Original Article

Retrospective Assessment of Occupational Exposures for the GENEVA Study of ALS among Military Veterans

Anila Bello^{1*}, Susan R. Woskie¹, Rebecca Gore¹, Dale P. Sandler²,
Silke Schmidt³ and Freya Kamel²

¹Work Environment Department, University of Massachusetts Lowell, One University Avenue, Lowell, MA 01854, USA; ²Epidemiology Branch, National Institute of Environmental Health Sciences, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709, USA; ³Department of Medicine, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27710, USA

*Author to whom correspondence should be addressed. Tel: +1-978-934-2839; e-mail: anila_bello@uml.edu

Submitted 22 July 2016; revised 14 October 2016; editorial decision 7 November 2016; revised version accepted 2 December 2016.

Abstract

Objective: This paper describes the retrospective exposure assessment conducted to assess occupational exposures for the Genes and Environmental Exposures in Veterans (GENEVA) study, a case-control study investigating the joint contribution of genetics and environmental exposures to the risk of amyotrophic lateral sclerosis (ALS) among military veterans.

Methods: Occupational histories for 1597 study participants collected as part of the GENEVA study were the basis for this retrospective exposure assessment. The data set included 15528 jobs held from 1924 to 2010, representing 4539 unique industry and occupation (I&O) combinations. Three industrial hygiene experts were recruited to independently rate occupational exposures to specific agents previously associated with an increased risk of ALS. Utilizing information on industry, job title, tasks performed, and materials used for each job held, raters assigned exposures associated with each I&O for the 'current time' defined as the period after 1995 (post-1995). The exposure assessment targeted agents identified as potential occupational risk factors for ALS. Experts rated semi-quantitatively exposure intensity in five exposure categories (0–4) for Group A agents (lead, formaldehyde, hydrocarbon solvents, and chlorinated solvents) and qualitatively as yes/no (1/0) exposed for Group B agents (mercury, selenium, arsenic, polychlorinated biphenyls, electromagnetic field, pesticides, and viral agents). Confidence scores (0–3) were reported for every I&O rated based on raters' experience with that industry and/or job. Each I&O was assigned an average exposure score of the raters and an alternative exposure rating was developed for each I&O by excluding low confidence (<2) scores before averaging. Exposure reconstruction for jobs held pre-1995 was done by comparing exposure data extracted from the OSHA Chemical Exposure and Health Database (CEHD) during pre-1995 and post-1995. For agents with limited exposure data in the CEHD, pre-1995 exposures were determined based on raters' judgment.

Results: The proportion of I&O combinations determined to be 'exposed' ranged from 0.1 to 26% across different agents, with the highest values corresponding to hydrocarbon solvents and the lowest to selenium. Industries with the highest proportion of exposed records include manufacturing, utilities, healthcare, and military with non-combat jobs. Analyses for raters' reliability showed the best agreement between the raters when rating exposure to viral agents ($\kappa = 0.67$), hydrocarbon solvents ($\kappa = 0.53$), and lead ($\kappa = 0.50$). The proportion of 'exposed' I&O combinations increased for hydrocarbon solvents, chlorinated solvents, and pesticides when exposure ratings were adjusted by raters' confidence. Compared to post-1995, exposures in the earlier period (pre-1995) were deemed higher or the same for most of the agents and lower for formaldehyde and electromagnetic field exposures.

Conclusions: Our results indicate that using raters' confidence assessment in determining exposure scores increases both the proportion of I&O combinations regarded as exposed and the intensity scores, suggesting raters tend to be conservative in their assessment when they lack detailed knowledge of an industry or job.

Keywords: amyotrophic lateral sclerosis (ALS); exposure ratings; GENEVA (Genes and Environmental Exposures in Veterans) study; industry and occupation; non-combat military jobs; retrospective exposure assessment

Introduction

The Genes and Environmental Exposures in Veterans (GENEVA) study, initiated in 2007, aims to evaluate the joint contribution of genetic susceptibility and environmental exposures to the risk of amyotrophic lateral sclerosis (ALS) among US military veterans (Schmidt *et al.*, 2008). Research suggests that only a small portion of ALS cases (5–10%) can be explained by genetic susceptibility and that environmental factors may play an important role in the onset of disease (Kunst, 2004; Das *et al.*, 2012; Vinceti *et al.*, 2012; Malek *et al.*, 2014). A number of occupational risk factors have been associated with an increased risk of ALS including exposure to agriculture chemicals, heavy metals, plastics in manufacturing, infection with HIV and other viruses, and electrical injury. Assessment of exposures for jobs held other than in military combat operations can provide important insights into the occupational factors that may have contributed to the increased rates of ALS observed among veterans (Smith *et al.*, 2000; Haley, 2003; Horner *et al.*, 2003; Weisskopf *et al.*, 2005). To aid in evaluating non-combat-related risk factors, we conducted a retrospective exposure assessment of all non-combat-related jobs held by the GENEVA cohort. This paper presents the retrospective exposure assessment for jobs held by the GENEVA cohort and evaluates changes in exposures over time. Results of this work will be used to assess personal exposures of cases and controls in GENEVA study and the risk of ALS associated with occupational exposures among veterans.

Methods

Exposure assessment process

GENEVA study design, recruitment strategies, and data collection have been described by Schmidt *et al.* (2008). Briefly, the study population consisted of cases ($n = 627$) who were ALS patients enrolled into the National Registry of Veterans and controls ($n = 970$) enrolled from the Beneficiary Identification and Records Locator System database maintained by the Veterans Benefit Administration. Lifetime occupational history was obtained through administration of a structured telephone interview for both cases and controls. For assistance with recall, participants were mailed occupational and residential history worksheets and a life timeline for their review prior to the phone interview. Subjects were asked about the jobs held for 6 months or longer from age 15 up to the reference date (the date of ALS diagnosis for cases and the date of interview for controls). For each job held, information obtained included data on the industry, job title, length of employment, tasks performed, and materials used for each task. To aid statistical analysis, every job was coded according to the Census Occupational Classification System, which was consistent with Standard Occupational Classification (SOC) Manual 2000 (Bureau of Labor Statistics, 2002; US Department of Health and Human Services Public Health Service, 2002). Each industry was coded according to the Census 2000 Industrial Classification System which was matched to the North American Industry Classification System (NAICS) 1997 (US Census, 1997; US Department of Health and Human Services Public Health Service, 2002).

