980). Diabetic status was determined by medical record review; a veteran was defined as diabetic if a doctor diagnosed him as diabetic or if his 2 h post-prandial glucose test result at any physical examination was >200 mg/dl.

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, hand and foot coordination, and tremor.

During the 1982 physical examination, nerve conduction studies were performed on the dominant ulnar (motor), peroneal (motor), and sural (sensory) nerves using standard techniques of percutaneous stimulation and surface recording. The studies were performed by a qualified technician under the supervision of a physician trained in neurophysiological methods. Ulnar conduction studies recorded motor responses from the abductor digiti quinti muscle associated with supramaximal stimulation at the wrist (8 cm from the recording electrode) and just below the ulnar groove of the elbow. Peroneal motor conduction studies recorded from the extensor digitorum brevis muscle, stimulating at the ankle (8 cm from the recording electrode) and at the knee, just distal to the head of the fibula. The sural sensory conduction studies were performed antidromically, recording from the ankle, stimulating midcalf (14 cm from the recording electrode). For motor studies, onset latencies (ms) were recorded for distal and proximal stimulation sites, and conduction velocities (m/s) in the forearm or leg segments were calculated by dividing measured distances (mm) between proximal and distal stimulation sites by the difference between the proximal and distal onset latencies. For the sural study, the distal latency to the peak of the sensory response was recorded. Nerve conduction velocities were not measured in 1985, 1987, 1992 or 1997.

At the 1992 and 1997 physical examinations, the Vibratron II® device was used to measure vibrotactile threshold on both the left and right great toes. The vibrotactile measurement was summarized using the method-of-limits (MOL) protocol (Gerr et al., 1990). Briefly, according to the MOL protocol, a subject is asked to rest his toe on the transducer delivering the stimulus. An easily detectable suprathreshold stimulus is presented and then reduced at a constant rate. The subject is asked to report verbally the earliest point at which he can no longer detect the stimulus. The value is recorded, and the subject is asked to lift his toe from the stimulator. The amplitude is then reduced to a value well below that of the previous trial, and the subject is asked to place his toe back on the stimulator. The stimulus intensity is gradually increased until the subject indicates that he can feel the vibration. The complete testing sequence consists of seven trials (four descending and three ascending).

Stimulus frequency was maintained at a constant 120 Hz, while vibration intensity was decreased on the first, third, fifth and seventh trials, and increased on the second, fourth and sixth trials. Veterans whose great toes could be examined, but who reported no detectable vibration at the highest instrument setting (i.e. 23.0 vibration units (VU)) were included in the study with a value set at 23.0 VU, a value greater than the highest recorded measurement in this study. The VU measurements were transformed to displacement in microns (D), using the formula (Letz and Grubbs, 1993) $D = 0.550 \times \mathrm{VU}^{2.02217}$. 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 comparison distribution of the minimum of the left

and right great toe measurements was determined and we defined the vibrotactile measurement of a Ranch Hand veteran as bilaterally abnormal if the measurements of both the left and right great toes exceeded the 90th percentile of the comparison distribution. Vibrotactile thresholds were not measured prior to 1992.

The measurements used for this study were selected for their sensitivity to detection of distal symmetrical polyneuropathies, such as those demonstrating stocking-glove distributions. These measures were relatively 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 any symmetrical peripheral abnormality as present if at least one of the following seven signs existed bilaterally: (1) abnormal light touch (foot), (2) abnormal pin prick (foot), (3) abnormal vibration (128 Hz, ankle), (4) abnormal joint position (great toe), (5) abnormal equilibrium (Romberg), (6) abnormal ankle/toe flexor strength, and (7) absent Achilles reflex. We defined possible peripheral neuropathy as present if at least one of the following three outcomes were found bilaterally: (1) absent Achilles reflex, (2) abnormal vibration at the ankle, or (3) abnormal pin prick (foot). We defined probable peripheral neuropathy as present if at least two of the previous three abnormalities were present bilaterally. We defined diagnosed peripheral neuropathy as present if there was probable peripheral neuropathy and the vibrotactile measurement was bilaterally abnormal.

