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Peripheral Neuropathy After Occupational Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

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Reports of human exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) describe signs and symptoms consistent with exposure-related peripheral neuropathy. In a cross-sectional study, prevalence of peripheral neuropathy was measured in 265 workers exposed 15 years earlier to chemicals contaminated with TCDD and in 244 unexposed, age-, race-, gender- and community-matched comparisons. Cases of peripheral neuropathy were defined from examination, electrophysiologic and quantitative sensory tests, and symptoms. Exposure was assessed by measuring lipid-adjusted serum TCDD levels. The mean serum TCDD level for workers (220 parts per trillion (ppt)) was significantly higher than for referents (7 ppt) ($p < .0001$). Thirty-two percent of both worker and referent groups met the case definition for peripheral neuropathy. In the logistic regression analyses, serum TCDD level was not related to peripheral neuropathy. These data suggest that despite continued high serum TCDD levels, peripheral neuropathy is not a long-term sequela of high exposure to TCDD-contaminated chemicals. However, the study cannot preclude the occurrence and subsequent resolution of acute effects caused by high exposure, as experienced in Seveso and possibly by some workers, while exposed to high levels of TCDD-contaminated substances.

Key words: peripheral neuropathy, dioxin, tetrachlorodibenzodioxins, cross-sectional study, occupational exposure, nerve conduction velocity, vibration sensitivity

INTRODUCTION

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is produced as an undesirable contaminant in the manufacture of sodium trichlorophenate (NaTCP). Occupational exposure to TCDD occurred during the production of NaTCP and derivative chemicals such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), after industrial accidents involving TCP reactors, or during the clean up of TCDD-contaminated wastes. En-

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vironmental exposure to the general public may occur through the food chain, from effluent of incineration products, and other industrial processes [NATO, 1988a; NATO, 1988b].

Signs and symptoms consistent with exposure-related peripheral neuropathy are among the many health effects reported among workers and community residents exposed to TCDD-contaminated substances. Within a short time after exposure to TCDD, fatigue, pain, weakness, alteration in muscle coordination, changes in sensory and motor function and activity of deep tendon reflexes, degeneration of distal axons, and altered sense of taste, hearing, smell, and visual field have been reported among workers in one or more case reports [Baader and Bauer, 1951; Bauer et al., 1961; Poland et al., 1971; Goldman, 1972; Jirasek et al., 1974; Oliver, 1975; Pocchiari et al., 1978] and among residents of Seveso, Italy [Filippini et al., 1981]. At least one report indicated that effects may persist for as long as 25 years post-exposure [Moses et al., 1984]. Our study reported here examines the prevalence of chronic peripheral neuropathy in a cohort of workers exposed to chemicals contaminated with TCDD 15–37 years earlier. Evaluation of peripheral neuropathy was one outcome examined in a large cross-sectional medical study designed to evaluate adverse health effects of exposure to TCDD contaminated materials.

MATERIALS AND METHODS

Study Population

The cross-sectional medical study included living workers who were previously employed for at least one day in one of two plants located in Newark, New Jersey and Verona, Missouri. From 1951 to 1969, 490 workers were employed at the New Jersey plant in the production of sodium 2,4,5-trichlorophenate (NaTCP), 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), and 2,4-dichlorophenoxy acetic acid (2,4-D). A high incidence of chloracne and other dermatologic abnormalities and cases of porphyria and hypomania were reported among the workers at the New Jersey facility [Poland et al., 1971; Bleiberg et al., 1964], which produced some of the most heavily TCDD-contaminated NaTCP and 2,4,5-T among production facilities whose products were surveyed [Fee et al., 1975]. (A review of chloracne and other dermatologic conditions in our study population is forthcoming.)

At the Missouri plant, NaTCP and 2,4,5-T were produced intermittently for four months in 1968, and NaTCP and hexachlorophene were produced continuously for twenty-two months, between April 1970 and January 1972. Prior to this cross-sectional study, the health of the 96 Missouri production workers had not been previously studied.