The final GENEVA data set used for this retrospective exposure assessment consisted of 15 528 jobs reported by the 1597 participants (an average of 9.7 jobs each). Jobs were held from 1924 to 2010 and covered 262 industries and 466 occupations, combined into 4539 unique industry and occupation (I&O) combinations. Exposure assessment was conducted for two time periods: (i) for the 'current' time period that was determined as the period after 1995 and (ii) for 'the earlier' time period covering the pre-1995 era (see exposure reconstruction section).

Exposure assessment for the 'current' time (>1995) was done by utilizing professional judgment of industrial hygienists/exposure assessors to rate historical occupational exposures. Three industrial hygiene (IH) experts, each individually with >20 years of experience conducting workplace hazard assessments, independently conducted exposure ratings. The raters were selected to represent three different geographic areas of the USA (East coast, Midwest, and West coast).

Exposure assessment targeted a number of agents that were identified by searching the literature on potential occupational risk factors for ALS, consisting of pesticides, lead, mercury, selenium, arsenic, polychlorinated biphenyls (PCBs), formaldehyde, electromagnetic fields (EMF), chlorinated solvents, hydrocarbon solvents, and viral agents (Johnson and Archison, 2009; Weisskopf *et al.*, 2009; Kamel *et al.*, 2012; Vinceti *et al.*, 2012; Capozzella *et al.*, 2014; Huss *et al.*, 2014). For each agent, we conducted background research to identify jobs and industries associated with its use, exposure levels in the workplace, and occupational standards using a number of web sources such as PUBMED, TOXNET, ILO Encyclopedia, NIOSH Health Hazard Evaluations, and CAREX Canada. OSHA's Chemical Health and Exposure Database (CEHD) was also used to extract quantitative exposure data from the reported IH samples collected in workplace from 1984 to 2010. Because quantitative exposure data were available mostly for lead, formaldehyde, chlorinated solvents, and hydrocarbon solvents, these agents were grouped together (Group A) and exposure intensity for them was assigned semi-quantitatively (see exposure categories section). For the rest of agents, PCBs, mercury, selenium, arsenic, pesticides, EMF, and viral agents (or Group B), exposures were assigned qualitatively as '1/0 = yes/no' exposure.

Due to the extensive number of jobs in the data set (15 528), it was deemed infeasible to rate exposures for each job held by each worker. Rather, unique I&O combinations were rated. An initial screening of all jobs and industries was conducted by the research team to determine jobs/industries associated with exposures

to these agents based on data from literature review. After initial screening, each rater received 1797 potentially 'exposed' I&O combinations spread out in several batches of 250 records and 2062 potentially 'unexposed' I&O combinations for verification. If a rater disagreed with the 'unexposed' categorization, that specific I&O combination was rated in the same way as the I&O combinations initially determined as 'exposed'. In addition, 680 non-combat military occupations assumed to be comparable to similar non-military jobs were rated. Examples of non-combat military jobs include managers, engineers, photographers, cooks, human resources, dentists, clerks, dispatchers, electricians, laborers, etc. To 'calibrate' the raters, a pilot rating exercise was initially conducted using 120 I&O records. For ~1 month, raters were involved in discussions through email and phone calls to clarify rating instructions and identify the best strategies for exposure ratings using generalized I&O codes. During the pilot phase, raters determined that they wanted to be provided a summary of the detailed information on task and materials compiled from the study questionnaires for each job history record in each unique I&O.

Results of exposure ratings during the pilot stage were compared between the raters, and the reasons for differences were discussed. In addition, similar discussions were conducted through conference calls after each batch of 250 I&O combinations was rated. All ratings and exposure verifications were completed between February and September 2013.

Exposure ratings for post-1995

Raters independently assigned exposure intensity categories to each agent for each I&O combination, and they provided a confidence score for that I&O rating. Exposure intensity categories for Group A agents (lead, formaldehyde, hydrocarbon, and chlorinated solvents) incorporated both exposure intensity and frequency averaged over a typical year [annual average as time weighted average (TWA)] during the period of 1995–2010 (Hewett *et al.*, 2006; Logan *et al.*, 2009). The intensity/frequency categories were defined in comparison to the permissible exposure limit (PEL) values we provided the raters for each Group A agent as:

- 0 = background environmental levels;
- 1 = annual average TWA < 10% PEL [exposure highly controlled with minimal contact];
- 2 = annual average TWA 10–50% PEL [exposure well controlled with most regular contact at low concentration and rare contact at high ($\geq$ PEL) concentrations];

3 = annual average TWA 50–100% PEL [exposure controlled with most regular contact at low concentration and infrequent contact at high ($\geq$ PEL) concentrations];

4 = annual average TWA > 100% PEL (exposure poorly controlled, often has contact at high or very high concentrations).

Based on experience or literature data, exposure intensity for Group B agents (PCBs, mercury, selenium, arsenic, pesticides, EMF, and viral agents) was assigned a simple '0/1' rating, where 1 = 'exposed' if exposure was assessed to be at levels higher than background.

For every I&O rated, raters reported confidence scores, defined based on their experience with that industry or job. Confidence scores were determined as follows (Stewart and Stewart, 1994):

0 = no confidence defined as no knowledge to base rating on;

1 = low confidence defined as no experience, judgment based on literature, or assumed similarity with other jobs or industries;

2 = moderate confidence defined as experience with similar job in similar industry;

3 = high confidence defined as direct experience with that I&O combination.

Exposure reconstruction for pre-1995

To reconstruct exposures for pre-1995 for Group A agents, we generated a scaling factor by comparing pre-1995 and post-1995 exposures utilizing industry-level exposure data reported in the OSHA CEHD. This is a database of IH samples collected by OSHA's compliance officers during workplace monitoring of exposures to chemical hazards. The database includes exposure data from personal, area, and bulk samples for a wide range of occupational chemical hazards. Sampling results have been recorded by the Salt Lake Technical Center information system from 1984 forward and the database became publicly available in 2010. We extracted exposure data from the OSHA CEHD website (OSHA) for two time periods 1984–1994 and 1995–2010. The cut point year of 1995 was selected as an approximate mid-point of the range of years covered by CEHD and as the most relevant year within that range representing workplace exposure changes due to the Hazard Communication rule issued in 1994. Only personal and area samples with sampling duration of >120 min in the OSHA CEHD were considered for the analysis. The non-detects for all compounds were replaced with the limits of detection of the analytical method divided by two and the corresponding air sample volume.