We conducted two rounds of statistical analyses, of primary and secondary importance, differing only in the way we defined exclusion criteria. In all primary analyses, we excluded veterans with a history of neurological disorders prior to service in Southeast Asia, and also those with no dioxin measurement. We also excluded veterans with quadriplegia (ICD 34,400, 34,404), paraplegia (ICD 3441), injuries or amputations (ICD 9072–9075, 9079, 8970, 8972, 8974) and alcohol related disorders (ICD 2912, 30300, 4255, 2918, 30301, 30390–30393, 30500–30503, 3575, 5710–5713), conditions that would interfere with an assessment of the peripheral nerves.

In the secondary analyses, conducted to address the possibility that diseases, disorders, exposures, or medications known to produce symptoms suggestive of neuropathy might have biased the primary results, we additionally excluded veterans with specific neurological disorders of known causes unrelated to dioxin exposure (e.g. inflammatory, congenital and traumatic disorders). The results of these secondary analyses are not tabled, but are summarized in the text.

Primary and secondary exclusions are summarized in Table 1 by exposure group (Ranch Hand, comparison).

Table 1
Group sizes by examination year

Group	Stratum	Year				
		1982	1985	1987	1992	1997
Comparison	Compliant	1223	1292	1298	1280	1251
	Pre-Southeast Asia neurological diseases	17	19	19	18	13
	Missing dioxin[a]	100	58	19	13	14
	No dioxin result[b]	7	8	8	2	2
	Paraplegia/quadriplegia	1	1	1	1	1
	Injury/amputation	2	5	8	7	8
	Alcohol related disorders	29	57	112	129	127
	Net for primary analysis	1067	1144	1131	1110	1086
	Secondary exclusions	256	288	301	509	611
	Net for secondary analysis	811	856	830	601	475
Ranch Hand	Compliant	1046	1017	996	953	870
	Pre-Southeast Asia neurological diseases	9	8	8	8	7
	Missing dioxin[a]	85	44	18	7	6
	No dioxin result[b]	3	3	3	0	0
	Paraplegia/quadriplegia	0	0	0	0	1
	Injury/amputation	0	2	2	2	2
	Alcohol related disorders	23	42	93	102	93
	Net for primary analysis	926	918	872	834	761
	Secondary exclusions	215	229	249	380	458
	Net for secondary analysis	711	689	623	454	303

[a] Due to refusal or non-compliance to physical examinations in 1987, 1992 or 1997.
[b] Due to failure of one or more laboratory quality control checks and insufficient sample to repeat the assay.

Table 2
Sample sizes for the primary analyses by year[a]

Exposure category	Year				
	1982	1985	1987	1992	1997
Comparison	1067	1144	1131	1110	1086
Ranch Hand					
Background	388	394	376	367	338
Low	269	260	249	233	213
High	269	264	247	234	210

[a] Excluding veterans with paraplegia, quadriplegia, injury, amputation or alcohol related disorders.

Resultant sample sizes for the primary analyses are given in Table 2 by exposure category.

A measure of drinking alcoholic beverages was derived from interview responses. We asked each veteran to identify periods during his life in which he drank alcoholic beverages and periods in which he did not drink. We asked him to specify how much he drank each day during each of the drinking periods. Based on this information, we computed the number of drink-years of alcohol consumption, where we defined one drink-year as the equivalent of drinking 1.5 oz of 80-proof whiskey (or, equivalently, 5 oz of wine or 12 oz of beer) per day for 1 year. Motivated by a recent study of peripheral nerve function in US Army Vietnam veterans (Gerr and Letz, 1994a), we categorized drink-years (Michalek et al., 2001) to four levels: nondrinkers (drink-years $= 0$), low (drink-*years* ≤ 40), and high (drink-years > 40). We estimated body mass index (BMI) as weight (kg) divided by the square of height (m^2).