For comparison, unexposed neighborhood referents were recruited using a random sampling procedure described by Sweeney et al. [1989]. Referents were selected if they reported no prior history of occupational exposure to TCDD, and matched the worker by age (within 5 years), race, and gender. A detailed description of the study population is included in the results.

Data Collection

Worker and referent health and exposure status was assessed in 1987–1988 through an interviewer-administered medical and occupational history and a physical

examination. The comprehensive physical examination was carried out over two and one-half days and included exhausting health and psychological assessments of all participating workers and referents. As a surrogate for cumulative exposure, serum TCDD levels were measured. Procedures for sample collection, preparation, adjustment for lipids, and statistical analysis were described in earlier reports [Fingerhut et al., 1989; Patterson et al., 1986; Sweeney, 1990].

A lifetime medical history was obtained from each examined participant by interviewers who were blind to the exposure status of the respondent. Relative to signs and symptoms of peripheral neuropathy, all participants were asked, "Did a doctor ever tell you that you had _____?" and "What year were you told?" The following items were inserted in the blank: carpal tunnel syndrome; sciatica (slipped disc); injuries to nerves; or problems with nerves due to illness. Self-report of symptoms related to peripheral neuropathy of the limbs were also elicited. The symptoms included severe cramping or weakness in the legs, weakness of the hands, numbness, tingling, burning, and persistent twitching or rippling of limb muscles. The interview also obtained a self-reported history of medications and conditions associated with peripheral neuropathy such as diabetes, arthritis, gout, genetic neuropathies, and some cancers (e.g., multiple myeloma). In a separate interview, we also obtained a complete employment history from age 16, which included a history of occupational exposure to potentially neurotoxic chemicals.

We evaluated the neurologic status of each participant through a standardized neurologic examination and electrophysiologic measurements and quantitative sensory tests of thermal and vibratory sensitivity [Sweeney, 1990]. The standard neurologic examination was conducted by board certified neurologists and included an evaluation of the cranial nerves, muscle strength in the upper and lower limbs, sensory perception of pain (pinprick), light touch (cotton puff), vibration (tuning fork), proprioception (position of the digits), activity of deep tendon reflexes (brachial, patellar, achilles), stance (balance), gait, coordination of hand and foot, and signs and symptoms of intentional or unintentional tremor.

The standard electrophysiologic and quantitative sensory tests were conducted by trained technicians who used techniques consistent with those outlined by Kimura [1984]. Electrophysiologic data including amplitude, latency, and conduction velocity were measured on sensory fibers of the median (distal and proximal), ulnar, and sural nerves, and motor fibers of the median and peroneal nerves of the dominant side. Vibration sensitivity provides an index of the integrity of neurons and receptors which regulate vibratory sensation and proprioception [Bove et al., 1986]. Vibratory thresholds were measured in vibration units and converted to microns on the Vibratron II. Thermal sensitivity evaluates the integrity of the small diameter neurons which detect temperature and pain stimuli [Bove et al., 1986]. Thermal thresholds were measured in degrees Centigrade on the Sensortek II Thermal Tester-NTE-2. Both thermal and vibration threshold were measured on the distal volar surface of the index finger and plantar surface of the great toe of the dominant side [Arezzo et al., 1986]. For the electrophysiologic tests, skin temperature was adjusted to 33.0°C ± 1°C for the upper limb or to 32.0°C ± 1°C for the lower limb; skin temperature was not adjusted prior to the quantitative sensory tests.

The reference values used to define the normal range for each of the electrophysiologic and quantitative sensory tests are provided in the Appendix. The unexposed referent group was used to define the reference values. We considered a test to

be out of the reference range if it fell outside the 95th percentile for latency, vibration, and thermal thresholds or the 5th percentile for conduction velocities and amplitudes.

Quality control procedures included an ongoing review of examination techniques to ensure adherence to the standardized protocol, and a review of all of the electrophysiologic tracings by a neurophysiologist (J.C.A.). To reduce observer bias, all examiners, technicians, and medical history interviewers were blind to the exposure status (worker or referent) of the participant. All tests were conducted in a quiet environment at a controlled ambient temperature.

