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Occupational Exposures and Amyotrophic Lateral Sclerosis

A Population-based Case-Control Study

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This population-based case-control study was conducted in three counties in western Washington State to evaluate associations between workplace exposures and the risk of amyotrophic lateral sclerosis (ALS). Cases (n = 174) were all newly diagnosed with ALS by neurologists during 1990–1994, and controls (n = 348), who were matched according to age (±5 years) and sex, were identified via random-digit dialing or Medicare enrollment files. Four industrial hygienists blindly assessed detailed lifetime job histories for exposures to metals, solvents, and agricultural chemicals. Case-control comparisons were made for jobs held between 15 years of age and 10 years prior to the cases' dates of diagnosis. After adjustment for age and education, ever exposure to agricultural chemicals was associated with ALS (odds ratio (OR) = 2.0, 95% confidence interval (CI) 1.1–3.5); this association was observed separately in men (OR = 2.4, 95% CI 1.2–4.8) but not in women (OR = 0.9, 95% CI 0.2–3.8). Among men, the odds ratio for low exposure to agricultural chemicals (below the median level for exposed controls) relative to no exposure was 1.5 (95% CI 0.4–5.3), and for high exposure, it was 2.8 (95% CI 1.3–6.1) (p for trend = 0.03). Similar analyses based on the panel's assessment of exposures to metals and solvents showed no associations. These findings suggest an association between ALS and agricultural chemicals in men. *Am J Epidemiol* 1997;145:1076–88.

agriculture; amyotrophic lateral sclerosis; metals; occupational exposure; solvents

Amyotrophic lateral sclerosis (ALS) is typically a lethal neurologic disease characterized by progressive muscular weakness with atrophy and fasciculations. Although the etiology of ALS is unknown, previous epidemiologic studies have suggested associations with exposures to various chemical agents in the workplace.

Much of the evidence concerns exposure to metals. Aran, in 1850, first described an association between some forms of motor neuron disease and exposure to lead (1). Three of his 11 patients developed progressive muscular atrophy following contact with lead, including two patients who had lead poisoning. Recent epidemiologic evidence that lead and other metals such as mercury and aluminum are associated with ALS is conflicting (2–9). Other studies have reported an association between ALS and certain occupations, including leather working (10, 11) and farming (12–17). However, many of these studies included small numbers of subjects, a mix of incident and prevalent cases, and uncertain workplace exposure information based solely on subjects' self-report.

This population-based case-control study was conducted to examine the possible relations between ALS and occupational exposures.

MATERIALS AND METHODS

Study population

During the 4-year period 1990–1994, efforts were made to identify, through a surveillance system, all patients aged ≥18 years who were newly diagnosed with ALS and resided in King, Pierce, and Snohomish counties in western Washington State (18). The population of these counties is approximately 2.5 million (19). Patients with progressive motor neuron disease

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Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio.

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affecting both upper and lower motor neurons (classic ALS) were included, as were cases with progressive bulbar palsy and progressive muscular atrophy, both considered clinical variants of ALS (20). Cases were excluded if they had primary lateral sclerosis or if the diagnosis of ALS was changed during the year following their initial diagnosis. In order to match the eligibility criteria for controls described below, cases who lacked a telephone or who did not speak English were excluded.

Two controls matched to each case according to sex and age (±5 years) were identified from the study counties using one of two techniques. The first was random-digit telephone dialing, using the Mitofsky-Waksberg sampling protocol (21, 22). The 1990 US Census indicated that more than 97 percent of the region's households have telephones (19). Since random-digit dialing proved to be inefficient for identifying controls over 65 years of age, we used Medicare eligibility lists for the target counties, obtained from the Health Care Financing Administration. Potential controls matched according to sex and birth year were randomly selected from the lists and recruited. Potential controls who did not speak English were excluded.

Over the 4 years of the study, 180 cases of ALS met the eligibility criteria, and 174 of these patients (96.7 percent) agreed to participate. Of these persons, 20 (11.5 percent) died prior to interview, and information had to be obtained from a proxy respondent for both the case and his or her matched controls. Through random-digit dialing, 4,209 (86.6 percent) of 4,858 residential telephone numbers were successfully screened for the presence of a potentially eligible person in the household. Of the 262 eligible controls found, 227 (86.6 percent) agreed to be interviewed, for an overall response rate of 75 percent. Of the potentially eligible controls sampled at random from the Health Care Financing Administration lists, 121 of 202 (60 percent) agreed to participate. Selected demographic information for cases and their matched controls is presented in table 1. Cases and controls were similar, with the exception that cases had less formal education than did controls.

All subjects gave written informed consent. The Human Subjects Committee at the University of Washington approved the study protocol.

TABLE 1. Demographic characteristics of cases and controls matched according to sex and age, western Washington State, 1990–1994

Demographic characteristic	Cases (n = 174)		Controls (n = 348)	
	No.	%	No.	%
Sex				
Men	95	54.6	190	54.6
Women	79	45.4	158	45.4
Age group (years)				
18–44	22	12.6	46	13.2
45–54	28	16.1	67	19.3
55–64	49	28.2	75	21.5
65–74	52	29.9	114	32.8
≥75	23	13.2	46	13.2
Ethnic group				
White	164	94.3	329	94.5
Other	10	5.7	19	5.5
Marital status				
Single	8	4.6	12	3.5
Married	119	68.4	242	69.5
Other	47	27.0	94	27.0
Educational status				
High school or less	83	47.7	124	35.6
More than high school	91	52.3	224	64.4

Exposure information

Demographic data and information on past exposures, including lifetime job history and workplace exposure to specific chemical agents, was collected from cases and controls during a structured in-person interview. Because of the obvious nature of ALS, no attempt was made to blind the interviewer to a participant's disease status.