Industry-level exposure data collected from IH samples from pre-1995 were compared with data collected from post-1995 period. Initially, a cross-walk between the industry codes in GENEVA database (Census 2000) and the 1987 SIC codes used in the OSHA CEHD was developed. Matching was done using two-digit industry codes, with exception of industries with an extensive number of IH samples, such as the manufacturing and services industries, which were matched at the three-digit code level. This resulted in a total of 33 industry group categories with CEHD exposure data extracted for both time periods (see Supplementary Table S1, available at *Annals of Work Exposures and Health* online). Each exposure measurement extracted from the CEHD data set was compared to the PEL value used by the raters to rate each Group A agent, and the % PEL was calculated as a scaled indicator of the exposure level for that I&O. Then, the median % PEL was determined for pre-1995 and post-1995 measurements for every agent and industry group. For the hydrocarbon and chlorinated solvents, the median % PEL was determined for all chemicals representing the group. Because both groups of solvents include a wide range of chemicals, only a subset of them that appeared more frequently in the CEHD data set were selected (see Supplementary Table S2, available at *Annals of Work Exposures and Health* online). Using the median % PEL, the exposure intensity category of 0–4 was determined for each industry group as previously defined (<10%, 10–50% PEL, 50–100% PEL, and >100% PEL).

The increase or decrease in the exposure intensity category for pre-1995 relative to post-1995 CEHD data was determined and used to estimate the pre-1995 exposure category by modifying the post-1995 exposure rating category determined by the raters scoring. For example, a + 1 factor for formaldehyde exposures in a certain industry group based on the CEHD data indicates that exposures pre-1995 were higher by one exposure category compared to post-1995 for that industry group. In this case, the rater exposure intensity categories assigned to each I&O record within that industry group for post-1995 was assigned a one-category higher exposure intensity for pre-1995.

To adjust exposures for Group B agents for pre-1995, raters were asked to identify agents for which the usage patterns differed greatly between the pre-1995 and post-1995 time periods. For most of the Group B agents, raters agreed that the same usage patterns (1/0 = yes/no) existed both pre-1995 and post-1995. However, for EMF, it was decided that due to widespread changes in the use of electronics some I&O combinations rated as exposed for post-1995 might be unexposed during

the pre-1995 time period. In addition, the potential for exposure to PCBs for selected industries such as electrical utilities and the manufacturing of electrical and electronic equipment was believed to be higher in the past due to the phase out of PCBs from many products. Thus, raters rated exposures to EMF and PCBs for pre-1995 for all I&O combinations originally rated as exposed to EMF and as unexposed to PCBs in the current time period. Ratings for all other Group B agents remained the same for both time periods.

Statistical analyses

Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Exposure summary metrics were calculated for each I&O combination and agent as (i) the average intensity score for all raters and (ii) the confidence-modified intensity score, where only scores with confidence of ≥ 2 were averaged when available (if not available, the intensity score remained the same). Average scores were rounded to the nearest integer. Raters' agreement was determined based on the overall proportion of agreement between the raters' exposure scores and the kappa statistic. For Group A agents (exposure intensity scores 0–4), the weighted kappa statistic was calculated for each pair of raters, then averaged for all three pair combinations. For Group B agents (exposure yes/no), unweighted kappas were calculated and also averaged over the three rater pairs.

Results

Exposure prevalence

An I&O combination was considered to involve exposure (be an 'exposed I&O') if the rounded average exposure intensity score by the raters was at least 1 (Group A) or if the rounded average exposure likelihood was 1 (Group B). The proportion of exposed I&O combinations varied by agent, ranging from 4.6 to 26.3% for Group A agents and from 0.1 to 5.9% for Group B agents (Table 1). The highest proportion of exposed I&O combinations was for hydrocarbon solvents (26.3%), while the lowest was for selenium (0.1%). Examination of the results for each individual rater revealed that, overall, rater # 1 assigned the highest number of exposed I&O combinations compared to the other two raters (Table 1).

Among the most predominant industries reported by the study participants was manufacturing (28.3% of total I&O combinations) and non-combat military (21.2% of total I&O combinations), the latter comprising non-combat jobs that participants held during their military service. When sorted by occupation, the frequency of I&O combinations was highest for management (12.7%), administrative (14.2%), production (13.4%), and transportation jobs (9.7%). The prevalence of exposed I&O combinations varied across different industries (see Supplementary Table S3, available at *Annals of Work Exposures and Health* online). For

Table 1. Percentage of 'exposed' I&O combinations based on intensity scores.

Agent	% ‘exposed’ I&O combinations ^a	% ‘exposed’ classified by individual raters ^b		
		1	2	3
Group A				
Lead	4.6	5.63	5.93	4.52
Formaldehyde	1.7	5.12	1.90	2.05
Hydrocarbon solvents	26.3	32.24	27.49	20.17
Chlorinated solvents	3.9	14.04	3.90	3.26
Group B				
PCB	0.6	1.15	0.31	0.99
Mercury	0.9	3.22	0.73	1.37
Selenium	0.1	1.08	0.02	0.29
Arsenic	0.5	1.04	0.26	1.30
Pesticides	4.2	9.36	2.85	6.53
EMF	5.9	8.01	8.18	6.66
Viral agents	3.7	4.15	4.08	3.48

^aAn I&O was considered to involve exposure (be 'exposed') if the rounded average exposure intensity score by the raters was ≥ 1 (Group A) or the rounded average exposure likelihood was = 1 (Group B). Percent was based on 4539 I&O combinations.

^b% exposed based on each individual raters' intensity score of >0 or exposure likelihood = 1. Percent is based on 4539 I&O combinations.

Group A agents, manufacturing, retail, transportation, and non-combat military were among the industries with the highest number of exposed I&O combinations. For Group B agents, the proportion of exposed I&O combinations was highest in manufacturing (for pesticides and EMF); healthcare (for viral agents and pesticides), and non-combat military (for EMF, pesticides, and viral agents). The smallest percentage of exposed I&O combinations corresponded to the finance, real estate, and management.

Exposure intensity scores for Group A agents.