We derived the odds ratio (OR) and its confidence interval (CI) from a main effects logistic regression model and analyzed nerve conduction velocities with a linear regression model. In the primary analyses, both models contained dioxin category, age, height (Gerr and Letz, 1994b), drink-year category, occupation, diabetes and BMI. In the secondary analyses, we dropped diabetes from the model, because veterans with diabetes were excluded. We used no stepwise reduction throughout. We report a *P*-value for trend as the *P*-value associated with the one degree of freedom test of the hypothesis that the coefficient of the logarithm of the dioxin level is zero. From among those Ranch Hand veterans with probable or diagnosed neuropathy, in the primary analyses, we report in footnotes the number of veterans with abnormal vibration at the ankle and absent Achilles tendon reflex, the first of these being a sensitive, but nonspecific measure of peripheral neuropathy and the second being the most specific of the seven measures we considered, and the number diabetic. We assessed the validity of our measures of peripheral neuropathy by computing odds ratios, adjusted for age, height, drink-year category and BMI, relating diabetes and each outcome measure in comparison veterans. We reanalyzed binary outcomes restricting to the enlisted veterans, the occupational subgroup with the highest dioxin levels and, presumably, the greatest herbicide exposure. To further address possibility of confounding by diabetic status, we also reanalyzed among diabetics and nondiabetics separately. We examined the strength of association between each covariate and the peripheral neuropathy measures, and summarized the results in text.

RESULTS

Table 3 summarizes dioxin levels and demographic characteristics of the cohorts in 1982 by dioxin category. Ranch Hands in the high category (average age 40.8 years) were younger than comparisons (average age 43.9 years). Ranch Hands in the high category were predominantly enlisted ground personnel and those in the background category were predominantly officers during the war.

We found no evidence of alteration in the mean nerve conduction velocities or distal latencies in the low or high exposure categories (Table 4). Veterans in the background category had a significantly longer mean ulnar motor distal latency than veterans in the comparison category. There were no significant trends for any of these measurements.

The odds of any symmetrical peripheral abnormality (Table 5) was significantly increased in the high category in 1997 (OR $= 1.8$, 95% CI 1.2–2.7) and there was a significant trend with increasing exposure (background: OR $= 1.0$, low: OR $= 0.9$, high: OR $= 1.8$, $P = 0.01$).

The odds of possible peripheral neuropathy (Table 6) was significantly increased in the high category in 1997 (OR $= 1.8$, 95% CI 1.2–2.7) and there was a significant trend with increasing exposure (background: OR $= 0.9$, low: OR $= 0.9$, high: OR $= 1.8$, $P = 0.02$).

The odds of probable peripheral neuropathy (Table 7) was increased with borderline significance in the high category in 1992 (OR $= 2.5$, 95% CI 0.9–6.6) and significantly increased in 1997 (OR $= 5.0$, 95% CI 2.2–11.2). There were significant trends with increasing exposure in 1992 (background: OR $= 1.3$, low:

Table 3
Distribution of dioxin and demographic characteristics in 1982 by exposure category

Dioxin category	Drink-year category						
	Non-drinker (%)	Low (%)	High (%)	Black (%)	Officer (%)	Enlisted flyer (%)	Enlisted ground crew (%)
Comparison	8.3	74.3	17.4	5.9	37.7	15.9	46.4
Background	8.1	76.2	15.7	5.4	60.3	12.6	27.1
Low	9.0	76.3	14.7	7.4	39.8	21.2	39.0
High	14.5	69.6	16.0	5.2	2.6	21.6	75.8

Exposure category	Measured dioxin, median (range)	Initial dioxin, median (range)	Age (years), mean (S.D.)	BMI[a], mean (S.D.)
Comparison	4.0 (0, 54.8)		43.9 (7.7)	27.9 (4.1)
Background	5.7 (0, 10)		44.7 (7.3)	26.6 (3.6)
Low	15 (10, 25.6)	52.3 (27.2, 94)	45.2 (7.6)	28.0 (3.9)
High	45.8 (18, 617.8)	194.9 (94.1, 3290.2)	40.8 (7.2)	29.0 (4.3)

[a] Body mass index.