The questions were linked to a reference date, which was the month and year of the case's diagnosis for both cases and their matched controls. Detailed information on all jobs held for at least 1 year was collected for the period from age 15 years to the reference date. For each job, subjects provided information on job title and industry, a detailed description of tasks performed, the year in which the job began and ended, and numbers of hours worked per week. Subjects also reported on exposures to 28 specific chemical agents and included information on percentage of time exposed. Subjects were asked whether they wore protective equipment on the job and, if so, the percentage of time the equipment was worn. Total hours of self-reported exposure to each agent for each year worked were calculated as the product of total hours worked per year and the subject's estimate of the percentage of time exposed.

Subjects were also asked the number of hours or times per month and the number of years in which they had engaged in home activities or hobbies from age 15 to the reference date, including leatherwork, ceramics, house or oil painting, woodworking, working on engines, building wooden or plastic models, and applying fertilizers or pesticides to the garden. Subjects were asked whether they had ever been exposed to metals, organic solvents, or agricultural chemicals in

large amounts because of an accident, spill, or explosion, on or off the job, prior to the reference date.

Panel assessment of occupational exposures

On the basis of consensus, a panel of four industrial hygienists assessed workplace exposures to 28 specific chemical agents. The panel was blinded to disease status and to self-reported exposures. The panel evaluated job history information to determine probable exposure to any of the substances of interest for each job, based on a scaling system adapted from a previous study (23, 24). Each job was rated according to exposure intensity (0 = none, 1 = low, 2 = medium, 3 = high). Ratings were based on the subject's description of tasks, the era of employment, use of appropriate protective equipment, and frequency of contact (1 = <5 percent of time on the job, 2 = 5–30 percent, 3 = >30 percent). Using government manuals to classify industries and jobs (25, 26), the panel selected for consideration jobs with the potential for the exposures of interest and a 10 percent random sample of jobs that would be less likely to have any of these exposures (e.g., accounting, secretarial work).

The panel also conducted a blinded repeat assessment of 179 job histories (17 percent) to determine reproducibility. The results showed good agreement for metals (90 percent agreement, kappa = 0.77), solvents (82 percent agreement, kappa = 0.64), and agricultural chemicals (97 percent agreement, kappa = 0.75).

Statistical analysis

On the basis of the panel's assessment, an exposure index was estimated as the product of concentration (1, 2, or 3) and frequency (1, 2, or 3) for each month that the subject had been exposed to a specific agent (23, 24). From these data, an annual index was calculated. For example, exposure to lead with a concentration of 2 and a frequency of 2 and a duration of exposure of 7 months yielded a yearly lead exposure index of 28 for that year. A cumulative index of lifetime exposure to each agent and to the broader classification of metals, solvents, and agricultural chemicals was calculated by summing the annual indices for all of the years from age 15 to 10 years prior to the reference date. Exposures incurred during the 10 years before the reference date were discarded in order to exclude exposures that may have occurred during cases' periods of subclinical disease. The index was analyzed both as a continuous variable and as a three-level variable. The three-level variable was based on information from controls which was used to estimate the median lifetime exposure to specific metals, solvents, and agricultural chemicals for subjects with at least some exposure. We defined three groups: persons without exposure (the reference category); those with low levels of exposure (less than the median value among exposed subjects); and those with high levels of exposure (the median value or higher).

Potential risk factors were assessed using conditional logistic regression (27, 28), matching on age, sex, and respondent type (self or proxy). Age was included in the models as a continuous variable to control for any residual confounding. Since relative risk estimates (odds ratios) did not differ according to whether the information was self-reported or proxy-derived, the results from all subjects were analyzed together and respondent type was taken into account as a matching factor in the analyses. Given the potential for confounding (table 1), education was also included as a covariate in regression analyses, although its inclusion had little effect on the relative risk estimates. The possibility of mutual confounding by metals, solvents, and agricultural chemicals was also assessed, and the risk estimates were not significantly affected. Effect modification between specific occupational exposures and education was also negligible.

Because we lacked an a priori biologic reason to suspect that men and women would be affected differently by exposure to these chemical agents, the main analyses were conducted for men and women combined. Since men are more likely than women to have been exposed to many of the agents of interest, effect modification between occupational exposures and sex was assessed. Where appropriate, the results are reported separately for men and women.

Other analyses examined exposures in a series of 10-year windows starting from the reference date and going back in time (29) (see figure 1). Similar analyses examined the data from age 15 years to age 55 years (figure 2) and for the calendar years 1930–1985 (figure 3). Odds ratios and 95 percent confidence intervals were estimated for each moving 10-year window. Curves that summarized these odds ratios and their 95 percent confidence intervals were constructed (30). The moving-window approach assured that transient increases or decreases in risk that had existed during some period in the past would not be missed by sole reliance on cumulative lifetime exposure.

RESULTS

Metals

Based on self-report, the association between ALS and overall exposure to metals was 1.6 (table 2). This was also true when all years prior to the reference date were included. The association of metals with ALS

