LETTERS

Job-related formaldehyde exposure and ALS mortality in the USA

Animal models and in vitro experiments suggest neurotoxic effects of formaldehyde that may be relevant for amyotrophic lateral sclerosis (ALS). Formaldehyde induces neuronal τ protein misfolding and aggregation, leading to neuronal apoptosis. Formaldehyde also increases mitochondrial membrane permeability and causes oxidative damage partly by reducing superoxide dismutase activity, mechanisms implicated in ALS.

Studies have had mixed findings regarding formaldehyde exposure and ALS mortality. A large prospective study found an elevated risk that did not quite reach statistical significance, but found a strong dose–response relationship with total years of exposure.[1] Two studies found no significant association,[1 2] although one found a suggestion of elevated risk among the very highly exposed.[2] We examine here the association of ALS mortality with job-related formaldehyde exposure in the National Longitudinal Mortality Study (NLMS), a US-representative cohort with occupation data collected prospectively.

METHODS

The NLMS is a multistage probability sample of the civilian non-institutionalised population (response rate ~96%). We included the 794 541 men and 674 694 women who were at ages 25+ when surveyed. Participants were asked about their current or most recent job. We used a formaldehyde exposure matrix constructed by industrial hygienists at the National Cancer Institute and previously described.[3] Intensity and probability of formaldehyde exposure were calculated for each occupation and industry, and coded as none, low, medium or high.[3] Intensity reflected the frequency and level of formaldehyde exposure; probability reflected the likelihood of any formaldehyde exposure.

NLMS records were matched to the National Death Index (NDI, 1979–2011) to obtain cause of death. ALS deaths were defined as International Classification of Diseases Ninth and 10th Edition (ICD)-9 335.2 or ICD-10 G12.2 as the underlying or contributing cause. Data were handled and analyses conducted as in prior publications (M G Weisskopf *et al*. Military service and ALS in a population-based cohort; Submitted). Briefly, we estimated HRs using survival analyses with age as the time metameter, adjusted for education, race/ethnicity and income. Participants contributed follow-up time from the time of their survey until time of death or last date of National Death Index (NDI) linkage. We calculated HRs separately for each probability and intensity level, using persons with no exposure as the reference group, separately by sex. We then calculated HRs for each intensity level using the same reference group, and restricting exposed respondents to those with high probability of exposure.

We conducted five sensitivity analyses. As ALS cases are less reliably diagnosed in persons >75 years, we restricted follow-up to age 75. We next conducted four analyses with exclusions that may have improved exposure ascertainment. First, as ALS symptoms may have affected employment, we excluded the first 5 years of follow-up. Second, as the occupation and industry of younger persons is less stable than older persons, we restricted analyses to persons at ages 35–75 at enrolment and ages 50–75 at enrolment. Third, estimated job-related formaldehyde exposure may be less accurate for persons unemployed versus employed at enrolment. We, therefore, restricted the analysis to persons employed at the time of the survey. Additionally, we further adjusted for military service and smoking in the subsample of this data.

RESULTS

Participants exposed versus unexposed to formaldehyde were slightly poorer, less educated, and less frequently non-Hispanic White (see online supplementary eTable S1). High probability of formaldehyde exposure versus no exposure predicted an almost three times higher rate of ALS mortality in men (table 1). Among women, few had high-exposure-probability jobs and there were no ALS deaths in this category; so the HR was inestimable (see online supplementary eTable S2). Intensity of formaldehyde exposure was less strongly associated with ALS (table 1). High-probability, high-intensity exposure was associated in men with increased rate of ALS mortality (HR=4.43, 95% CI 1.16 to 16.85, $p<0.05$), although there were only two ALS deaths among these highly exposed men. Results were robust to further adjustment for military service and smoking. All men with high-probability, high-intensity exposure were funeral directors. Among men, all sensitivity analyses resulted in higher HR estimates than the main analysis (table 1).

DISCUSSION

Men in jobs with high probability of exposure versus no formaldehyde exposure had almost three times greater rate of ALS mortality. We did not find increased risk of ALS in women associated with formaldehyde exposure. Only 99 women in our sample reported jobs with high-probability, high-intensity formaldehyde exposure; thus, our sample of exposed women may have been too small to detect a possible increased risk of ALS. Moreover, all men (N=493) and all but one woman (99%, N=98) in our study in jobs with high-probability high-intensity formaldehyde exposure were funeral directors. In the USA, female versus male funeral directors are more likely to interact with bereaved clients and less likely to perform embalming, where exposure to formaldehyde occurs. Thus, formaldehyde exposure may vary by sex in this profession.