OR = 0.8, high: OR = 2.5, $P = 0.03$) and 1997 (background: OR = 1.5, low: OR = 1.4, high: OR = 5.0, $P < 0.001$). The odds of probable peripheral neuropathy was not significantly increased in the low or background categories at any examination. Of the two veterans in the high category with probable peripheral neuropathy in 1982, one (50%) had probable neuropathy in 1997 and one (50%) was normal in 1997. Odds

Table 4
Nerve conduction velocities and latencies in 1982 by exposure category

Nerve/attribute	Mean	*P*-value for trend	Mean difference	95% CI[a]
Ulnar motor				
Conduction velocity (m/s)		0.2		
Comparison	60.3			
Background	59.7		−0.6	−1.25, 0.02
Low	60.4		0.1	−1.61, 0.82
High	60.7		0.4	−0.33, 1.15
Distal latency (ms)		0.35		
Comparison	2.8			
Background	2.8		0.1	0.01, 0.10
Low	2.8		0.0	−0.02, 0.08
High	2.8		0.0	−0.07, 0.03
Peroneal motor				
Conduction velocity (m/s)		0.51		
Comparison	47.1			
Background	47.7		0.5	−0.02, 1.06
Low	47.1		0.0	−0.63, 0.59
High	47.3		0.1	−0.52, 0.75
Distal latency (ms)		0.58		
Comparison	4.4			
Background	4.4		0.0	−0.08, 0.11
Low	4.4		0.0	−0.10, 0.12
High	4.4		0.0	−0.08, 0.14
Sural sensory				
Distal latency (ms)		0.27		
Comparison	3.8			
Background	3.8		0.0	−0.08, 0.01
Low	3.8		0.0	−0.03, 0.07
High	3.8		0.0	−0.04, 0.06

[a] Confidence interval.

Table 5
Any symmetrical peripheral abnormality by exposure category and examination year

Year	Exposure category	Number (%)	*P*-value for trend	Odds ratio	95% CI[a]
1982	Comparison	111 (10.4)	0.84	1.0	
	Background	35 (9.0)		0.9	0.6, 1.4
	Low	27 (10.1)		0.9	0.6, 1.4
	High	27 (10.1)		1.3	0.8, 2.1
1985	Comparison	63 (5.5)	0.99	1.0	
	Background	17 (4.3)		0.9	0.5, 1.6
	Low	12 (4.7)		0.8	0.4, 1.5
	High	11 (4.2)		0.9	0.4, 1.7
1987	Comparison	62 (5.5)	0.33	1.0	
	Background	16 (4.3)		0.8	0.4, 1.5
	Low	17 (6.9)		1.1	0.6, 2.0
	High	10 (4.1)		0.8	0.4, 1.7
1992	Comparison	87 (7.9)	0.17	1.0	
	Background	27 (7.4)		1.0	0.6, 1.7
	Low	25 (10.7)		1.1	0.7, 1.8
	High	21 (9.0)		1.3	0.7, 2.2
1997	Comparison	160 (14.7)	0.01	1.0	
	Background	44 (13)		1.0	0.7, 1.4
	Low	34 (16)		0.9	0.6, 1.4
	High	45 (21.4)		1.8	1.2, 2.7

[a] Confidence interval.

ratio heterogeneity was examined by diabetic status in 1997 to determine whether the odds ratio was appreciably different in veterans with and without diabetes. Among nondiabetic veterans, the odds of probable peripheral neuropathy was significantly increased in the high category (OR = 8.7, 95% CI 1.9–39.3), while among diabetic veterans similar results were found (OR = 3.5, 95% CI 1.3–9.4).