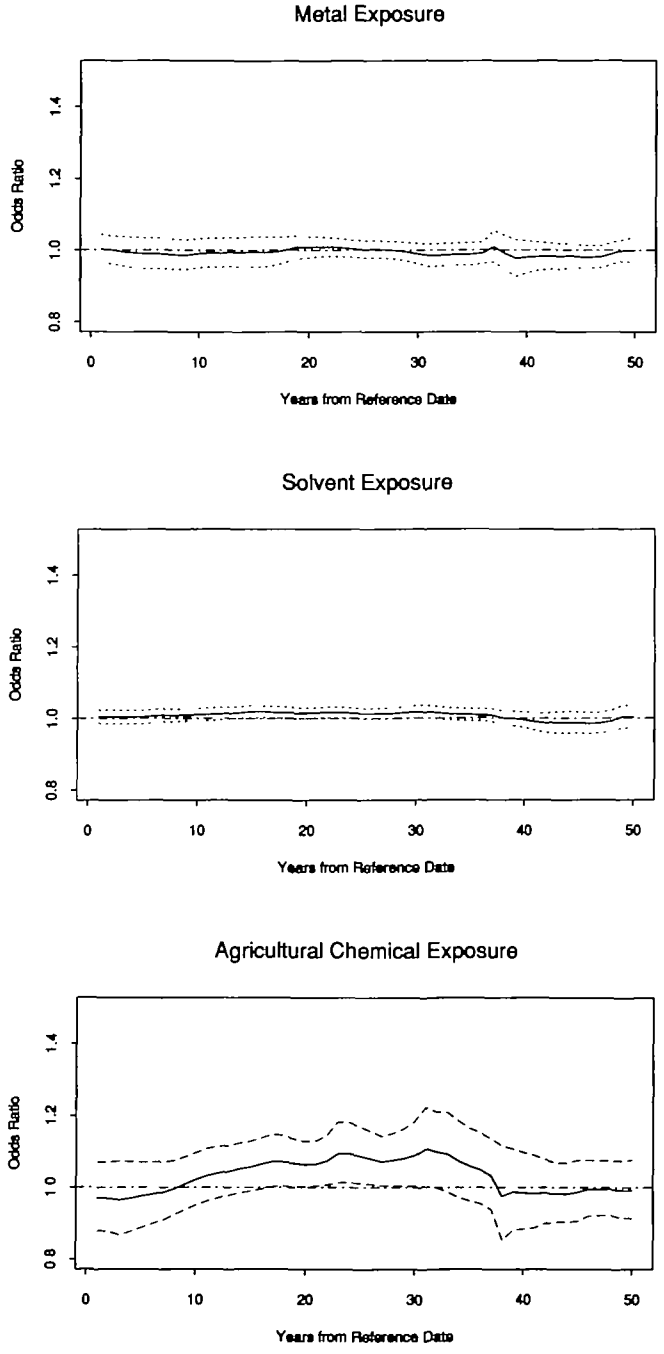

FIGURE 1. Results of a sliding-window analysis in which the curves represent odds ratios (—) and 95% confidence intervals (- - -) for the association between amyotrophic lateral sclerosis and occupational exposure to metals, solvents, and agricultural chemicals as a function of time, western Washington state, 1990–1994. The horizontal line (– - –) represents unity. The time frame ranges from the reference date backward to age 15 years (i.e., number of years back from the reference date). The curve represents odds ratios from conditional logistic regression analysis containing age, education, and the mean values from a cumulative index of exposure for each 10-year window.

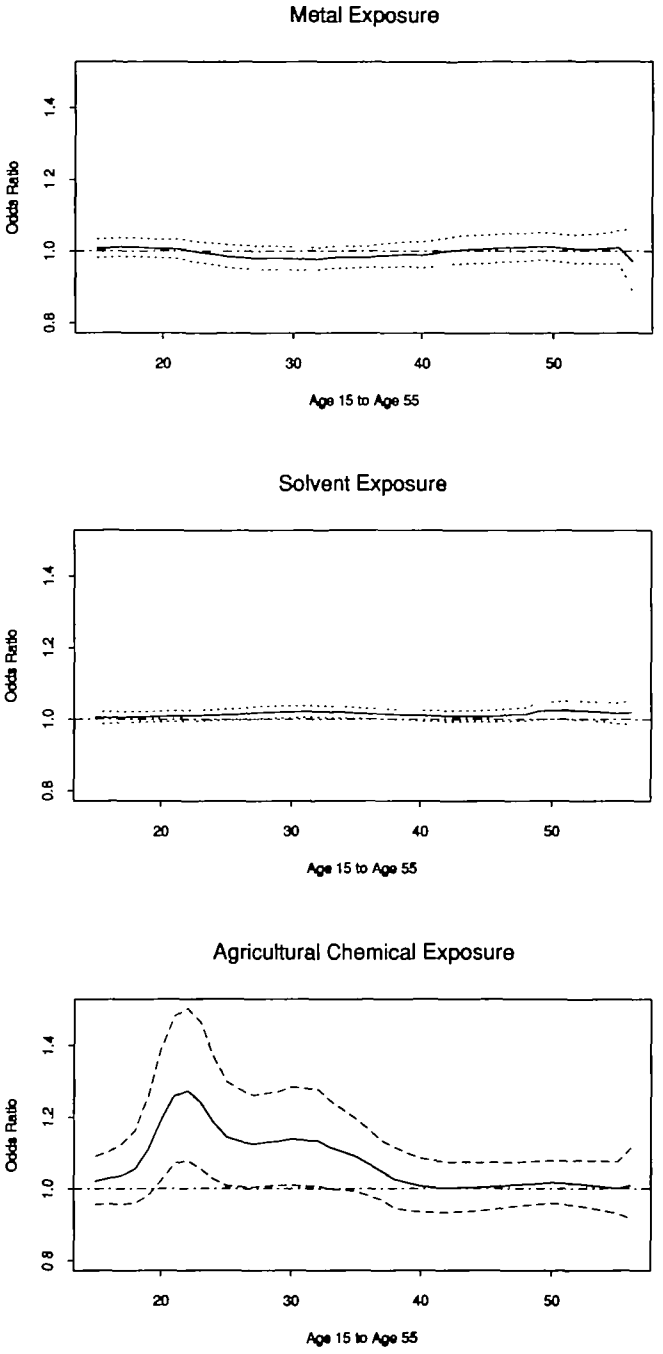

FIGURE 2. Results of a sliding-window analysis in which the curves represent odds ratios (—) and 95% confidence intervals (- - -) for the association between amyotrophic lateral sclerosis and occupational exposure to metals, solvents, and agricultural chemicals as a function of time, western Washington state, 1990–1994. The horizontal line (– - –) represents unity. The time frame ranges from age 15 years to age 55 years. The curve represents odds ratios from conditional logistic regression analysis containing age, education, and the mean values from a cumulative index of exposure for each 10-year window.