Two prior studies found no association of ALS with job-related formaldehyde exposure. A study of garment workers (geometric mean formaldehyde exposure=0.15 ppm) found no elevated ALS mortality compared with the general population.[4] As garment work does not involve high-probability or high-intensity exposure, these results may not be inconsistent with ours. Funeral directors experience high-intensity and high-probability formaldehyde exposure, with exposure ranging from 0.15 to 9.2 ppm during embalming.[5 6] Additionally, formaldehyde is absorbed through the skin during embalming (at 49.2 mg/h).[6] A second study found no overall association between estimated occupational formaldehyde exposure and ALS. However, in the small subset of participants with the highest exposure to formaldehyde (>60 000 h, N=4 cases, N=4 controls), a large, non-statistically-significant odds for ALS was found (OR=3.0, 95% CI 0.7 to 12.9).

Our results should be interpreted cautiously. Jobs involving both high probability and high intensity of formaldehyde are relatively uncommon in the USA, and ALS is also rare; there were only two ALS deaths among men in such jobs. Moreover, we did not find a dose–response association between formaldehyde exposure and ALS. Formaldehyde exposure was estimated from a single report at enrolment. This single job report likely did not accurately capture lifetime exposure. As non-differential error in exposure classification typically leads to attenuation of the true association of exposure with disease, our estimated HRs could have been attenuated and any trend obscured.

In addition to formaldehyde, funeral directors are exposed to other chemicals used in embalming, as well as to viral, bacterial and prion pathogens. Thus, further study of the association of ALS with high

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Table 1 Adjusted HRs* and 95% CIs for ALS mortality by level of occupational formaldehyde exposure, National Longitudinal Mortality Study, men ages 25 years and older, 1973–2011

	Respondents	Person-years	ALS deaths	HR (95% CI)*
Intensity				
Unexposed	607 416	9 815 195	372	1.0 (Reference)
Low	97 301	1 641 068	55	0.99 (0.74 to 1.30)
Medium	86 766	1 427 789	43	0.63 (0.44 to 0.90)
High	3058	46 188	2	1.53 (0.40 to 5.80)
Intensity, exposed restricted to probability=high				
Unexposed	607 416	9 815 195	372	1.0 (Reference)
Low	0	0	0	–
Medium	361	6954	0	–
High	493	8539	2	4.43 (1.16 to 16.85)
Probability				
Unexposed	607 416	9 815 195	372	1.0 (Reference)
Low	98 228	1 681 862	51	0.85 (0.63 to 1.15)
Medium	88 043	1 417 659	47	0.76 (0.54 to 1.06)
High	854	15 493	2	2.98 (0.78 to 11.30)
Probability, excluding first 5 years of follow-up				
Unexposed	492 489	9 501 370	331	1.0 (Reference)
Low	82 155	1 637 260	47	0.87 (0.64 to 1.18)
Medium	71 598	1 372 603	39	0.77 (0.54 to 1.10)
High	758	15 230	2	3.49 (0.92 to 13.26)
Probability, follow-up to age 75 only				
Unexposed	604 116	9 794 521	332	1.0 (Reference)
Low	97 959	1 680 822	41	0.79 (0.57 to 1.11)
Medium	86 760	1 407 671	40	0.66 (0.44 to 0.99)
High	832	15 315	2	4.13 (1.09 to 15.69)
Probability, respondents 35≤age≤75 at enrolment				
Unexposed	427 530	6 493 151	332	1.0 (Reference)
Low	65 736	1 046 575	47	0.91 (0.67 to 1.24)
Medium	60 675	921 096	43	0.79 (0.56 to 1.12)
High	568	9731	2	3.41 (0.89 to 13.01)
Probability, respondents 50≤age≤75 at enrolment				
Unexposed	175 376	2 441 370	197	1.0 (Reference)
Low	25 611	377 534	31	1.00 (0.67 to 1.49)
Medium	27 247	393 151	27	0.75 (0.47 to 1.19)
High	270	4125	2	4.76 (1.16 to 19.49)
Probability, respondents employed at enrolment				
Unexposed	548 645	8 876 712	331	1.0 (Reference)
Low	85 041	1 459 452	45	0.88 (0.65 to 1.21)
Medium	76 249	1 238 082	38	0.71 (0.50 to 1.03)
High	770	14 063	2	3.26 (0.86 to 12.38)

*Adjusted for race/ethnicity, education and household income as a percentage of the poverty line.
ALS, amyotrophic lateral sclerosis.

levels of formaldehyde exposure and among funeral directors is warranted.

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Funeral directors may be at heightened risk of progressive neurodegenerative disease

Link with amyotrophic lateral sclerosis (ALS) may be formaldehyde in embalming fluid

Funeral directors, who prepare bodies for burial, may be at heightened risk of the neurodegenerative disease amyotrophic lateral sclerosis, or ALS for short, as a result of the formaldehyde used in embalming fluid, suggests research published online in the ***Journal of Neurology Neurosurgery & Psychiatry.***

ALS, also known as Lou Gehrig's disease, was the subject of last year's ice bucket challenge. It is progressive, causing muscle weakness, paralysis, and eventually respiratory failure and death. There is no cure for the condition, which is thought to affect 450,000 people worldwide.

Some environmental factors have been mooted as possibly increasing the risk of developing ALS, including formaldehyde.