Table 6
Possible symmetrical peripheral neuropathy by exposure category and examination year

Year	Exposure category	Number (%)	*P*-value for trend	Odds ratio	95% CI[a]
1982	Comparison	107 (10.1)	0.99	1.0	
	Background	32 (8.3)		0.8	0.5, 1.3
	Low	24 (9.0)		0.8	0.5, 1.3
	High	25 (9.4)		1.2	0.7, 2.0
1985	Comparison	62 (5.4)	0.89	1.0	
	Background	17 (4.3)		0.9	0.5, 1.6
	Low	11 (4.2)		0.7	0.4, 1.4
	High	10 (3.8)		0.8	0.4, 1.6
1987	Comparison	61 (5.4)	0.40	1.0	
	Background	16 (4.3)		0.8	0.5, 1.5
	Low	17 (6.9)		1.2	0.6, 2.1
	High	9 (3.6)		0.8	0.4, 1.6
1992	Comparison	84 (7.6)	0.14	1.0	
	Background	26 (7.1)		1.0	0.6, 1.7
	Low	25 (10.7)		1.1	0.7, 1.9
	High	19 (8.1)		1.2	0.7, 2.0
1997	Comparison	157 (14.5)	0.02	1.0	
	Background	41 (12.1)		0.9	0.6, 1.3
	Low	34 (16)		0.9	0.6, 1.4
	High	44 (21)		1.8	1.2, 2.7

[a] Confidence interval.

Table 7
Probable symmetrical peripheral neuropathy by exposure category and examination year

Year	Exposure category	Number (%)	*P*-value for trend	Odds ratio	95% CI[a]
1982	Comparison	9 (0.8)	0.80	1.0	
	Background	3 (0.8)		1.2	0.3, 4.7
	Low	3 (1.1)		1.2	0.3, 4.6
	High	2 (0.7)			
1985	Comparison	14 (1.2)	0.22	1.0	
	Background	6 (1.5)		1.1	0.4, 3.4
	Low	1 (0.4)			
	High	4 (1.5)		2.1	0.6, 7.5
1987	Comparison	9 (0.8)	0.37	1.0	
	Background	4 (1.1)		1.6	0.4, 5.9
	Low	2 (0.8)			
	High	2 (0.8)			
1992	Comparison	20 (1.8)	0.03	1.0	
	Background	6 (1.6)		1.3	0.5, 3.4
	Low	5 (2.1)		0.8	0.2, 2.4
	High	7 (3.0)		2.5	0.9, 6.6
1997	Comparison	22[b] (2.0)	<0.001	1.0	
	Background	8 (2.4)		1.5	0.6, 3.5
	Low	8[c] (3.8)		1.4	0.6, 3.4
	High	14[d] (6.7)		5.0	2.2, 11.2

[a] Confidence interval.
[b] Abnormal vibration at ankle: 13 (59.1%), absent Achilles reflex: 19 (86.4%), diabetic: 13 (59.1%).
[c] Abnormal vibration at ankle: 6 (75.0%), absent Achilles reflex: 7 (87.5%), diabetic: 7 (87.5%).
[d] Abnormal vibration at ankle: 9 (64.3%), absent Achilles reflex: 12 (85.7%), diabetic: 9 (64.3%).

Table 8
Vibrotactile abnormality and diagnosed peripheral neuropathy by exposure category and examination year

Year	Exposure category	Number (%)	*P*-value for trend	Odds ratio	95% CI[a]
Vibrotactile abnormality					
1992	Comparison	104 (9.4)	0.15	1.0	
	Background	34 (9.3)		1.1	0.7, 1.8
	Low	26 (11.3)		1.1	0.6, 1.8
	High	23 (9.8)		1.3	0.8, 2.3
1997	Comparison	110 (10.5)	0.10	1.0	
	Background	26 (8.2)		0.9	0.6, 1.5
	Low	29 (13.9)		1.2	0.7, 1.9
	High	25 (12.8)		1.5	0.9, 2.6
Diagnosed peripheral neuropathy					
1992	Comparison	11 (1.0)	0.01	1.0	
	Background	6 (1.6)		2.4	0.8, 7.2
	Low	3 (1.3)		1.5	0.4, 5.7
	High	6 (2.6)		4.9	1.5, 15.3
1997	Comparison	10[b] (0.9)	<0.001	1.0	
	Background	1 (0.3)			
	Low	5[c] (2.3)		1.9	0.6, 5.9
	High	8[d] (3.8)		5.8	2.0, 17.1

[a] Confidence interval.
[b] Abnormal vibration at ankle: 7 (70.0%), absent Achilles reflex: 8 (80.0%), diabetic: 5 (50.0%).
[c] Abnormal vibration at ankle: 5 (100%), absent Achilles reflex: 4 (80.0%), diabetic: 4 (80.0%).
[d] Abnormal vibration at ankle: 5 (62.5%), absent Achilles reflex: 7 (87.5%), diabetic: 7 (87.5%).