was stronger in women (odds ratio (OR) = 2.3, 95 percent confidence interval (CI) 1.1–4.7) than in men (OR = 1.2, 95 percent CI 0.7–2.1). Associations for specific metals are provided in table 3. Relative risk

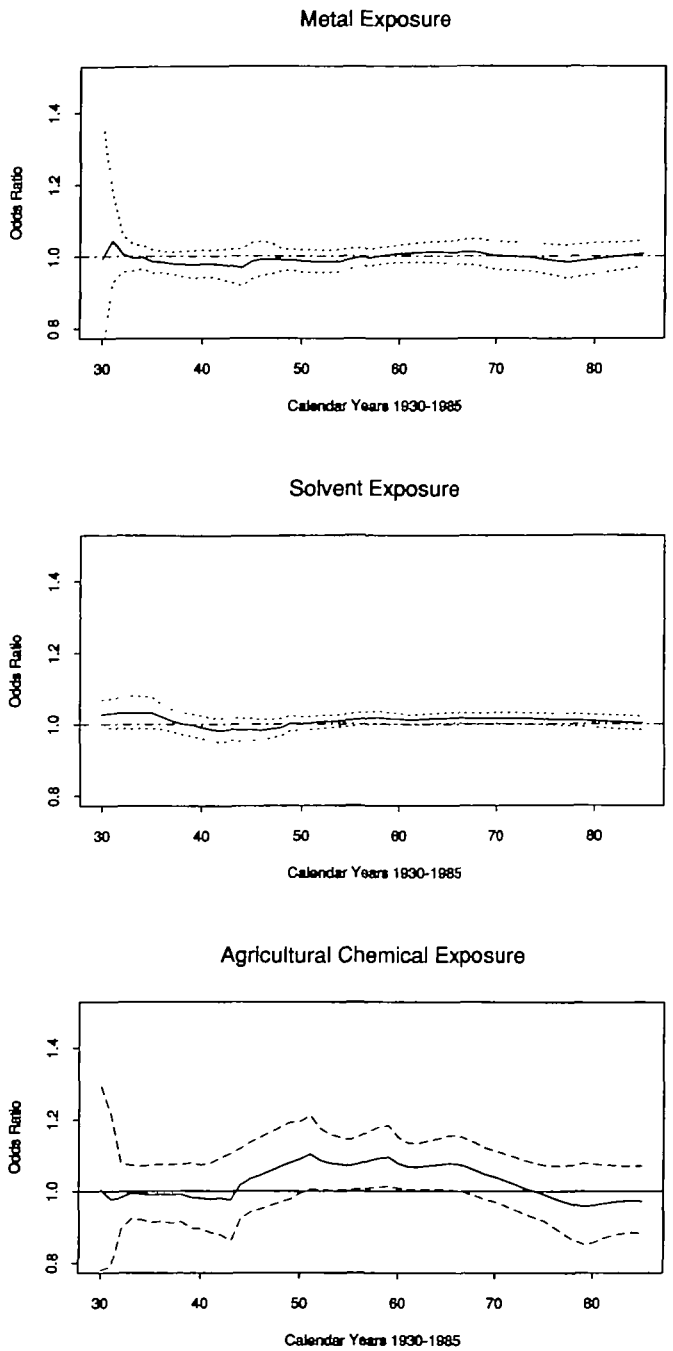

FIGURE 3. Results of a sliding-window analysis in which the curves represent odds ratios (—) and 95% confidence intervals (- - -) for the association between amyotrophic lateral sclerosis and occupational exposure to metals, solvents, and agricultural chemicals as a function of time, western Washington state, 1990–1994. The horizontal line (– – –) represents unity. The time frame ranges from 1930 to 1985. The curve represents odds ratios from conditional logistic regression analysis containing age, education, and the mean values from a cumulative index of exposure for each 10-year window.

estimates were increased for self-reported exposure to chromium (OR = 2.5) and lead (OR = 1.9). Neither result showed a dose-response trend. We next considered any exposure to lead, including lead-content paint and leaded gasoline fumes, which we classified as a solvent in other analyses (table 3). For men and women combined, exposure to any lead was associated with ALS (OR = 1.6, 95 percent CI 1.04–2.5), and this finding was similar for men (OR = 1.6) and women (OR = 1.9) when data were analyzed separately. A dose response was present: The odds ratio was 1.0 (95 percent CI 0.5–1.8) for low exposure and 2.4 (95 percent CI 1.4–4.1) for high exposure (p for trend = 0.001), with a similar trend for men and women.

On the basis of the panel's assessments of exposure for both men and women, little association was found between ALS and overall exposure to metals (table 2) or exposure to specific metals, such as lead (table 3). The relative risk associated with any exposure to lead (as defined above) was 1.2 (95 percent CI 0.7–2.0). No trend with increasing exposure to any lead was observed. The 10-year moving-window analyses for metals, based on the panel's assessment for both men and women, did not show any strong associations with respect to reference date, age, or calendar year (figures 1–3, top sections).

Solvents

On the basis of self-report, solvent exposure was associated with an increased risk of ALS (table 2), especially in women (OR = 2.4, 95 percent CI 1.3–4.3), but not in men (OR = 1.1, 95 percent CI 0.6–2.1). When specific solvents were examined (table 3), exposures to cleaning solvents and degreasers, leaded gasoline fumes, and styrene were associated with an increased relative risk. The increased risk associated with cleaning solvent and degreaser exposures was found among women (OR = 3.6, 95 percent CI 1.8–7.3) but not among men (OR = 1.2, 95 percent CI 0.7–2.07), with no dose-response trend observed. Exposure to leaded gasoline fumes for both sexes together did show a dose-response trend (p = 0.01). Comparing low exposure to gasoline fumes with no exposure, the odds ratio was 1.4 (95 percent CI 0.6–3.5), and for high exposure, the odds ratio was 2.4 (95 percent CI 1.1–5.5).