Across Group A agents, the raters rated exposure intensity as zero for 73.7–98.3% of all I&O combinations. Out of five exposure intensity categories (0–4), none of the I&O combinations were rated as category 4 (annual average TWA > 100% PEL). The most predominant intensity score assigned by the raters was ‘1’ (annual average TWA < 10% PEL). The average intensity scores

for all ‘exposed’ I&O combinations within each industry remained ~1 (Table 2). Even the manufacturing and non-combat military industry groups, which had the highest number of exposed I&O combinations, had an average intensity score ~1. The highest average score was for formaldehyde exposures in art, entertainment, and recreation and other services (average 1.7), although that was based on only a small number of records. Only management had no exposed I&O combinations across all Group A agents (Table 2).

Raters’ reliability

The proportion of I&O combinations given the same intensity scores by all three raters for all agents (70.5–98.4%) indicates very good overall agreement between the raters (Table 3). However, kappa analyses indicated less agreement between the raters compared to overall agreement. The magnitude of agreement assessed using kappa varied by agent with the highest for viral agents

Table 2. Average exposure intensity scores for ‘exposed’ I&O combinations by industry group.

Industry categories	N total I&O	Lead		Formaldehyde		HC solvents		Cl solvents	
		<i>n</i> ^a	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
Agriculture	38	3	1.0 (0.0)	0	—	22	1.0 (0.0)	2	1.0 (0.0)
Mining	49	2	1.0 (0.0)	1	1.0 (.)	14	1.1 (0.4)	0	—
Utility	120	12	1.1 (0.3)	0	—	35	1.1 (0.0)	3	1.0 (0.0)
Construction	92	11	1.1 (0.3)	4	1.0 (0.0)	36	1.0 (0.2)	5	1.0 (0.0)
Manufacturing	1283	71	1.1 (0.4)	56	1.0 (0.1)	472	1.1 (0.3)	70	1.0 (0.1)
Wholesale	230	3	1.3 (0.6)	3	1.0 (0.0)	47	1.1 (0.2)	1	1.0 (.)
Retail	355	7	1.1 (0.4)	0	—	70	1.1 (0.3)	7	1.0 (0.0)
Transport and warehousing	177	10	1.0 (0.0)	0	—	57	1.0 (0.1)	15	1.0 (0.0)
Information	154	6	1.0 (0.0)	1	1.0 (.)	18	1.0 (0.0)	2	1.0 (0.0)
Finance and insurance	109	0	—	0	—	1	1.0 (.)	0	—
Real estate and rental and leasing	50	3	1.0 (0.0)	0	—	10	1.1 (0.3)	1	1.0 (.)
Professional, science, and technology services	195	5	1.0 (0.0)	1	1.0 (.)	21	1.0 (0.0)	4	1.3 (0.5)
Management	4	0	—	0	—	0	—	0	—
Administrative and support	86	2	1.0 (0.0)	0	—	34	1.0 (0.2)	2	1.0 (0.0)
Education services	140	4	1.0 (0.0)	1	1.0 (.)	34	1.1 (0.3)	6	1.0 (0.0)
Healthcare and social assistance	185	4	1.0 (0.0)	3	1.5 (0.6)	53	1.0 (0.0)	3	1.0 (0.0)
Art, entertainment, and recreation	80	3	1.0 (0.0)	2	1.7 (0.7)	21	1.1 (0.3)	1	1.0 (.)
Accommodation and food services	75	0	—	0	—	13	1.1 (0.0)	0	—
Other services	158	11	1.1 (0.3)	3	1.7 (0.6)	48	1.1 (0.3)	16	1.12 (0.3)
Non-combat military	959	54	1.0 (1.2)	4	1.0 (0.0)	200	1.0 (1.2)	38	1.0 (0)

(.) indicates missing SD data. Cl, chlorinated; HC, hydrocarbon.

^aN = number of ‘exposed’ I&O records with a rounded average intensity score ≥1 for each specific agent.

(weighted $\kappa = 0.67$) and hydrocarbon solvents (weighted $\kappa = 0.53$) and the weakest (unweighted $\kappa = 0.04$) for selenium.

Confidence-modified exposure scores

Raters' confidence ranged from 0 to 3 based on their experience working with specific industries and occupations (Table 4). Rater 1 reported a relatively higher degree of confidence compared to the other raters. This rater had 38 years' experience working as occupational safety and health compliance officer, manager, and private IH consultant, with 10% direct experience with I&O combinations compared to other raters who had <1% direct experience (Table 4). Raters 2 and 3, although certified industrial hygienists with many years

of consulting, government and/or academic experience, reported no experience with >50% of the I&O combinations rated. We recalculated exposure intensity and likelihoods including only those exposure ratings that corresponded to rater confidence scores ≥ 2 where available, and leaving the original score when all confidence scores were <2 (Table 5). The resulting percentage of I&O combinations categorized as 'exposed' increased for each agent when this confidence criterion was applied. In particular, there was an increase in the proportion of I&O combinations that switched from unexposed to exposed for formaldehyde (2.4%), hydrocarbon solvents (5.7%), chlorinated solvents (8.9%), and pesticides (3.9%).

Historical reconstruction of exposures for pre-1995

Historical reconstruction of exposures to Group A agents for pre-1995 was done by adjusting the expert rated I&O exposure intensity category with an exposure change factor obtained from examination of the OSHA CEHD pre-1995 and post-1995 data by industry group (see Supplementary Table S4a–d, available at *Annals of Work Exposures and Health* online).

Most of the exposure changes from the OSHA CEHD data indicate lead, formaldehyde, and chlorinated solvents had higher exposures during pre-1995. No change for any industry group was observed for hydrocarbon solvents pre-1995 and post-1995. Utilizing the exposure change factors from the OSHA CEHD data, pre-1995 exposures for lead were one exposure category higher than post-1995 for manufacturing of food, rubber and textile mill products, electronic and transportation equipment, printing and petroleum industries, transportation, and wholesale. Similarly, exposures to chlorinated solvents for pre-1995 were one-category higher than post-1995 for manufacturing of apparel and other finished products, fabricated products, and miscellaneous services. Industries with one-category higher exposure intensity for formaldehyde during pre-1995 compared to

Table 3. Measurers of agreement between the raters on rating exposures to each agent.