Data Analysis

The measurements used for this study were sensitive to detection of distal symmetrical polyneuropathies of the stocking-glove type; the measures were insensitive to other types of polyneuropathies, such as unilateral proximal mononeuropathies. We adapted an operational case definition of distal peripheral neuropathy from prototypes developed for epidemiologic studies by Dyck et al. [1985] and the American Diabetes Association [1988]. For this study, a case of peripheral neuropathy was defined as the presence of an out-of-range latency, amplitude, or conduction velocity, *plus* at least one of the following: one abnormal clinical sign diagnosed during the neurologic exam, an out-of-range quantitative sensory test, or at least two positive symptoms. Severity of peripheral neuropathy was determined by assigning a value of one to each out-of-range test, abnormality diagnosed in the neurologic examination, or positive symptom. The greater the number, the more severe the condition. The unadjusted means of the severity score between workers and referents were tested by a two sample Student's t-test.

The intent of the study was to conduct a matched analysis of examined study participants. However, a matched analysis would have resulted in the exclusion of 70 (25%) workers and 49 (23%) referents whose matched partners refused participation in the examination. Therefore, to maximize the power of the study, we performed both matched and unmatched analyses.

For the unmatched data, we conducted unconditional logistic regressions to evaluate the relationship between cases of peripheral neuropathy and exposure to TCDD-contaminated processes. The effect of exposure was assessed using each of two exposure indicators in separate models: status as a worker or referent or serum TCDD level measured at the time of the examination, which is significantly correlated with length of exposure in TCDD-contaminated process ($r = 0.72$, $p < 0.0001$). Potential confounders examined included age at the time of the examination, lifetime alcohol consumption, race, gender, history of musculoskeletal disorders or peripheral nerve injury (carpal tunnel syndrome, sciatica, or traumatic injuries to the nerves), and history of occupational exposure to solvents and heavy metals. Lifetime alcohol consumption was determined by calculating alcohol years, the product of the average number of alcoholic drinks consumed per day and the number of years alcohol was consumed. Adjusted odds ratios (OR) were calculated by exponentiating the beta of the dichotomous exposure variable, and tested for significance by one-sided 90% confidence intervals (CI).

To examine the matched data, conditional logistic regression models were constructed, taking into consideration the same covariates assessed in the logistic regression models with exposure status designated by worker-referent status. For either model, we retained in the model any covariate significant at the $p > 0.05$ level or

when the inclusion of the variable modified the regression coefficient of the serum TCDD level by more than 5%. Two-way interactions between the exposure variable and the covariates were also examined.

We excluded from all regressions workers and referents with conditions related to peripheral neuropathy in the absence of TCDD exposure, such as stroke, debilitating trauma to the spine or limbs, genetically-related neuropathies, and multiple myeloma. Although diabetes is a well-known risk factor for peripheral neuropathy, recent data from the US Air Force Ranch Hand Study suggest that TCDD exposure may increase the risk for diabetes or abnormal glucose levels [Wolfe et al., 1991]. To examine the effect of diabetes on the prevalence of peripheral neuropathy in the presence of TCDD exposure, we constructed three different models; one excluded diabetics; in the other two models, we included diabetics, with and without an indicator variable for diabetic status. Because diabetes may be on the causal pathway in the hypothesized relationship between TCDD exposure and peripheral neuropathy, the model which we discuss in this report includes diabetics without an indicator variable.

In this study, we defined diabetes by history of physician-diagnosed diabetes or a fasting serum glucose level of 140 mg/dl or greater for two consecutive days [National Diabetes Data Group, 1979].