Based on the panel's assessment, overall exposure to solvents for men and women combined was not significantly associated with ALS (table 2). Specific solvent exposures associated with ALS were alcohol and ketones, benzene, toluene, and xylene, and cleaning solvents and degreasers (table 3), although no trends with increasing exposure to these solvents were observed. The association for alcohol and ketones was stronger in men (OR = 2.6, 95 percent CI 1.1–6.1) than in women (OR = 1.2, 95 percent CI 0.4–3.7).

TABLE 2. Risk of amyotrophic lateral sclerosis according to various categories of occupational exposure, western Washington State, 1990–1994

Exposure	No. of cases (n = 174)	No. of controls (n = 348)	OR*,†	95% CI*
Both sexes combined				
Metals				
Self-report				
Never exposed	87	209	1.0	
Ever exposed	84	139	1.6	1.0–2.5
Panel assessment				
Never exposed	124	266	1.0	
Ever exposed	49	82	1.2	0.8–1.9
Solvents				
Self-report				
Never exposed	57	152	1.0	
Ever exposed	114	196	1.6	1.1–2.5
Panel assessment				
Never exposed	88	193	1.0	
Ever exposed	85	155	1.2	0.8–1.9
Agricultural chemicals				
Self-report				
Never exposed	138	300	1.0	
Ever exposed	33	48	1.6	1.0–2.7
Panel assessment				
Never exposed	149	320	1.0	
Ever exposed	24	28	2.0	1.1–3.5
Men (95 sets)				
Metals				
Self-report				
Never exposed	31	73	1.0	
Ever exposed	63	117	1.2	0.7–2.1
Panel assessment				
Never exposed	49	123	1.0	
Ever exposed	45	67	1.5	0.9–2.6
Solvents				
Self-report				
Never exposed	21	50	1.0	
Ever exposed	73	140	1.1	0.6–2.1
Panel assessment				
Never exposed	28	70	1.0	
Ever exposed	66	120	1.3	0.7–2.3
Agricultural chemicals				
Self-report				
Never exposed	66	155	1.0	
Ever exposed	28	35	2.1	1.1–3.8
Panel assessment				
Never exposed	73	169	1.0	
Ever exposed	21	21	2.4	1.2–4.8
Women (79 sets)				
Metals				
Self-report				
Never exposed	56	136	1.0	
Ever exposed	21	22	2.3	1.1–4.7
Panel assessment				
Never exposed	75	143	1.0	
Ever exposed	4	15	0.5	0.2–1.4
Solvents				
Self-report				
Never exposed	36	102	1.0	
Ever exposed	41	56	2.4	1.3–4.3
Panel assessment				
Never exposed	60	123	1.0	
Ever exposed	19	35	1.1	0.6–2.2
Agricultural chemicals				
Self-report				
Never exposed	75	145	1.0	
Ever exposed	5	13	0.8	0.3–2.4
Panel assessment				
Never exposed	76	151	1.0	
Ever exposed	3	7	0.9	0.2–3.8

* OR, odds ratio; CI, confidence interval.

† Results of conditional logistic regression analysis, adjusted for age and education. Data are based on self-report and on assessment by a panel of industrial hygienists for exposures occurring from age 15 years to 10 years prior to the case's date of diagnosis. Data were missing for three cases based on self-report (one male and two females) and for one case based on the panel's assessment (one male).

There was a slight increase in relative risk 15–20 years prior to the reference date for solvent exposure, based on the panel's assessment of men and women (figure 1, middle section). Increased odds ratios were not observed with respect to age or calendar year (figures 2 and 3).

Agricultural chemicals

Based on self-report, agricultural chemicals were associated with ALS (table 2), especially in men (OR = 2.1, 95 percent CI 1.1–3.8), but not in women (OR = 0.8, 95 percent CI 0.3–2.4), with a dose-response trend (p = 0.02). Comparing low exposure with no exposure to agricultural chemicals in men, the odds ratio was 1.5 (95 percent CI 0.6–4.1), and for high exposure, the odds ratio was 2.7 (95 percent CI 1.3–5.7). Exposure to specific agricultural chemicals was not strongly associated with increased risk of ALS (table 3).

Based on the panel's assessment, exposure to agricultural chemicals was associated with ALS (tables 2 and 4). As with the self-report data, the association of agricultural chemicals with ALS was largely confined to men (OR = 2.4, 95 percent CI 1.2–4.8) and was not seen in women (OR = 0.9, 95 percent CI 0.2–3.8). Information was obtained on specific agricultural chemicals—fertilizers and pesticides. "Pesticides" included herbicides, fungicides, insecticides, and other pesticides (table 3). Both fertilizer and herbicide use showed a slight association with disease status, but with additional analyses, neither demonstrated a significant increase in relative risk with increasing exposure. In analyses confined to men, an exposure-response trend was observed for agricultural chemicals (table 4). The associations with ALS were statistically significant for pesticide use in men, specifically for

TABLE 3. Risk of amyotrophic lateral sclerosis according to various occupational exposures in both sexes combined, western Washington State, 1990–1994