The odds of vibrotactile abnormality (Table 8) was not significantly increased in any Ranch Hand exposure category in 1992 or 1997.

The odds of diagnosed peripheral neuropathy (Table 8) was significantly increased in the high category in 1992 (OR = 4.9, 95% CI 1.5–15.3) and 1997 (OR = 5.8, 95% CI 2.0–17.1). There was a significant trend with increasing exposure in 1992 (background: OR = 2.4, low: OR = 1.5, high: OR = 4.9, $P = 0.01$) and 1997 (low: OR = 1.9, high: OR = 5.8, $P < 0.001$). Of the six veterans in the high category with diagnosed peripheral neuropathy in 1992, three (50%) had diagnosed peripheral neuropathy in 1997, one (16.7%) had normal measurements in 1997, one (16.7%) had missing measurements in 1997 and one (16.7%) did not attend the 1997 examination. The small number of nondiabetic veterans with diagnosed peripheral neuropathy in 1997 prevented an analysis of odds ratio heterogeneity according to diabetic status. Among diabetic veterans, the risk of diagnosed peripheral neuropathy in 1997 was significantly increased in the high category (OR = 5.8, 95% CI 1.6–20.2).

The odds of any symmetrical peripheral abnormality, possible peripheral neuropathy and probable peripheral neuropathy were significantly increased among diabetic comparison veterans in all years (Table 9).

We found diabetes to be significantly associated with all measures of peripheral neuropathy ($P < 0.05$), with the exception of the peroneal motor and sural sensory distal latencies, any symmetrical peripheral abnormality in 1982, and vibrotactile abnormality in 1992. Greater height was significantly associated with all peripheral neuropathy measures ($P < 0.02$), other than probable peripheral neuropathy in 1992. Increasing age was associated with all measures of peripheral neuropathy ($P < 0.001$). With the exception of mean peroneal motor velocities and latencies, which were not significantly different from those of comparison enlisted veterans, Ranch Hand enlisted veterans experienced borderline significantly increases in the odds ($P < 0.10$) of all measures of peripheral neuropathy in 1982. Ranch Hand enlisted veterans experienced significantly increased odds of abnormal vibrotactile measurements in 1992 ($P < 0.001$), and borderline significantly increased odds of abnormal vibrotactile measurements in 1997 ($P < 0.07$). Other than probable peripheral neuropathy, BMI contributed significantly to all logistic models of peripheral neuropathy measures in 1997 ($P < 0.03$). Drink-year category contributed significantly to the linear model of peroneal motor conduction velocity ($P < 0.03$) and to the logistic model for probable peripheral neuropathy ($P < 0.05$).