The researchers therefore looked at the links between death from ALS and occupational exposure to formaldehyde, using the US National Longitudinal Mortality Study (NLMS), involving almost 1.5 million adults.

When they were 25 or older, participants were asked about their current or most recent job. Their exposure to formaldehyde at work was estimated, using criteria developed by industrial hygienists at the National Cancer Institute.

The intensity (frequency and level) and probability (likelihood) of exposure to formaldehyde were calculated for each job and industry sector.

Men in jobs with a high probability of exposure to formaldehyde were around three times as likely to die of ALS as those who had not been exposed to this chemical at all.

But women with a high probability of exposure did not have an increased risk of ALS, possibly because too few had jobs that exposed them to high levels of formaldehyde, making it difficult to calculate risk level, say the researchers.

Men whose intensity and probability of exposure were rated as high were more than four times as likely to die of ALS as those with no exposure, although there were only two ALS deaths in this group.

All the 493 men with high intensity and probability of exposure to formaldehyde were funeral directors as were nearly all the women, none of whom died of ALS.

This gender discrepancy in death rates might be because women funeral directors in the US are more often involved in dealing with bereaved relatives than in embalming, which would limit their exposure to formaldehyde, suggest the researchers.

This is an observational study so no definitive conclusions can be drawn about cause and effect, and the authors caution that jobs involving a high level of exposure to formaldehyde are relatively rare, added to which funeral directors are exposed to other chemicals used in embalming as well as to bacteria, and prions.

But experimental research has linked formaldehyde to nerve damage, increased permeability of the energy powerhouses of cells—mitochondria—and harmful free radical production, all of which are implicated in ALS, they say.

eTable 1. Participant characteristics by occupational formaldehyde exposure status, National Longitudinal Mortality Study, 1973-2011

	Men				Women			
Characteristic	**Exposed**[†]		**Not exposed**		**Exposed**[†]		**Not Exposed**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Race/ethnicity								
White, non-Hispanic	134293	(71.77)	461905	(76.04)	93072	(69.13)	399211	(73.92)
Black, non-Hispanic	14399	(7.69)	45761	(7.53)	17109	(12.71)	54553	(10.10)
Hispanic	26317	(14.06)	59748	(9.84)	13898	(10.32)	51674	(9.57)
Other, non-Hispanic	7835	(4.19)	28596	(4.71)	7700	(5.72)	26055	(4.82)
Missing	4281	(2.29)	11407	(1.88)	2850	(2.12)	8572	(1.59)
Education								
<High School	48129	(25.72)	84776	(13.96)	25109	(18.65)	60005	(11.11)
High School	73406	(39.23)	193842	(31.91)	46998	(34.91)	199930	(37.02)
Some College	34093	(18.22)	138919	(22.87)	35415	(26.31)	133213	(24.67)
College graduate	15610	(8.34)	116438	(19.17)	18399	(13.67)	94300	(17.46)
Postgraduate	15854	(8.47)	73344	(12.07)	8690	(6.45)	52564	(9.73)
Missing	33	(0.02)	98	(0.02)	18	(0.01)	53	(0.01)
Household income as a percentage of the poverty line								
<=200	52538	(28.08)	103650	(17.06)	35519	(26.38)	115021	(21.30)
201-300	38216	(20.42)	107303	(17.67)	26131	(19.41)	97904	(18.13)
301-500	49751	(26.59)	180826	(29.77)	36417	(27.05)	154560	(28.62)
>500	38276	(20.45)	190363	(31.34)	30385	(22.57)	149520	(27.69)
Missing	8344	(4.46)	25275	(4.16)	6177	(4.59)	23060	(4.27)

[†]Potential exposure includes any person with a job exposure intensity>0 or a job exposure probability>0.

eTable 2. Adjusted hazard ratios (HR)[†] and 95% confidence intervals (CI) for ALS mortality by level of occupational formaldehyde exposure, National Longitudinal Mortality Study, women ages 25 years and older, 1973-2011

	Respondents	**Person-years**	**ALS deaths**	**HR (95% CI)[†]**
Probability				
Unexposed	540,065	8,720,055	224	1.0 (Reference)
Low	44,714	845,175	29	1.31 (0.90, 1.93)
Medium	89,340	1,383,436	32	1.02 (0.71, 1.47)
High	575	10,592	0	---
Intensity				
Unexposed	540,065	8,720,055	224	1.0 (Reference)
Low	69,311	1,164,134	33	1.19 (0.83, 1.70)
Medium	62,300	1,024,504	27	1.06 (0.71, 1.59)
High	3,018	50,458	1	1.35 (0.23, 7.97)
Intensity (exposed restricted to probability=high)				
Unexposed	540,065	8,720,055	224	1.0 (Reference)
Low	0	0	0	--
Medium	476	9,382	0	--
High	99	1,210	0	--

[†]Adjusted for race/ethnicity, education, and household income as a percentage of the poverty line.