Ever exposure*	No. of cases (n = 174)	No. of controls (n = 348)	OR†,‡	95% CI†
Metals				
Aluminum				
Self-report	39	64	1.3	0.8–2.1
Panel assessment	8	12	1.2	0.5–2.9
Cadmium				
Self-report	5	8	1.2	0.4–3.6
Panel assessment	2	2	2.0	0.3–14.4
Chromium				
Self-report	12	9	2.5	1.0–6.7
Panel assessment	0	2		
Lead				
Self-report	21	24	1.9	1.0–3.6
Panel assessment	17	31	1.1	0.6–2.1
Lead-content paint				
Self-report	34	53	1.3	0.8–2.1
Panel assessment	11	16	1.3	0.6–3.1
Manganese				
Self-report	7	10	1.2	0.4–3.5
Panel assessment	2	1	4.7	0.4–53.3
Mercury				
Self-report	5	12	0.9	0.3–2.5
Panel assessment	1	4	0.5	0.1–4.5
Metal dust or fumes				
Self-report	38	72	1.0	0.6–1.6
Panel assessment	20	34	1.1	0.6–2.0
Welding dust or fumes				
Self-report	35	58	1.2	0.7–2.0
Panel assessment	11	23	0.8	0.4–1.8
Other metals				
Self-report	12	17	1.5	0.7–3.5
Panel assessment	5	6	1.7	0.5–5.7
Solvents				
Adhesives, glues, or coatings				
Self-report	40	75	1.1	0.7–1.7
Panel assessment	18	24	1.4	0.7–2.6
Alcohols or ketones				
Self-report	33	65	1.1	0.6–1.8
Panel assessment	21	26	2.0	1.0–4.0
Benzene, toluene, or xylene				
Self-report	16	36	1.0	0.5–1.9
Panel assessment	26	32	1.7	0.9–3.0
Cutting or lubricating oils				
Self-report	37	71	1.0	0.6–1.7
Panel assessment	44	77	1.2	0.7–2.1
Cleaning solvents or degreasers				
Self-report	69	99	1.8	1.2–2.8
Panel assessment	43	60	1.9	1.1–3.3
Leaded gasoline fumes				
Self-report	39	53	1.8	1.1–3.0
Panel assessment	28	45	1.5	0.8–2.6
Machine fuels				
Self-report	30	44	1.5	0.9–2.5
Panel assessment	12	30	0.7	0.3–1.5
Solvents (continued)				
Paint, varnish, or stain				
Self-report	31	52	1.2	0.7–1.9
Panel assessment	23	37	1.2	0.7–2.2
Phenols				
Self-report	4	11	0.8	0.2–2.5
Panel assessment	2	3	1.2	0.2–7.2
Plastic fumes or resins				
Self-report	13	32	0.8	0.4–1.6
Panel assessment	8	10	1.5	0.6–4.2
Solvent-based inks or dyes				
Self-report	16	24	1.4	0.7–2.9
Panel assessment	5	20	0.5	0.2–1.3
Styrene				
Self-report	7	5	2.6	0.8–8.3
Panel assessment	21	2	1.1	0.1–12.5
Other solvents				
Self-report	5	5	2.2	0.6–7.5
Panel assessment	3	12	0.5	0.1–1.8
Agricultural chemicals				
Fertilizers				
Self-report	19	30	1.4	0.7–2.6
Panel assessment	12	12	2.3	1.0–5.5
Pesticides				
Fungicides	10	14	1.7	0.7–4.2
Self-report	4	0		
Panel assessment				
Herbicides	11	15	1.7	0.7–3.9
Self-report	7	5	3.0	0.9–9.6
Panel assessment				
Insecticides	15	33	1.0	0.5–1.8
Self-report	18	18	2.1	1.1–4.1
Panel assessment				
Other pesticides	1	1	1.5	0.1–25.6
Self-report	1	5	0.3	0.0–3.0
Panel assessment				

* Reference category, never exposed.
† OR, odds ratio; CI, confidence interval.
‡ Results of conditional logistic regression analysis, adjusted for age and education. Data are based on self-report and on assessment by a panel of industrial hygienists for exposures occurring from age 15 years to 10 years prior to the case's date of diagnosis. Data were missing for three cases based on self-report (one male and two females) and for one case based on the panel's assessment (one male).

insecticide use, with a trend test giving a significant result (table 4).

When the 10-year moving-window analysis was performed on the panel's assessment of exposure for men and women combined, the relative risk of ALS was slightly increased for exposure to agricultural chemicals beginning 15–20 years prior to the reference date (figure 1, bottom section). When this same analysis was performed on the data from age 15 to age 55 (figure 2), the odds ratios peaked at 22 years of age, representing the 10-year window from age 22 to age 32. With the calendar year analysis (figure 3), the odds ratio for ALS was slightly increased for exposure to agricultural chemicals from 1950 to 1965.

The data were examined in a manner that considered occupational exposure information based on self-

TABLE 4. Risk of amyotrophic lateral sclerosis according to exposure to agricultural chemicals in men, based on the assessment of a panel of industrial hygienists, western Washington State, 1990–1994

Exposure	No. of cases (n = 95)	No. of controls (n = 190)	OR*,†	95% CI*	Trend test (p value)‡
Agricultural chemicals					
Never exposed	73	169	1.0		
Low exposure	4	8	1.5	0.4–5.3	
High exposure	17	13	2.8	1.3–6.1	
Ever exposed	21	21	2.4	1.2–4.8	0.03
Fertilizers					
Never exposed	85	180	1.0		
Low exposure	3	5	1.8	0.4–8.3	
High exposure	6	5	2.5	0.7–8.6	
Ever exposed	9	10	2.2	0.8–6.1	0.11
Any pesticide					
Never exposed	75	174	1.0		
Low exposure	6	8	1.6	0.5–5.0	
High exposure	13	8	3.3	1.3–8.4	
Ever exposed	19	16	2.5	1.2–5.1	0.02
Insecticides					
Never exposed	78	176	1.0		
Low exposure	4	5	2.0	0.5–7.7	
High exposure	12	9	2.8	1.1–6.8	
Ever exposed	16	14	2.5	1.2–5.3	0.05
Herbicides					
Never exposed	89	186	1.0		
Ever exposed	5	4	2.7	0.7–10.7	
Fungicides					
Never exposed	90	190	1.0		
Ever exposed	4	0			
Other pesticides					
Never exposed	93	188	1.0		
Ever exposed	1	2	0.7	0.0–13.4	

* OR, odds ratio; CI, confidence interval.

† Results of conditional logistic regression analysis, adjusted for age and education. Data are based on assessment by a panel of industrial hygienists for exposures occurring from age 15 years to 10 years prior to the case's date of diagnosis. Data were missing for one case.