Table 9
Peripheral nerve status of comparison veterans by diabetic status

Year	Outcome	Diabetic status		Odds ratio	*P*-value	95% CI[a]
		Diabetic (% abnormal)	Nondiabetic (% abnormal)			
1982	Any symmetrical peripheral abnormality	12 (19.7)	99 (9.9)	2.2	0.03	1.1, 4.4
	Possible symmetrical peripheral neuropathy	12 (19.7)	95 (9.5)	2.3	0.02	1.1, 4.6
	Probable symmetrical peripheral neuropathy	4 (6.6)	5 (0.5)	12.2	<0.001	2.9, 51.1
1985	Any symmetrical peripheral abnormality	17 (18.5)	46 (4.4)	4.4	<0.001	2.3, 8.6
	Possible symmetrical peripheral neuropathy	17 (18.5)	45 (4.3)	4.4	<0.001	2.5, 8.7
	Probable symmetrical peripheral neuropathy	6 (6.5)	8 (0.8)	9.0	<0.001	2.8, 29.5
1987	Any symmetrical peripheral abnormality	15 (15.5)	47 (4.5)	3.3	<0.001	1.7, 6.7
	Possible symmetrical peripheral neuropathy	14 (14.4)	47 (4.5)	3.0	<0.001	1.5, 6.1
	Probable symmetrical peripheral neuropathy	6 (6.2)	3 (0.3)	31.8	<0.001	6.7, 151.5
1992	Any symmetrical peripheral abnormality	34 (24.3)	53 (5.5)	4.2	<0.001	2.5, 7.1
	Possible symmetrical peripheral neuropathy	33 (23.6)	51 (5.3)	4.2	<0.001	2.5, 7.1
	Probable symmetrical peripheral neuropathy	12 (8.5)	8 (0.8)	5.9	<0.001	2.2, 16.1
	Diagnosed peripheral neuropathy	4 (2.8)	7 (0.7)	2.7	0.17	0.7, 10.7
	Vibrotactile abnormality	22 (15.7)	82 (8.5)	1.9	0.04	1.0, 3.4
1997	Any symmetrical peripheral abnormality	59 (31.1)	101 (11.3)	2.6	<0.001	1.8, 4.0
	Possible symmetrical peripheral neuropathy	57 (30)	100 (11.2)	2.5	<0.001	1.7, 3.8
	Probable symmetrical peripheral neuropathy	13 (6.8)	9 (1.0)	5.2	<0.001	2.0, 13.4
	Diagnosed peripheral neuropathy	5 (2.6)	5 (0.6)	2.4	0.22	0.6, 9.5
	Vibrotactile abnormality	40 (22.1)	70 (8.1)	2.8	<0.001	1.7, 4.6

[a] Confidence interval.

Table 10
Frequency of bilateral examination abnormalities in 1997 by exposure category

Bilateral examination abnormality	Exposure category			
	Comparison	Background	Low	High
Light touch (feet)	25 (2.1)	12 (3.2)	9 (3.8)	9 (3.8)
Pin prick (feet)	38 (3.1)	16 (4.3)	12 (5.0)	17 (7.1)
Vibration (ankles)	21 (1.7)	10 (2.7)	7 (2.9)	9 (3.8)
Joint position (great toes)	7 (0.6)	5 (1.3)	1 (0.4)	2 (0.8)
Equilibrium (Romberg)	6 (0.5)	5 (1.3)	1 (0.4)	1 (0.4)
Ankle/toe flexor strength	5 (0.4)	3 (0.8)	1 (0.4)	1 (0.4)
Absent Achilles reflexes	162 (13.4)	45 (12.0)	38 (15.8)	39 (16.3)

In the secondary analyses, after excluding veterans with diseases, disorders, exposures, or medications known to produce symptoms suggestive of neuropathy, the numbers of veterans with abnormalities were too small to analyze.

Table 10 gives the numbers of veterans with the physical signs used in the four indices of peripheral neuropathy in 1997.

DISCUSSION

Data collected during the period 1992 and 1997 indicated a statistically significant increased odds of probable peripheral neuropathy and diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, among Ranch Hand veterans with higher dioxin levels. We observed no interaction between diabetes category and Ranch Hand exposure in the analysis of probable peripheral neuropathy in 1997. Subsequent stratified analyses by diabetic category revealed strong odds ratios for probable peripheral neuropathy among non-diabetic veterans and diabetic veterans in 1997, conforming with the absence of interaction between diabetes and Ranch Hand exposures. We observed an interaction between diabetes and current dioxin in the analyses of diagnosed peripheral neuropathy in 1997, but small numbers of abnormalities precluded deeper investigation into the differences in the high exposure category, in the two diabetes strata. Our secondary analysis, additionally excluding veterans with diseases, disorders and other exposures that may have produced symptoms suggestive of neuropathy resulted in counts too small to analyze. An elevation in the sensory threshold for vibrotactile stimuli in the great toe is a sensitive measure of distal axonopathy associated with genetic, metabolic and neurotoxic neuropathies (Bove et al., 1986; Dyck et al., 1984). Nerve conduction measures are generally sensitive to early signs of dysfunction and are considered the most specific indicators of peripheral neuropathy. Unfortunately, nerve conduction studies were not performed as part of the 1997 examinations, and therefore, electrodiagnostic confirmation of peripheral neuropathy is unavailable.

