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Assessment of ALS mortality in a cohort of formaldehyde-exposed garment workers

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Introduction

The etiology of ALS is unknown. Although some investigators have evaluated the role of occupational exposures (1), their role is poorly understood.

Among subjects with known exposure duration in the American Cancer Society's Cancer Prevention Study II cohort (~1 million subjects), the ALS mortality rate was more than two times higher for subjects with self-reported formaldehyde exposure, compared to unexposed subjects (rate ratio 2.47, 95% confidence interval (CI) 1.58–3.86, 1120 unexposed and 22 exposed cases), and strongly associated with exposure duration (2). Compared to unexposed subjects, the rate ratios were 1.5, 2.1, and 4.1 for subjects with <4, 4–10, and >10 years of self-reported formaldehyde exposure, respectively. In contrast, formaldehyde exposure (inferred from occupation) was not associated with ALS in a small case-control study (109 cases, 253 controls) by Fang et al. (1). In this study, no association was observed with weighted exposure duration although an imprecise three-fold increase of ALS, based on four cases, was observed among a subgroup of the highest exposure tertile.

We evaluated ALS mortality among a cohort of formaldehyde-exposed garment workers (3–5).

Materials and methods

The cohort included 11,098 employees who were exposed to formaldehyde-treated fabric for at least three months at any of three garment manufacturing facilities (late 1950s through the early 1980s). In the early 1980s, formaldehyde levels were similar across departments and facilities (overall geometric mean concentration 0.15 ppm, geometric standard deviation 1.90) (3). Although historical data were not available, formaldehyde levels were believed to have decreased over time due to improvements to resins used to treat permanent press fabrics.

Year of first exposure and exposure duration were used as exposure surrogates. Exposure duration was calculated as the duration of employment after formaldehyde was introduced into the process, but was underestimated for 1226 cohort members actively employed when the records were obtained, because the date these cohort members were last employed is unknown.

Vital status was ascertained through 2008 (5). ALS was defined as International Classification of Diseases (ICD)-10 code G12.2, ICD-9 code 335.2, ICD-8 code 348.0, and ICD-7 code 356.1.

Mortality was analyzed using a life-table analysis program, LTAS.NET (6). US population ALS mortality rates (beginning on 1 January 1960) were created from National Center for Health Statistics mortality data and US census population estimates. Cohort members with a missing birth date ($n=55$) or who died ($n=8$) or were lost to follow-up ($n=13$) prior to the rate file start date were excluded from all analyses. Person-years at risk (PYAR) began at the later of the rate file start date or the completion date of the three-month eligibility period, and ended at the earliest of the date of death for deceased cohort members, the study end-date (31 December 2008) for living cohort members, or the date last observed for persons lost to follow-up. The PYAR were stratified into five-year intervals by age and calendar time and multiplied by the appropriate gender and race-specific mortality rates to calculate the expected number of ALS deaths. The ratio of the observed to the total expected number of deaths was expressed

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as the standardized mortality ratio (SMR), and 95% CIs were calculated assuming that the number of observed deaths follows a Poisson distribution. SMRs were stratified, using cut-points retained from previous studies of the cohort, by year of first exposure, exposure duration, and time since first exposure.

The study was approved by the National Institute for Occupational Safety and Health Institutional Review Board.

Results

The study included 11,022 workers contributing 414,313 PYAR. Workers were predominantly white (76%) and female (82%) (Table I). Forty-two percent of the cohort was first exposed before 1963, when formaldehyde levels were thought to be highest. The median exposure duration was 3.3 years and median time since first exposure was 39.4 years.

There were eight ALS deaths based on underlying cause of death (Table II); no additional ALS deaths were identified from contributing causes listed on the death certificate. All eight ALS deaths occurred among females. ALS mortality was not elevated compared to the US population, and there was not a clear pattern in risk when SMRs were stratified by year of first exposure, exposure duration, or time since first exposure.

Discussion

In contrast to Weisskopf et al. (2), we found no evidence of an association between ALS and formaldehyde exposure. Fang et al. (1) also found little evidence for such an association.