Agent	Overall % agreement for all I&O records rated ^a (N = 4359)	Kappa (κ) ^b (95% CI)
Group A		
Lead	91.9	0.50 (0.45 to 0.55)
Formaldehyde	93.1	0.28 (0.21 to 0.36)
Hydrocarbon solvent	70.5	0.53 (0.51 to 0.55)
Chlorinated solvents	84.8	0.30 (0.26 to 0.35)
Group B		
PCB	98.1	0.34 (0.20 to 0.48)
Mercury	96.0	0.32 (0.22 to 0.42)
Selenium	98.4	0.04 (−0.02 to 0.11)
Arsenic	97.7	0.24 (0.12 to 0.37)
Pesticides	89.0	0.41 (0.35 to 0.46)
EMF	88.4	0.46 (0.42 to 0.52)
Viral agents	95.9	0.67 (0.51 to 0.72)

^aIncludes all I&O combinations (N = 4359) most of which were rated as zero intensity or likelihood by all three raters.

^bWeighted kappa for Group A and unweighted kappa for Group B.

Table 4. Reported confidence scores across all I&O combinations rated by each rater.

Rater	Confidence scores ^a (%)			
	0 (no experience/ no knowledge)	1 (no experience but knowledge)	2 (experience with similar job/industry)	3 (direct experience with I&O)
1	0.5	36.2	53.2	10.1
2	0	86.4	13.4	0.2
3	2.4	93.5	3.9	0.2

^aConfidence scores of 0–3 were reported by the raters based on their experience with a specific I&O combination. Higher scores indicate more experience.

Table 5. Distribution of the rated I&O records for each exposure intensity category with and without confidence modification.^a

Agent	Average exposure intensity scores for all raters (% I&O)				Average exposure intensity scores including confidence-modified exposure intensity scores (% I&O)				Number of I&O records that changed the exposure category after using confidence-modified scores (% I&O)	
	0	1	2	3	0	1	2	3	Exposed to unexposed	Unexposed to exposed
Group A										
Lead	95.4	4.27	0.37	0	94.51	4.8	0.66	0.04	16 (0.4)	54 (1.2)
Formaldehyde	98.3	1.61	0.13	0	96.03	3.8	0.18	0	5 (0.1)	106 (2.4)
Hydrocarbon solvent	73.7	24.7	1.43	0.11	69.4	27.9	2.31	0.35	52 (1.2)	248 (5.7)
Chlorinated solvents	96.1	3.79	0.09	0	87.7	11.8	0.46	0.02	6 (0.1)	388 (8.9)
Group B										
PCB	99.4	0.57			99.1	0.9			2 (0.0)	16 (0.4)
Mercury	99.1	0.9			97.8	2.2			8 (0.2)	65 (1.5)
Selenium	99.9	0.09			99.7	0.3			3 (0.1)	12 (0.3)
Arsenic	99.5	0.46			99.3	0.7			4 (0.1)	13 (0.3)
Pesticides	95.8	4.2			92.3	7.7			10 (0.2)	172 (3.9)
EMF	94.1	5.9			93.4	6.6			31 (0.7)	63 (1.4)
Viral agents	96.3	3.7			96.1	3.8			13 (0.3)	18 (0.4)

^aThe confidence-modified exposure intensity score was calculated as the average of raters' scores with confidence of ≥ 2 . If no rates had confidence of ≥ 2 , then the initial average exposure intensity score was maintained for the I&O.

post-1995 included manufacturing of food, stone, clay, glass and rubber products, transportation equipment, and public administration. On the other hand, formaldehyde exposures pre-1995 were one-category lower for manufacturing of leather and leather products, wholesale, and agriculture.

Exposures to most Group B agents were deemed the same for both time periods, with the exception of PCB and EMF exposures. Based on the raters' reassessment of 333 I&O combinations rated as unexposed to PCBs for post-1995, ~2.4% were rerated as exposed for pre-1995. On the other hand, among the 268 I&O combinations initially rated as exposed to EMF for post-1995, ~19% were rerated as unexposed for pre-1995.

Discussion

The overarching objective of this work was to retrospectively estimate exposures to 11 agents per group for the GENEVA study participants. Using expert judgment to assess exposures in population-based case-control studies is a common practice. A number of studies have discussed the issues related to retrospective exposure assessment in population-based studies (Benke *et al.*,

1997; Siemiatycki *et al.*, 1997; Teschke *et al.*, 2002). Although alternative approaches that use Bayesian methods combining expert assessment and measurement data (Ramachandran and Vincent, 1999; Friesen *et al.*, 2011) or physical deterministic and empirical models with expert input (Frittschi *et al.*, 2009; Sottas *et al.*, 2009; Pronk *et al.*, 2012; Wheeler *et al.*, 2013) have been suggested, the information available in this data set did not permit the use of these methods.

Due to the large number of work history records in the GENEVA data set, it was considered impractical to rate each individual job record. Instead, exposures for every unique I&O combination were rated. In addition to the I&O codes, the IH experts utilized text fields containing all the information recorded in the work histories about the tasks and materials for each unique I&O. To minimize exposure misclassification associated with the expert based assessment, we used three expert raters instead of the one or two commonly used. Studies have shown that the validity of the exposure assessment is improved when the average of several raters is used (de Cock *et al.*, 1996; Semple *et al.*, 2001; Friesen *et al.*, 2011). To further improve the accuracy and reproducibility of the assessments we provided background

information on occupational exposures for each target agent to the raters prior to conducting exposure ratings, conducted a pilot rating to allow raters to discuss and agree on similar approaches (Stewart and Stewart, 1994; Logan *et al.*, 2009), and initiated phone calls to discuss any rater questions or uncertainties after the rating of each batch of ~250 I&O combinations. Additionally, we conducted initial sorting of likely exposed and unexposed I&O records, which helped the raters to spend more time reviewing the potentially exposed compared to the unexposed I&O combinations. Fritschi *et al.* (2009) emphasized that due to the low prevalence of exposure in population-based case-control studies, focusing more on potentially exposed jobs can be cost efficient and reduce the potential for exposure misclassification.