We also compared, between the worker and referent groups, the unadjusted results of each component of the neurologic assessment. Odds ratios were calculated for outcomes of the neurologic examination and electrophysiologic and quantitative sensory tests and were tested for statistical significance by the Cochran-Mantel-Haenszel Chi Square [SAS Institute, 1987]. Unadjusted means for electrophysiologic and quantitative sensory tests were compared by Student's t-test. The prevalence of workers and referents reporting symptoms, other conditions, and exposures related to peripheral neuropathy were tested by the Cochran-Mantel-Haenszel Chi Square [SAS Institute, 1987].

RESULTS

Five hundred and eighty-six (586) workers were eligible for inclusion in the study, of which 400 (68.3%) were living, 142 (24.2%) were deceased, and 44 (7.5%) could not be located. All 400 living workers were invited to participate in the study; 281 (70%) were examined. The goal of the study was to examine matched worker-referent pairs. To obtain a matched referent for a minimum 75% of the examined workers, we were obliged to invite a total of 938 individuals from the community to participate in the study. Two hundred and sixty referents (28%) participated in the study.

A detailed description of the demographic characteristics of the study population was previously reported [Sweeney, 1989]. Briefly, workers did not differ from referents in mean age (workers = 55.4 years, range = 33–84; referents = 56.0 years, range = 31–78), race, gender, income, education, or lifetime cigarette consumption, measured in pack years. However, referents consumed significantly more alcohol than workers, based on mean lifetime alcohol consumption expressed as alcohol years ($p < 0.01$). This difference was due mainly to the very high number of alcohol years of seven referents [Calvert et al., 1992]. When the seven were omitted from the calculation of the mean, lifetime alcohol consumption of the remaining

TABLE I. Workers and Referents With Conditions Associated With Peripheral Neuropathy

	Workers (N = 281)		Referents (N = 260)	
Condition	No.	(%)	No.	(%)
Diabetes	27	(10)	16	(7)
Neurotoxic[a,d] medication	6	(2)	4	(1)
Stroke[d]	8	(3)	9	(3)
Other conditions[d]	6[b]	(2)	4[c]	(1)
Missing data[d]			1	(1)
Total	43	(15)	30	(11)

[a]Dilantin, hydralazine, dapsone, and phenytoin.
[b]Refused to complete exam (N = 3); paralyzing spinal cord injury (N = 1); elbow deformity (N = 1); ankle deformity (N = 1).
[c]Multiple myeloma (N = 1); Charcot-Marie-Tooth Syndrome (N = 2); both legs and nerves damaged in accident (N = 1).
[d]No significant difference in proportion of workers and referents.

referents was the same as observed in the workers. However, the seven workers were retained in this analysis.

As expected, based on Student's t-test of the log TCDD levels, the mean lipid-adjusted serum TCDD level for workers (220 parts per trillion (ppt)) was statistically significantly greater than that for referents (7 ppt) ($p < 0.001$).

Excluded a priori from the logistic models were 16 (5.7%) workers and 16 (6.1%) referents with a history of stroke, severe trauma to the spine or limbs, or genetically-related peripheral neuropathy (based on the assessment of the examining neurologist and self-reported medical history), or who were taking potentially neurotoxic medications (dilantin, hydralazine, dapsone, or phenytoin) at the time of the study, or who refused to complete all or part of the neurologic assessment (Table I). Ten percent of the examined workers and 7% of the examined referents were classified as diabetics. The proportions of workers and referents excluded from the analysis or identified as diabetic were not significantly different.

Of the 265 examined workers and 244 examined referents included in the analysis, 32% of each group (85 workers, 78 referents) met the study case definition. The unadjusted mean severity score of 13 for cases in workers was not significantly different than the mean of 14 for cases in referents. The mean serum TCDD level among workers who met the case definition for peripheral neuropathy (250 ppt) did not differ significantly from that of workers who did not meet the case definition (190 ppt). While over 75% of the cases of peripheral neuropathy occurred among New Jersey workers, the proportion of cases among all examined workers was approximately the same for those with employment in the 2,3,7,8-TCDD-contaminated processes at the Missouri plant (31%) and those who worked at the New Jersey facility (33%).