‡ Test for trend of never exposure, low exposure, and high exposure.

report only, the panel's assessment only, and the concordance between the two methods (table 5). The association between agricultural chemicals and ALS was strongest for men when both the panel assessment and self-report indicated that exposure had occurred.

The agricultural chemical data were also analyzed by duration of exposure 10 or more years prior to the reference date. Comparing less than 3 years of exposure to agricultural chemicals with no exposure, the odds ratio in men was 1.2 (95 percent CI 0.3–4.1). For greater than 3 years of exposure to agricultural chemicals, the odds ratio was 2.7 (95 percent CI 1.3–5.5) (p for trend = 0.03).

Excess exposure to any type of agricultural chemical due to an accident or spill, based on self-report, was associated with ALS for men and women combined (OR = 4.4, 95 percent CI 1.1–17.7); however, the number of individuals exposed was small (six cases and three controls). We found weaker associations with accidents involving metals (OR = 2.2, 95 percent CI 0.6–7.7) or solvents (OR = 1.3, 95 percent CI 0.7–2.7).

Among hobbies, adding fertilizers to the lawn or garden showed a slight increase in risk among women only (OR = 1.8, 95 percent CI 1.01–3.1), not among men (OR = 1.2, 95 percent CI 0.6–2.3), with no significant dose-response trend. Adding weed killers or insecticides to the lawn was not associated with ALS in men, in women, or in the combined group (OR = 1.2, 95 percent CI 0.8–1.7).

The associations between exposure to agricultural chemicals at home, in the workplace, and in both settings were examined from age 15 years to the reference date. Each level of exposure was compared

TABLE 5. Risk of amyotrophic lateral sclerosis according to various occupational exposures based on self-report, assessment by a panel of industrial hygienists, or both, western Washington State, 1990–1994

Exposure	No. of cases	No. of controls	OR*,†	95% CI*
Metals				
Men and women (174 sets)				
Neither self-report nor panel	81	198	1.0	
Self-report only	41	68	1.6	1.0–2.7
Panel assessment only	6	11	1.4	0.5–4.1
Self-report and panel	43	71	1.6	0.9–2.7
Solvents				
Men and women (174 sets)				
Neither self-report nor panel	43	128	1.0	
Self-report only	43	65	2.0	1.1–3.3
Panel assessment only	14	24	1.6	0.7–3.6
Self-report and panel	71	131	1.7	1.0–3.0
Agricultural chemicals				
Men and women (174 sets)				
Neither self-report nor panel	130	289	1.0	
Self-report only	17	31	1.3	0.6–2.5
Panel assessment only	8	11	1.6	0.6–4.4
Self-report and panel	16	17	2.2	1.1–4.6
Men only (95 sets)				
Neither self-report nor panel	59	146	1.0	
Self-report only	14	23	1.6	0.7–3.5
Panel assessment only	7	9	1.9	0.6–5.9
Self-report and panel	14	12	3.0	1.3–7.0
Fertilizers				
Men and women (174 sets)				
Neither self-report nor panel	147	311	1.0	
Self-report only	12	25	1.0	0.5–2.1
Panel assessment only	5	7	1.5	0.5–4.8
Self-report and panel	7	5	3.7	1.1–13.2
Men only (95 sets)				
Neither self-report nor panel	74	162	1.0	
Self-report only	11	18	1.3	0.5–3.0
Panel assessment only	2	6	0.7	0.1–3.9
Self-report and panel	7	4	5.3	1.3–22.4
Pesticides				
Men and women (174 sets)				
Neither self-report nor panel	137	300	1.0	
Self-report only	12	26	1.1	0.5–2.3
Panel assessment only	8	10	1.7	0.6–4.4
Self-report and panel	14	12	2.5	1.1–5.7
Men only (95 sets)				
Neither self-report nor panel	66	156	1.0	
Self-report only	9	18	1.3	0.5–3.2
Panel assessment only	7	8	1.8	0.6–5.4
Self-report and panel	12	8	3.3	1.3–8.4

* OR, odds ratio; CI, confidence interval.

† Results of conditional logistic regression analysis, adjusted for age and education. Data were missing for three cases based on self-report and for one case based on the industrial hygiene panel's assessment.

with no exposure to agricultural chemicals (table 6). The greatest relative risk was associated with exposure to agricultural chemicals in both the workplace and the home combined. We examined the data for a linear trend, assuming that there would be less exposure to agricultural chemicals in the home than in the workplace. The test for trend gave a marginally significant result for men and women and for men only. Restrict-

TABLE 6. Risk of amyotrophic lateral sclerosis according to exposure to agricultural chemicals in the workplace (based on assessment by a panel of industrial hygienists) and in the home (based on self-report), western Washington State, 1990–1994

Exposure	No. of cases	No. of controls	OR*,†	95% CI*	Trend test (*p* value)
Agricultural chemicals					
Men and women (174 sets)					
Never exposed	56	136	1.0		
Home exposure	93	183	1.4	0.9–2.1	
Workplace exposure	6	12	1.2	0.4–3.7	
Home and workplace exposure	19	17	3.5	1.6–7.8	0.04
Men only (95 sets)					
Never exposed	22	52	1.0		
Home exposure	51	116	1.2	0.6–2.2	
Workplace exposure	5	8	1.2	0.3–4.3	
Home and workplace exposure	17	14	3.8	1.4–10.1	0.06
Fertilizers					
Men and women (174 sets)					
Never exposed	68	166	1.0		
Home exposure	93	169	1.5	1.0–2.2	
Workplace exposure	5	5	1.9	0.5–7.5	
Home and workplace exposure	8	8	3.6	1.2–10.8	0.09
Men only (95 sets)					
Never exposed	28	63	1.0		
Home exposure	57	116	1.2	0.7–2.2	
Workplace exposure	3	5	1.2	0.3–5.5	
Home and workplace exposure	7	6	3.8	0.9–15.5	0.10
Pesticides‡					
Men and women (174 sets)					
Never exposed	69	156	1.0		
Home exposure	84	172	1.2	0.8–1.8	
Workplace exposure	6	9	2.2	0.8–6.0	
Home and workplace exposure	12	11	2.8	1.2–6.7	0.09
Men only (95 sets)					
Never exposed	28	65	1.0		
Home exposure	49	109	1.1	0.6–2.0	
Workplace exposure	7	6	2.2	0.6–7.4	
Home and workplace exposure	11	10	2.9	1.1–7.9	0.10