Despite these measures, a number of factors in our study could have contributed to exposure misclassification. Exposure ratings were based on the assumption of similar exposures across all jobs within one unique I&O combination. The number of similar job titles within each combination varied from 1 to 175, and the types of tasks reported varied across these 'similar' jobs. Although the information on tasks performed was very helpful for the exposure ratings, raters recognized that there was often variability in the potential exposures of the different tasks that were reported for that I&O. In addition, the ratings were based on the assumption of a constant average annual exposure category for every year of the post-1995 period, since it was not possible to rate exposures for each year.

As in other studies, we found that most I&O combinations were not associated with exposure to the target agents (considered 'unexposed' I&O combinations). The proportion of 'exposed' I&O combinations was much higher for Group A agents (1.7–26.3%) than for Group B agents (0.1–5.9%). These findings compare well with a study of prenatal maternal occupational exposures to solvents, polycyclic aromatic hydrocarbons, and heavy metals, where only 0.1–9.8% of the jobs rated were considered exposed (Rocheleau *et al.*, 2011). Peters *et al.* (2014) reported highly varying exposure prevalence (1.6–19.9%) across a variety of different agents in case by case assessment of parental occupational exposures and childhood leukemia. Compared to this study, a higher proportion of exposed jobs (19.7–24.7%) were reported in a US population-based case-control study by Pronk *et al.* (2012).

The exposure intensity reported in our study for Group A agents was generally quite low (<10% PEL), which was not surprising since the scoring was designed to reflect the annual average exposure level of an I&O

combination. Few have reported retrospective exposure intensity scores. A study by Mannetje *et al.* (2003) that focused on assessing exposure to 70 agents for 19 jobs reported that the highest % of exposed jobs was in the low exposure intensity category (3.1–11.8%) compared to jobs in the medium (1.8–5.9%) and the high exposure intensity categories (0.4–1.5%). Pronk *et al.* (2012) defined exposure intensity categories based on the levels of respirable elemental carbon (as: 1 for >0 to <5; 2 for 5 to <20; 3 for >20 $\mu\text{g m}^{-3}$), while rating diesel exhaust exposures for 14 961 jobs. The authors report a higher percentage of exposed jobs in the low exposure category (at 17.9%) compared to the medium & high categories (at 4.2 and 2.42%, respectively). Similarly, we found a higher percentage of I&O combinations in the low (score = 1) exposure category (range 3.8–27.9% of I&O combinations) compared to higher (score = 2 and 3) exposure categories (range 0.18–2.31% and 0–0.35%, respectively). Given the low prevalence of exposed jobs, as is typical for case-control studies, it could be asked whether this extensive exposure assessment was necessary. The literature shows that for dichotomous exposures (0/1) in low exposure prevalence studies, that non-differential misclassification is most likely to attenuate effect estimates toward the null (Dosemeci and Stewart, 1996; Teschke *et al.*, 2002). The impact of misclassification among 'exposed' categories is less clear, although there is some evidence that all directions of misclassification can impact relative risk estimates in case-control studies (Dosemeci and Stewart, 1996).

Although the use of confidence scores by raters has been recommended for some time (Stewart and Stewart, 1994), little has been reported in the literature about the impact of rater confidence on exposure scoring. A number of studies have reported raters' confidence when scoring intensity, probability, and frequency, as well as their agreement on confidence scores. Pronk *et al.* (2012) found poor agreement between the raters' confidence scores assigned specifically for each probability, intensity, and frequency rating (weighted kappa = 0.35–0.56). The highest confidence for intensity ratings was assigned when exposure data for that scenario were reported in the literature. Mannetje *et al.* (2003) reported that the confidence was higher for agents with high and low agreement, concluding that confidence is not a good predictor for the reliability analysis. In our study, confidence was defined based on raters experience with a certain industry or job. Rater 1 reported more experience with a higher percentage of I&O combinations compared to other raters and also assigned an 'exposed' rating to more records compared to other raters. To give more

weight to ratings associated with higher confidence, we applied a 'confidence rule', which was based on averaging only exposure intensity scores associated with confidence scores of ≥ 2 . As a result, we found an increase on the number of I&O combinations determined to be exposed for both group A and B agents, compared to the initial strategy of averaging the scores for the three raters independent of their confidence rating. The most noticeable increase was observed for chlorinated solvents, where a 2-fold increase of exposed I&O combinations (from 3.9 to 8.9%) was observed when the confidence rule was applied. This suggests that raters without knowledge of an I&O assume no exposure is present and only rate I&O combinations as exposed when they have some experience with the industry or job. In population-based studies with low exposure prevalence misclassification of records with little or no information on exposure as 'unexposed' has been shown to attenuate risk estimates (Dosemeci and Stewart, 1996; Kromhout and Vermeulen, 2001).

The overall proportion of agreement between the raters was very high, mostly due to the high percentage of I&O combinations in the unexposed category. However, the kappa statistics for Group A (weighted kappa) and Group B (unweighted kappa) indicated less agreement between ratings compared to the overall proportion of agreement. This is due to the fact that kappa values, calculated as the measure of agreement beyond that expected by chance, do not indicate if the disagreement is due to chance or due to other systemic differences such as a true disproportionate frequency of unexposed I&O combinations (Sim and Wright, 2005). Limiting the kappa calculation to exposed records would have produced unstable results due to the very small number of records. The highest kappa was observed for viral agents, for which raters agreed that exposure assessment was relatively straightforward. The lowest agreement was for selenium, for which raters reported no prior experience or knowledge of workplace exposures.

There is substantial evidence that worker exposures in North America and Europe have declined over time (Kromhout and Vermeulen, 2000; Creely *et al.*, 2007; de Vocht *et al.*, 2008; Lavoue *et al.*, 2008). However, within a case-control study using expert raters it is difficult to evaluate changes in exposure over time. The use of the OSHA CEHD data provided a means to estimate historical exposure trends, yet this approach was associated with a number of limitations (Lavoue *et al.*, 2013). Because OSHA compliance sampling targets high exposure jobs within an industry, rather than providing a representative random sample from the industry, it cannot be used to estimate the average exposures directly.

In addition, the CEHD database does not include information on occupations within the industry, so it does not allow a nuanced evaluation of exposures within the industry. Categorization of exposures pre-1995 and post-1995 from the OSHA CEHD data was based on number of assumptions including the assumption of similar exposures for each subgroup industry within the two-digit code. Industry matching at the subgroup level was not possible due to (i) missing CEHD data for both time periods for the majority of industry subgroups and (ii) challenges associating with matching of SIC 1987 codes with Census 2000 industry codes.