Separate logistic regression models examined the relationship between peripheral neuropathy and exposure, controlling for potential confounders. In the final logistic regression model, using serum TCDD level as the exposure variable (Table II) and including diabetics without an indicator variable, age at examination, race, and a history of occupational lead exposure remained as statistically significant covariates. This relationship was the same whether or not diabetics were in the model or

TABLE II. Multiple Logistic Regression Model for Cases of Peripheral Neuropathy*

Variable	Beta	Standard error	Chi square	p-value
Intercept[a]	−3.5732	0.6063	34.7	0.0001
Serum TCDD	−0.00002	0.0003	0.003	0.9956
Age	0.0603	0.0106	32.4	0.0001
Lead[a] (0 = no, 1 = yes)	0.7464	0.2624	8.09	0.0045
Race (0 = other, 1 = white)	−0.7626	0.085	6.11	0.0134

*Sample size = 503 observations.
[a]Self-reported occupational history.

whether the analysis considered only matched pairs. Categorization of TCDD levels into equal groups, <20 ppt, 20–150 ppt, or >150 ppt, showed no consistent increase in the prevalence of peripheral neuropathy with increasing TCDD level. In all models, diabetic status was significant when included in the model as an indicator variable ($p < 0.001$).

In the model in which the dichotomous worker-referent exposure term was used, workers reporting a history of occupational lead exposure were three times as likely to be a case than unexposed referents (OR = 2.91, 95% lower confidence limit (LCL) = 1.63). However, workers reporting no lead exposure showed no significant excess of peripheral neuropathy (OR = 1.17, 95% LCL = 0.60). In the model in which we included the continuous exposure variable, serum TCDD, no significant interactions occurred.

Tables III–VI summarize the findings of the data from the neurologic examination, electrophysiologic and quantitative sensory tests, and self-reported symptoms, all of which make up the case definition. Details of the results for specific muscle groups and nerves have been described elsewhere [Sweeney, 1990]. In general, the individual components of the case definition were not significantly different for examined workers and referents. The unadjusted odds ratios were similar between workers and referents for abnormal findings observed in the neurologic examination (Table III), self-reported symptoms related to peripheral neuropathy (Table IV), and the unadjusted, arithmetic means of the electrophysiologic measurements (Table V) and thermal and vibratory threshold (Table V). However, the unadjusted proportion of self-reported history of exposure to chemicals related to peripheral neuropathy was significantly higher among workers for arsenic, mercury, carbon disulfide, n-hexane, methyl-*n*-butyl ketone, organophosphate pesticides, and dimethyl-aminopropionitrile, but not for lead (Table VI). We could not definitively corroborate these findings with objective work history data collected from the plants.

DISCUSSION

The purpose of this analysis was to compare the prevalence of chronic peripheral neuropathy in workers previously exposed to substantial levels of TCDD and an unexposed comparison group. Seven previous cross-sectional studies systematically evaluated the persistence of peripheral neuropathy in five different populations with potential for exposure to TCDD contaminated chemicals: US Air Force Ranch Hand

TABLE III. Unadjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for Abnormalities Detected by Neurologic Exam for Workers and Referents

	Workers		Referents			
	No.	(%)	No.	(%)	OR	95% CI
Muscle strength	37	(14)	27	(11)	1.3	0.8–2.2
Tendon reflexes	159	(60)	151	(62)	0.9	0.6–1.3
Tremor	67	(25)	58	(24)	1.1	0.7–1.6
Station & gait	87	(33)	79	(32)	1.0	0.7–1.5
Coordination	99	(37)	97	(40)	0.9	0.6–1.3
Light touch	36	(14)	33	(14)	1.0	0.6–1.7
Pinprick	138	(52)	93	(38)	1.8	1.2–2.5
Position	18	(7)	16	(7)	1.0	0.5–2.1

TABLE IV. Percent and Number of Workers and Referents Reporting Symptoms Related to Peripheral Neuropathy*