Occupational exposure for former employees in our study was known. The main limitation of the study of the Cancer Prevention Study II cohort by Weisskopf et al. was the reliance on self-reported exposure (2). They also had no information about the frequency and intensity of exposure or about exposure after 1982, when the self-reported data were collected. Another strength of our study is cohort members' lack of occupational exposure to other chemicals and metals that might be associated with ALS (3).

The main limitation of our study is the small number of ALS cases. This precluded internal analyses to evaluate exposure-response relations using the exposure surrogates. The study by Weisskopf et al. (2) was much larger and thus had greater power to detect an association. They also had data on smoking, an accepted risk factor for ALS (7). We had no data on smoking. However, mortality from lung cancer and chronic obstructive pulmonary disease in the cohort (5) suggests that smoking in the overall cohort was similar to or greater than that in the general population. Thus, differences in smoking between the cohort and general population may have biased the overall SMR for ALS away from the null, but were unlikely to have biased it towards the null.

Both our study and the study by Weisskopf et al. relied on mortality data to identify cases of ALS. Mortality is a good surrogate of ALS incidence since ALS is fatal with a median survival of approximately three years (8), and death certificate accuracy is reasonable for identifying ALS deaths (9,10). ICD-9 and ICD-10 codes used to identify ALS, however, are for motor neuron disease and not specific for ALS. The sensitivity and positive predictive value of ICD-10 code G12.2 for ALS are 85% and 65%, respectively (11). In the current study, all eight deaths mapped to the ALS death category were

Table I. Characteristics of the study population.

Characteristic	No.	%
Excluded from analysis*	76	1
Number of workers	11,022	100
Race/gender		
White male	1609	14.6
Non-white male	404	3.7
White female	6724	61.0
Non-white female	2285	20.7
Vital status (as of 12/31/2008)		
Alive	7004	63.5
Dead†	3907	35.4
Lost to follow-up	111	1.0
Year of first exposure		
<1963	4651	42.2
1963–1970	3813	34.6
1971 or later	2558	23.2
Time since first exposure		
<10 years	281	2.5
10–19 years	393	3.6
20+ years	10,348	93.9
Duration of exposure		
<3 years	5275	47.9
3–9 years	3138	28.5
10+ years	2609	23.7

*Cohort members were excluded when date of birth was missing ($n = 55$), date of death was prior to 1960 ($n = 8$), or when date lost to follow-up was prior to 1960 ($n = 13$).
†Deaths from 1960 to 2008.

Table II. Mortality from ALS overall and by year of first exposure, duration of exposure, and time since first exposure among garment workers, 1960–2008.

	Obs	SMR (95% CI)
Overall	8	0.89 (0.38, 1.75)
Year of first exposure		
Prior to 1963	5	0.84 (0.27, 1.96)
1963–1970	3	1.29 (0.27, 3.78)
1971 or later	0	0.00 (0.00, 4.92)
Duration of exposure		
<3 years	2	0.61 (0.07, 2.21)
3–9 years	3	1.17 (0.24, 3.41)
10+ years	3	0.94 (0.19, 2.75)
Time since first exposure		
<10 years	1	3.50 (0.09, 19.52)
10–19 years	0	0.00 (0.00, 4.19)
20+ years	7	0.89 (0.36, 1.83)

OBS: observed number of ALS deaths based on underlying cause; SMR: standardized mortality ratio (US referent rates); CI: confidence interval.

specifically due to ALS, according to the death certificates.

Other limitations of our study include the lack of quantitative exposure data and the relatively low levels of formaldehyde measured in the workplace in the early 1980s. Exposure levels were believed to be much higher in earlier years, but the actual level of exposure in the 1960s and 1970s is unknown.

Most cohort members were females, and ALS is more common in males, but our comparisons were adjusted for gender. Further, the gender difference in ALS may be due to differing neurotoxicant exposures (12).

In conclusion, the results of our study do not suggest that ALS is associated with formaldehyde exposure. However, due to the small number of deaths and the low levels of exposure by the early 1980s, an association cannot be ruled out. At least 12 other cohorts of formaldehyde-exposed workers exist (13,14). Examining ALS mortality in the larger cohorts and pooling data from several cohorts might be helpful in elucidating whether formaldehyde exposure is associated with ALS.

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