* OR, odds ratio; CI, confidence interval.
† Results of conditional logistic regression analysis, adjusted for age and education.
‡ Includes herbicides and insecticides only.

ing the analysis to pesticide use in the workplace and the home produced a similar result (table 6).

DISCUSSION

Among reported associations of ALS with environmental agents, a relation with lead exposure has received the most attention. However, the findings have been conflicting (4–6, 9, 31–37). Since toxic lead levels produce symptoms similar to those of motor neuron disease, this association has biologic plausibility. Two recent case-control studies reported a fivefold increase in risk for ALS among men exposed to lead (4–5), although the body burden of lead has not been found to be consistently elevated at the time of diagnosis (38, 39). In our study, the associations suggested by self-report were not confirmed when exposure to lead was assessed by the industrial hygienists. This discrepancy suggests that either cases may overreport exposures to lead or the information on job tasks that was supplied to the panel was insufficient to identify real exposures.

Several studies have reported an association between ALS and exposure to solvents (5, 14, 34, 40), whereas other studies have not (13, 32, 41, 42). A recent twin study indicated that petroleum products and solvent-based chemicals, such as paint, were risk factors for ALS (40). On the basis of the panel's assessment, we saw no effect of overall exposure to

solvents. Our study did suggest associations between ALS and exposure to alcohol and ketones and to cleaning solvents and degreasers; however, the data did not show an increased risk with higher levels of exposure.

The most noteworthy finding of our study was an association with agricultural chemicals in men, specifically insecticides. The lack of an association in women may have been due to a lack of power to detect an association because of small numbers of exposed subjects. Two studies have suggested a twofold increase in relative risk between ALS and exposure to pesticides (32, 42), although the associations were not statistically significant. Two other studies did not show an association (5, 13). These studies relied solely on self-report of occupational exposures.

Agricultural chemicals were suspected of playing a role when three professional football players who had played for the same team in the 1960s were all diagnosed with ALS in the 1980s (43). Several studies have observed an increased risk of ALS among farmers (12–17). In another report, two men from Brazil who mixed and sprayed farming areas with organochlorine insecticides subsequently developed ALS (44). Organochlorine insecticides are considered central nervous system toxicants whose mechanism of action is not completely known (45, 46).

Pall et al. (47) reported on a patient with ALS who was exposed to toxic levels of an insecticide containing chlordane, an organochlorine, and pyrethrin. Steventon et al. (48, 49) reported that ALS patients have a defect in sulfur oxidation and consequently sulfate conjugation, which is required for the metabolism and elimination of pyrethrins (50, 51). Other researchers have been unable to confirm these findings (51). Pyrethrins are natural insecticides derived from certain species of chrysanthemums (50), and they were introduced into Europe in the 19th century (52), before Aran's description of motor neuron disease in 1850 (1).

We were unable to find evidence for acute effects of agricultural chemicals. Instead, risk of ALS was elevated 15–25 years prior to the reference date. When we analyzed the agricultural chemical data from age 15 to age 55, the highest risk occurred for the decade from age 22 to age 32. These findings support the abiotrophic theory that injury to the motor neuron by a neurotoxicant may occur many years prior to the diagnosis of ALS (53).

This study had several strengths and limitations. Cases and controls were identified in a defined geographic population, thus avoiding the potential weaknesses of clinic or hospital-based studies. Only newly diagnosed cases of ALS were included in the study. Six cases refused to participate, but they are unlikely to have exerted a major influence on the results. A similar concern regarding control subjects is not so easily dismissed. Approximately one third of the control subjects identified through random-digit dialing and the Health Care Financing Administration refused to participate. Since controls were more likely than cases to have some college education, the controls may have been less likely to have worked in occupations with the exposures of interest. However, we included education as a covariate in the logistic regression models in an attempt to adjust for this difference. In a study from Upstate New York that compared information from control subjects identified by random-digit dialing with that obtained from subjects identified by a privately conducted census (54), the control subjects identified by random-digit dialing were found to be better educated than the general population, but the authors did not find major differences with regard to specific occupations, such as farming, construction work, and machine operation.

In the absence of direct measurements of exposure, the use of an industrial hygienist or a panel of industrial hygienists is considered the most accurate method for assessing past chemical exposures in population-based studies (55, 56). Unlike self-reported exposure information, assignment of exposure level by a panel is not influenced by disease status, since the panel is blinded to the subject's case/control status and to the subject's self-reported exposure information. Misclassification bias may be reduced when two methods are used to assess exposure (57). In our study, the associations for agricultural chemicals were strongest when the panel and the subject independently indicated that the exposure had occurred. However, the panel's rating of exposure was dependent on self-reported job descriptions. If cases gave more extensive job descriptions than controls, this could have influenced the panel's assessment of a person's exposure. The absence of strong associations with lead or mercury, for which well-known hypotheses exist, gives some assurance that overreporting by cases was not a major source of bias in exposure assessment.

The unexpected finding of an association between agricultural chemical use and ALS in this population-based case-control study needs to be explored further. The association was found in men only and mainly for pesticides, specifically insecticides, although the number of exposed subjects was small. These results should be considered exploratory, not confirmatory. Future studies should obtain more detailed information on types of insecticides used and should attempt to address the issue of genetic susceptibility.

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