	Workers		Referents	
	No.[a]	(%)	No.[b]	(%)
Numbing	67	(6.3)	66	(6.8)
Tingling	69	(6.5)	81	(8.3)
Burning	26	(2.5)	35	(3.6)
Weakness	9	(0.9)	19	(2.0)
Muscle twitching	40	(3.8)	26	(2.3)
Difficulty handling small objects	17	(6.4)	18	(7.4)
Cramping[c]	78	(29.6)	45	(18.5)
Difficulty balancing	36	(13.6)	23	(9.5)

*Reported in medical history.
[a]Sample sizes differ due to missing measurements and number of exclusions. Sample size range: 263–264.
[b]Sample size range: 243–244.
[c]$p < .05$, x^2 1 d.f.

personnel [Lathrop et al., 1984, 1987; Wolfe et al., 1991], TCP workers in Nitro, West Virginia [Moses et al., 1984; Suskind and Hertzberg, 1984], Missouri residents [Webb et al., 1989], and residents of Seveso, Italy [Filippini et al., 1981]. These studies examined their populations for signs and symptoms associated with peripheral nerve dysfunction because previous case reports described such conditions in workers exposed to TCDD-contaminated areas as a function of their daily work or after TCP reactor releases [Baader and Bauer, 1951; Bauer et al., 1961; Poland et al., 1971; Goldman, 1972; Jirasek et al., 1974; Oliver, 1975].

The lack of an excess of chronic peripheral neuropathy in our study is consistent with the findings of the cross-sectional studies of occupational groups but not of Seveso residents [Filippini et al., 1981]. A significantly higher prevalence of peripheral neuropathy occurred among Seveso residents who, for the purposes of the study, were considered as exposed to TCDD because they exhibited clinical signs of exposure defined as elevated liver enzymes and chloracne [Filippini et al., 1981]. Measurement of lipid-adjusted TCDD levels (range to 50,000 ppt) in serum collected within one year of the accident confirmed substantial exposure of some residents [Mocarelli et al., 1990].

TABLE V. Unadjusted Arithmetic Means and Standard Deviations (sd) for Electrophysiologic and Quantitative Sensory Tests

	Workers			Referents		
Measure	Sample[a] size	Mean	(sd)	Sample[a] size	Mean	(sd)
Nerve conduction velocity						
Median motor	265	54.7	(5.6)	244	54.9	(4.5)
Median sensory-D	264	48.3	(7.5)	242	48.1	(6.8)
Median sensory-P	254	57.5	(5.8)	241	57.4	(5.6)
Ulnar sensory	264	50.8	(6.4)	243	51.3	(6.4)
Peroneal motor	261	44.9	(6.4)	241	45.1	(4.8)
Sural sensory	246	43.0	(5.3)	233	43.4	(6.1)
Amplitude						
Median motor	265	9968	(3593)	244	10,215	(3472)
Median sensory	264	18.3	(8.5)	243	19.3	(10.4)
Ulnar sensory	264	17.2	(8.7)	243	18.1	(11.1)
Peroneal motor	246	5316	(2480)	221	5571	(2586)
Sural sensory	246	14.4	(8.4)	233	14.4	(9.0)
Latency						
Median motor-D	265	3.7	(0.7)	244	3.7	(0.7)
Median motor-P	265	9.0	(1.1)	244	8.9	(0.9)
Median sensory-D	264	3.1	(0.6)	243	3.1	(0.6)
Median sensory-P	254	8.1	(0.9)	242	8.1	(1.1)
Ulnar sensory	264	2.5	(0.4)	243	2.5	(0.4)
Peroneal motor-D	261	4.6	(1.1)	241	4.4	(1.0)
Peroneal motor-P	261	12.0	(2.1)	241	11.7	(1.7)
Sural sensory	246	3.4	(0.6)	233	3.4	(0.7)
F Wave[b]	255	50.8	(5.2)	237	49.8	(5.5)
Vibration Threshold[c]						
Index finger	265	0.7	(0.2)	244	0.7	(0.2)
Great toe	265	12.0	(5.4)	244	10.1	(4.8)
Thermal threshold[d]						
Index finger	265	1.0	(1.4)	244	0.9	(0.6)
Great toe	265	2.0	(4.3)	244	1.4	(3.3)

[a]Sample sizes differ due to missing measurements and number of exclusions.
[b]$p < .05$, Student's t-test.
[c]Measured in micron of vertical displacement at 128 Hz.
[d]Measured in degrees Centigrade with reference to a comparison of 25°C.