Because the CEHD covers only post-1984 data our comparisons of 'current' versus 'earlier' exposures were limited to that time period. Thus, every work history in the GENEVA data set that corresponds to the pre-1995 era will be assigned the same exposure score independent of the year, a limitation that could potentially contribute to exposure misclassification. In this study, we did find that a number of industries had higher exposures in the pre-1995 period. Occupational exposures may have declined over time in specific industries due to the introduction of a number of OSHA and other regulations aimed in reducing occupational and environmental risks. The most relevant example is the decline in occupational lead exposures after the phase-out of leaded gasoline in 1973 and the ban of the lead-based paint in 1978. A number of studies have reported declines on lead exposures based on data from blood and air monitoring. Koh *et al.* (2015) found 2–11% decrease in exposure per year from blood measurements, while Okun *et al.* (2004) reports a 10-fold decrease in lead exposures from 1978 to 1997. Our study results indicate that exposures to lead after 1995 declined by one exposure category for a number of industry groups including petroleum industries, transportation, and wholesale.

We did not observe any change in hydrocarbon solvents exposures for pre-post-1995. Interestingly, all of the CEHD samples for hydrocarbon solvents when compared to the median PEL resulted in an exposure intensity category of '1' for both time periods. The main trends for most of the agents indicate decreasing exposure after 1995. Similar trends have been reported from other studies that have used the OSHA IMIS (Integrated Management Information System) database to determine historical exposure changes. Utilizing this database, Lavoue *et al.* (2008) found an 18% yearly decrease in formaldehyde exposures across different industries when comparing earlier time periods (1979–1987) and a slower decrease for the most current time periods (5% per year). Similarly, we found that formaldehyde exposures decreased for a number of industry groups

including manufacturing and services. However, our data show an increase on formaldehyde exposures during post-1995 in agriculture, manufacturing of leather products, and wholesale compared to pre-1995. This increase in several subgroup industries could be explained by the increase in demand for decontamination and disinfection.

Overall, we demonstrate how using a scaling factor developed from historical CEHD data can be applied to rater based annual average exposure category assignments to develop historical assignments of annual average exposure category estimates for each I&O combination. This approach utilizes the CEHD data for historical trend estimates but does not use the point estimates from this data, which are compliance data collected in worst case scenarios. Instead, the CEHD trend estimates are applied to the annual average TWA category estimates developed by the expert raters to better represent the average exposures of most workers in an I&O.

Conclusion

Our results indicate that using raters' confidence assessment in determining exposure scores increases both the proportion of I&O combinations regarded as exposed and the intensity scores, suggesting raters tend to be conservative in their assessment when they lack detailed knowledge of an industry or job. A sensitivity analysis of the impact of excluding low confidence scores will be investigated during the exposure-response analysis. I&O exposure category assignments resulting from this work were blind to the health outcomes of the study participants. In the epidemiologic analysis to assess the ALS risk from workplace exposures, personal exposures for cases and controls will be determined based on these I&O combinations ratings combined with each individual's job history and duration.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

Acknowledgements

We are very thankful to DeEtta Burrows, Judith Sparer, and James Jones for their contribution with occupational exposure ratings. In addition, we would like to acknowledge Jean Keller, Westat Inc., and staff at Social and Scientific Systems Inc. for conducting the I&O coding. Funding for this work was provided by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health

Sciences (Z01-ES-049005), by grants from the National Institutes of Health, National Institute of Environmental Health Sciences (R01-ES-013244), and the ALS Association (ALSA-1230). The National Registry of Veterans with ALS and its DNA bank were supported by the Office of Research and Development, Cooperative Studies Program, Department of Veterans Affairs (CSP #500A). The authors declare no conflict of interest relating to the material presented. Its contents, including any opinions and conclusions expressed, are solely those of the authors.

References

- Benke G, Sim M, Forbes A *et al.* (1997) Retrospective assessment of occupational exposure to chemicals in community-based studies: validity and repeatability of industrial hygiene panel ratings. *Int J Epidemiol*; 26: 635–42.
- Bureau of Labor Statistics. (2000) Standard Occupational Classification (SOC) Archived Materials. Available at <http://www.bls.gov/soc/#archives>. Revised February 16, 2016. Accessed December 8, 2016.
- Capozzella A, Sacco C, Chighine A *et al.* (2014) Work related etiology of amyotrophic lateral sclerosis (ALS): a meta-analysis. *Ann Ig*; 26: 456–72.
- Creely KS, Cowie H, Van Tongeren M *et al.* (2007) Trends in inhalation exposure—a review of the data in the published scientific literature. *Ann Occup Hyg*; 51: 665–78.
- Das K, Nag C, Ghosh M. (2012) Familial, environmental, and occupational risk factors in development of amyotrophic lateral sclerosis. *N Am J Med Sci*; 4: 350–5.
- de Cock J, Kromhout H, Heederik D *et al.* (1996) Experts' subjective assessment of pesticide exposure in fruit growing. *Scand J Work Environ Health*; 22: 425–32.
- de Vocht F, Vermeulen R, Burstyn I *et al.*; EU-EXASRUB Consortium. (2008) Exposure to inhalable dust and its cyclohexane soluble fraction since the 1970s in the rubber manufacturing industry in the European Union. *Occup Environ Med*; 65: 384–91.
- Dosemeci M, Stewart PA. (1996) Recommendations for reducing the effects of exposure misclassification on relative risk estimates. *Occup Hyg*; 3: 169–76.
- Friesen MC, Coble JB, Katki HA *et al.* (2011) Validity and reliability of exposure assessors' ratings of exposure intensity by type of occupational questionnaire and type of rater. *Ann Occup Hyg*; 55: 601–11.
- Fritschi L, Friesen MC, Glass D *et al.* (2009) OccIDEAS: retrospective occupational exposure assessment in community-based studies made easier. *J Environ Public Health*; 2009: 957023.
- Haley RW. (2003) Excess incidence of ALS in young Gulf War veterans. *Neurology*; 61: 750–6.
- Hewett P, Logan P, Mulhausen J *et al.* (2006) Rating exposure control using Bayesian decision analysis. *J Occup Environ Hyg*; 3: 568–81.
- Horner RD, Kamins KG, Feussner JR *et al.* (2003) Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology*; 61: 742–9.