The strong relation between diabetes and all of the outcomes we studied and a relation between dioxin and diabetes in Ranch Hand veterans (Henriksen et al., 1997) complicate the interpretation. We found no clear evidence of effect modification by diabetes on the association between dioxin and peripheral neuropathy. We reviewed the 1997 examination records of all veterans with probable or diagnosed peripheral neuropathy in the high exposure category (Tables 6 and 7). Of the fourteen veterans with probable peripheral neuropathy, nine had diabetes and four others had findings suggestive of pre-clinical diabetes. Similarly, of the eight veterans with diagnosed peripheral neuropathy in the high exposure category, seven had diabetes, and one had findings suggestive of pre-clinical diabetes. Based on these observations, we remain cautious in our interpretation about the possible association between exposure to dioxin in Operation Ranch Hand and subsequent development of peripheral neuropathy. It remains possible that the association is due in part to residual confounding by diabetes that did not satisfy clinical criteria for diagnosing diabetes mellitus. As discussed, these data also are consistent with a possible effect of dioxin exposure in the Ranch Hand group. Most known neurotoxic syndromes that produce peripheral neuropathy occur in association with a massive acute exposure or a chronic, long-term exposure to the neurotoxic agent. It is biologically plausible, however, for a remote neurotoxic exposure to produce subclinical neuronal damage that becomes unmasked as a consequence of age-related neuronal attrition (Calne et al., 1986, Albers et al., 1988). This ambiguity and biological plausibility may be clarified

by information derived from the next scheduled follow-up examination.

Our findings were inconsistent with those of Sweeney et al. (1993), 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. (1988), 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 diagnosed peripheral neuropathy was similar to that of Barbieri et al. (1988), who required the presence of at least two bilateral and symmetric clinical signs and two electrophysiological abnormalities (including reduced conduction velocities). Sweeney et al. (1993) 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. (1988) was collected within 6 years of the Seveso accident, and the data of Sweeney et al. (1993) 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 and medical review of potential outliers reduced errors that would bias the study toward the null result.

The study is limited by incomplete knowledge of dioxin exposure. We are uncertain about the exposure status of Ranch Hands in the background category; some of these veterans may not have received an elevated level during their service in the Ranch Hand and others could have received elevated dioxin levels in Vietnam, but their body burden decreased to background levels in the intervening time period, causing us to misclassify some of them. However, a recent study of skin exposure to herbicides in Ranch Hand enlisted veterans showed that veterans assigned to administrative duties and those reporting no skin exposure had the lowest measured dioxin levels (approximately 60% had background levels) and >75% of those reporting high skin exposure had measured dioxin levels above background (Michalek et al., 1995). Thus, it appears that most Ranch Hand veterans with background levels were probably unexposed or received minimal exposure to herbicides in Vietnam.

Confounding is another concern. Although we adjusted for all known confounders, there is the possibility that others exist that we have not taken into account. Ranch Hand veterans in the high category were younger and heavier than those in the background category. These differences are most likely due to the greater percentage of enlisted personnel in the high category (75.8%) than in the background category (27.1%), because officers are generally older and college educated, whereas most enlisted personnel are younger and have only a high school education. To further examine the increased risk in the high category we reanalyzed the measures of peripheral neuropathy restricting to the enlisted personnel. The results were similar to those reported here and did not cause us to change our interpretation.

Our overall interpretation is limited by the small number of abnormalities in the high exposure category and changes in abnormal status from one assessment to the next in some veterans. These patterns may be attributable to an exposure metric determined many years after the initial exposure, the observational nature of the study, intervening factors, and confounding not addressed by our adjustments.

In summary, 1992 and 1997 results indicate a consistent pattern of increased risk of probable and diagnosed peripheral neuropathy among Ranch Hand veterans with higher dioxin levels. These results are suggestive of an adverse relation between dioxin exposure and peripheral neuropathy.

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