There is probably no single explanation for the disparity in the findings among the cross-sectional studies, the case reports, and the Seveso study. The differences may be ascribed to a number of factors including amount of exposure to TCDD (and classification of exposure to TCDD), the length of time between exposure to TCDD-contaminated chemicals and the evaluation of peripheral neuropathy, the technical limitations of the earlier studies, and the definition of peripheral nerve dysfunction used by the researchers.

Among the studies of occupational and community exposure to TCDD-contaminated materials, our study of workers from New Jersey and Missouri is the only study in which the relationship between serum TCDD and neurologic endpoints was examined in a cohort of occupationally exposed individuals. Our data indicate that

TABLE VI. Percent and Number of Workers and Referents Reporting Selected Conditions, Injuries, and Chemical Exposures Related to Peripheral Nerve Dysfunction

	Workers[d]		Referents[e]	
	No.	(%)	No.	(%)
Condition[a]/injury[b]				
Slipped disc	24	(9)	32	(13)
Surgery on back or spine	19	(7)	11	(5)
Sciatica	20	(8)	24	(10)
Carpal tunnel syndrome	1	(0.4)	5	(2)
Head injury with loss of consciousness	30	(11)	46	(19)
Rheumatoid arthritis	4	(2)	2	(0.8)
Osteoarthritis	15	(6)	14	(6)
Gout	13	(5)	12	(5)
Exposures[c]				
Arsenic[c]	17	(10)	5	(2)
Mercury[c]	26	(9)	10	(4)
Carbon disulfide[c]	23	(9)	7	(3)
N-hexane[c]	26	(14)	5	(2)
Methyl-*n*-butyl[c]	30	(11)	8	(3)
Acrylamide	6	(2)	1	(0.4)
Lead	44	(17)	37	(15)
Organophosphate pesticides[c]	17	(6)	0	—
Dimethylaminopropionitrile	15	(6)	3	(1)

[a]Reported in occupational history.
[b]Reported in the medical history.
[c]$p < .05$, x^2 1 d.f.
[d]Sample size = 265.
[e]Sample size = 244.

among worker cases of peripheral neuropathy, the mean serum TCDD level was not significantly above that of workers who were not cases. The serum TCDD levels at the time of the exam in both worker cases and noncases were approximately 30 times that of the cases in the unexposed referent group. Furthermore, at the time of last occupational exposure, the levels in the exposed workers might have been as high as 300 times that of the unexposed referents [Fingerhut et al., 1991]. Moreover, the estimated power of our study to detect a two-fold increase in peripheral nerve dysfunction, specifically decreased pinprick sensation, in workers compared to referent was high, approximately 100%. Therefore, if peripheral nerve dysfunction was related to serum level of TCDD, a strong positive relationship between serum TCDD level and the risk of chronic peripheral neuropathy would have been observed.

The period between initial exposure to TCDD and the neurologic assessment varies considerably among the cross-sectional studies and case reports. The workers in our study, as well as all other populations included in the cross-sectional studies [Moses et al., 1984; Suskind and Hertzberg, 1984; Lathrop et al., 1984, 1987; Wolfe et al., 19991], except Seveso residents, were examined from 15 to 37 years after exposure terminated. In contrast, the Seveso residents, some of whom may have been heavily exposed, were examined in 1978 and 1979, two to three years after the accidental TCP reactor release [Filippini et al., 1981]. Similarly, the case reports of adverse health effects in TCP workers generally described effects which occurred