- Huss A, Spoerri A, Egger M *et al.*; For the Swiss National. (2014) Occupational exposure to magnetic fields and electric shocks and risk of ALS: the Swiss National Cohort. *Amyotroph Lateral Scler Frontotemporal Degener*; 16: 80–5.
- Johnson FO, Atchison WD. (2009) The role of environmental mercury, lead and pesticide exposure in development of amyotrophic lateral sclerosis. *Neurotoxicology*; 30: 761–5.
- Kamel F, Umbach DM, Bedlack RS *et al.* (2012) Pesticide exposure and amyotrophic lateral sclerosis. *Neurotoxicology*; 33: 457–62.
- Koh DH, Locke SJ, Chen YC *et al.* (2015) Lead exposure in US worksites: a literature review and development of an occupational lead exposure database from the published literature. *Am J Ind Med*; 58: 605–16.
- Kromhout H, Vermeulen R. (2000) Long-term trends in occupational exposure: are they real? What causes them? What shall we do with them? *Ann Occup Hyg*; 44: 325–7.
- Kromhout H, Vermeulen R. (2001) Application of job-exposure matrices in studies of the general population: some clues to their performance. *Eur Respir Rev*; 11: 80–90.
- Kunst CB. (2004) Complex genetics of amyotrophic lateral sclerosis. *Am J Hum Genet*; 75: 933–47.
- Lavoue J, Friesen MC, Burstyn I. (2013) Workplace measurements by the U.S. Occupational Safety and Health Administration since 1979: descriptive analysis and potential uses for exposure assessment. *Ann Occup Hyg*; 57: 681–3.
- Lavoue J, Vincent R, Gerin M. (2008) Formaldehyde exposure in U.S. industries from OSHA air sampling data. *J Occup Environ Hyg*; 5: 575–87.
- Logan P, Ramachandran G, Mulhausen J *et al.* (2009) Occupational exposure decisions: can limited data interpretation training help improve accuracy? *Ann Occup Hyg*; 53: 311–24.
- Malek AM, Barchowsky A, Bowser R *et al.* (2014) Environmental and occupational risk factors for amyotrophic lateral sclerosis: a case-control study. *Neurodegener Dis*; 14: 31–8.
- Mannetje A, Fevotte J, Fletcher T *et al.* (2003) Assessing exposure misclassification by expert assessment in multicenter occupational studies. *Epidemiology*; 14: 585–92.
- Okun A, Cooper G, Bailer AJ *et al.* (2004) Trends in occupational lead exposure since the 1978 OSHA lead standard. *Am J Ind Med*; 45: 558–72.
- Occupational Safety and Health Administration (OSHA). Chemical exposure health data. Available at <https://www.osha.gov/opengov/healthsamples.html>. Accessed December 8, 2016.
- Peters S, Glass DC, Milne E *et al.*; Aus-ALL Consortium. (2014) Rule-based exposure assessment versus case-by-case expert assessment using the same information in a community-based study. *Occup Environ Med*; 71: 215–9.
- Pronk A, Stewart PA, Coble JB *et al.* (2012) Comparison of two expert-based assessments of diesel exhaust exposure in a case-control study: programmable decision rules versus expert review of individual jobs. *Occup Environ Med*; 69: 752–8.
- Ramachandran G, Vincent JH. (1999) A Bayesian approach to retrospective exposure assessment. *Appl Occup Environ Hyg*; 14: 547–57.
- Rocheleau CM, Lawson CC, Waters MA *et al.* (2011) Inter-rater reliability of assessed prenatal maternal occupational exposures to solvents, polycyclic aromatic hydrocarbons, and heavy metals. *J Occup Environ Hyg*; 8: 718–28.
- Schmidt S, Allen KD, Loiacono VT *et al.* (2008) Genes and environmental exposures in veterans with amyotrophic lateral sclerosis: the GENEVA study. Rationale, study design and demographic characteristics. *Neuroepidemiology*; 30: 191–204.
- Seemple SE, Proud LA, Tannahill SN *et al.* (2001) A training exercise in subjectively estimating inhalation exposures. *Scand J Work Environ Health*; 27: 395–401.
- Siemiatycki J, Fritschi L, Nadon L *et al.* (1997) Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *Am J Ind Med*; 31: 280–6.
- Sim J, Wright CC. (2005) The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther*; 85: 257–68.
- Smith TC, Gray GC, Knoke JD. (2000) Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *Am J Epidemiol*; 151: 1053–9.
- Sottas PE, Lavoue J, Bruzzi R *et al.* (2009) An empirical hierarchical Bayesian unification of occupational exposure assessment methods. *Stat Med*; 28: 75–93.
- Stewart PA, Stewart WF. (1994) Occupational case-control studies: II. Recommendations for exposure assessment. *Am J Ind Med*; 26: 313–26.
- Teschke K, Olshan AF, Daniels JL *et al.* (2002) Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med*; 59: 575–93; discussion 594.
- US Census. (1997) North American Industry Classification System. Available at https://www.census.gov/eos/www/naics/reference_files_tools/1997/1997.html. Revised February 16, 2016. Accessed December 8, 2016.
- US Department of Health and Human Services Public Health Service. (2002) *Industry and occupation coding for death certificates, effective 2003 N.C.f.H. Statistics* (ed.). Hyattsville, MD.
- Vinceti M, Bottecchi I, Fan A *et al.* (2012) Are environmental exposures to selenium, heavy metals, and pesticides risk factors for amyotrophic lateral sclerosis? *Rev Environ Health*; 27: 19–41.
- Vinceti M, Fiore M, Signorelli C *et al.* (2012) Environmental risk factors for amyotrophic lateral sclerosis: methodological issues in epidemiologic studies. *Ann Ig*; 24: 407–15.
- Weisskopf MG, Morozova N, O'Reilly EJ *et al.* (2009) Prospective study of chemical exposures and amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*; 80: 558–61.
- Weisskopf MG, O'Reilly EJ, McCullough ML *et al.* (2005) Prospective study of military service and mortality from ALS. *Neurology*; 64: 32–7.
- Wheeler DC, Burstyn I, Vermeulen R *et al.* (2013) Inside the black box: starting to uncover the underlying decision rules used in a one-by-one expert assessment of occupational exposure in case-control studies. *Occup Environ Med*; 70: 203–10.