while the exposure continued [Bauer et al., 1961; Goldman, 1972; Poland et al., 1971] or within a short time after exposure ended [Baader and Bauer, 1951; Jirasek et al., 1974]. The consistency in the findings in the Seveso residents [Filippini et al., 1981] and in the early case reports of workers suggest that the reported neurologic effects *may occur shortly after exposure* [Bauer et al., 1961; Goldman, 1972]. Because the large cross-sectional studies (including our study) were conducted many years after the termination of exposure, it is not possible to determine whether or not neurologic effects occurred due to TCDD in these exposed populations and resolved over time. Additionally, histories of self-reported symptoms related to peripheral nerve dysfunction were not in excess among the exposed groups, suggesting that either the workers forgot they had the symptoms or that the symptoms never occurred.

Our study found that age, race, and a history of occupational lead exposure were significantly associated with peripheral nerve dysfunction. These relationships, particularly between peripheral neuropathy and advancing age or lead exposure, are well documented [Dyck et al., 1984; Seppalainen et al., 1975]. We also found a statistically significant interaction (OR = 2.91, $p < 0.05$) between history of occupational lead exposure and status as a TCDD-exposed worker. However, this interaction was not statistically significant in models which included the continuous exposure variable, serum TCDD level instead of work/referent status. In general, worker cases reporting lead exposure were more likely than worker cases reporting no lead exposure to have a lower mean serum TCDD level (126 ppt vs. 302 ppt), one-half the exposure to TCDD-contaminated chemicals (495 days vs. 951 days), and less severe peripheral neuropathy (severity score of 11.5 vs. 13.3). A review of the self-reported work histories suggests potential exposure to lead by many of the cases, as pipefitters, maintenance mechanics, and employees in paint manufacturing plants and smelting operations. However, NaTCP, 2,4,5-T, or hexachlorophene productions operations at the New Jersey and Missouri plants were not sources for lead exposure. Thus, the data suggest that the elevated odds ratio for peripheral neuropathy among workers compared to referents is not due to increasing levels of TCDD exposure but may be an artifact of a dichotomous exposure variable which places equal importance on cases with high and low TCDD exposure.

CONCLUSIONS

The data presented in this report showed that exposure to TCDD was not related to chronic peripheral neuropathy in a group of workers exposed 15–37 years earlier compared to unexposed referents. These data suggest that despite continued high serum TCDD levels, peripheral neuropathy is not a long-term sequela of high exposure to TCDD-contaminated chemicals. However, given the previous reports in the literature indicative of peripheral nerve dysfunction among workers and Seveso residents, the study cannot preclude the occurrence and subsequent resolution of acute effects caused by high exposure, as experienced in Seveso and possibly by some workers, while exposed to high levels of TCDD-contaminated substances.

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APPENDIX. Reference Values for Electrophysiologic and Quantitative Sensory Tests

Measure	Reference Value
Latency (m/sec)	
Median motor-distal	≥4.96[a]
Median motor-proximal	≥10.64
Median sensory-distal	≥4.16
Median sensory-proximal	≥9.68
Ulnar sensory	≥3.36
Peroneal sensory-distal	≥6.16
Peroneal motor-proximal	≥14.40
Sural sensory	≥4.56
F wave	≥58.40
Amplitude (mV)	
Median motor	≤4589
Median sensory	≤6.46
Ulnar sensory	≤4.39
Peroneal motor	≤879
Sural sensory	≤3.59
Nerve conduction velocity (m/sec)	
Median motor	≤47.32
Median sensory-distal	≤35.49
Median sensory-proximal	≤47.95
Ulnar sensory	≤40.54
Peroneal motor	≤37.25
Sural sensory	≤35.71
Vibration threshold (micron displacement at 128 Hz)	
Index finger	≥2.153
Great toe	≥42.090
Thermal threshold (°C)	
Index finger	≥2.012
Great toe	≥2.5875

[a]Reference limits were based on the 5th percentile of referents for nerve conduction velocities and amplitude measurements and on the 95th percentile of referents for latency, vibration, and thermal thresholds.