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Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: A systematic review

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Abstract

Environmental exposure to chemicals and metals may contribute to the risk of sporadic amyotrophic lateral sclerosis (ALS). Two systematic reviews of the literature on these topics performed according to the well-established MOOSE guidelines are presented. Literature cited in MEDLINE, EMBASE, CINAHL, and Cochrane databases (up to March 2007) as well as references of relevant articles were screened for case-control or cohort studies investigating the associations between sporadic ALS and exposure to chemical agents or metals. Methodology of selected studies was appraised according to Armon's classification system for ALS risk factor studies as well as a newly developed classification system for quality of exposure assessment. Seven of the 38 studies concerning exposure to chemicals and three of the 50 studies concerning exposure to metals fulfilled the validity criteria. In two independent studies meeting the validity criteria, a significant association with increased ALS risk was reported for exposure to pesticides. This systematic review demonstrated the difficulty in attaining a high level of evidence due to lack of high quality of methodological and exposure assessment components. Although pesticide exposure was identified as candidate risk factor, more well-designed studies are needed to provide a definitive answer about exogenous factors of ALS.

Key words: *Amyotrophic lateral sclerosis, ALS, motor neuron disease, systematic review, risk factor studies*

Introduction

Sporadic ALS is considered to be a multifactorial disease with multiple genetic and environmental factors causing motor neuron degeneration (1–4). Recently published associations between ALS and paraoxonase gene polymorphisms, which play a role in the biochemical pathways of detoxification and protection against oxidative stress, illustrate that genetic susceptibility combined with exposure to environmental agents may precipitate sporadic ALS (5–7). Exposure to organophosphate compounds in individuals with genetically determined slower hydrolysis has been proposed as an explanation for the increased risk of sporadic ALS in Gulf War veterans (8).

To date, reports on chemical agents and metals as risk factors for ALS have been inconsistent and inconclusive (9). Reviews on risk factor studies of exogenous exposure to chemical agents and metals in ALS have been narrative or semi-systematic (9,10). Few have defined an extensive search strategy, given inclusion criteria or compared study methodology to enable reasonable comparisons.

To evaluate the existing evidence on whether lifetime exposure to chemical agents and heavy metals increases the risk of developing ALS, we carried out systematic reviews, according to the MOOSE guidelines for performing and reporting a meta-analysis or systematic review of observational studies (11) on exposure to exogenous agents in patients with ALS. In addition, we paid considerable attention to the quality of the assessment of exposure to exogenous agents.

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Methods

Search strategy

We performed two systematic reviews (chemical agents and metals) according to the MOOSE guidelines (11). A search was performed in the MEDLINE, EMBASE, CINAHL, and Cochrane databases up to March 2007. The detailed search strategies for each database are shown in E-Tables E1 for chemical agents and E2 for metals.

The search string consisted of a combination of medical subject headings [MeSH] and text words. The search terms for ALS included 'motor neurone disease', 'amyotrophic lateral sclerosis', 'progressive spinal muscular atrophy', 'motor neuropathy' and related synonyms. These were combined with search terms for the exposure. Besides 'chemical*' and synonyms, terms for various chemicals, such as 'pesticide*', 'benzene*' and 'styrene*', were applied in the search strategy to detect studies dealing with chemical agents. Besides 'metal' and synonyms, terms for a great number of metals, such as 'mercury*', 'arsenic*' and 'magnesium*' were applied in the search strategy to detect studies dealing with metals. The search was limited to human studies.

Inclusion criteria

Inclusion criteria were as follows: 1) design had to be case-control or cohort; 2) exposure had to be a chemical agent or metal; 3) outcome had to be sporadic ALS (studies performed in Guam, the Kii Peninsula or other endemic areas were excluded); 4) language was restricted to English, French, German or Dutch. After removal of duplicate titles, all titles were screened according to these criteria (Figures 1 and 2). Articles not meeting the inclusion criteria were excluded. The abstracts and, at the next step, the full text of the remaining articles were then evaluated by two reviewers (NAS, JHV) according to the specified quality assessment criteria. The

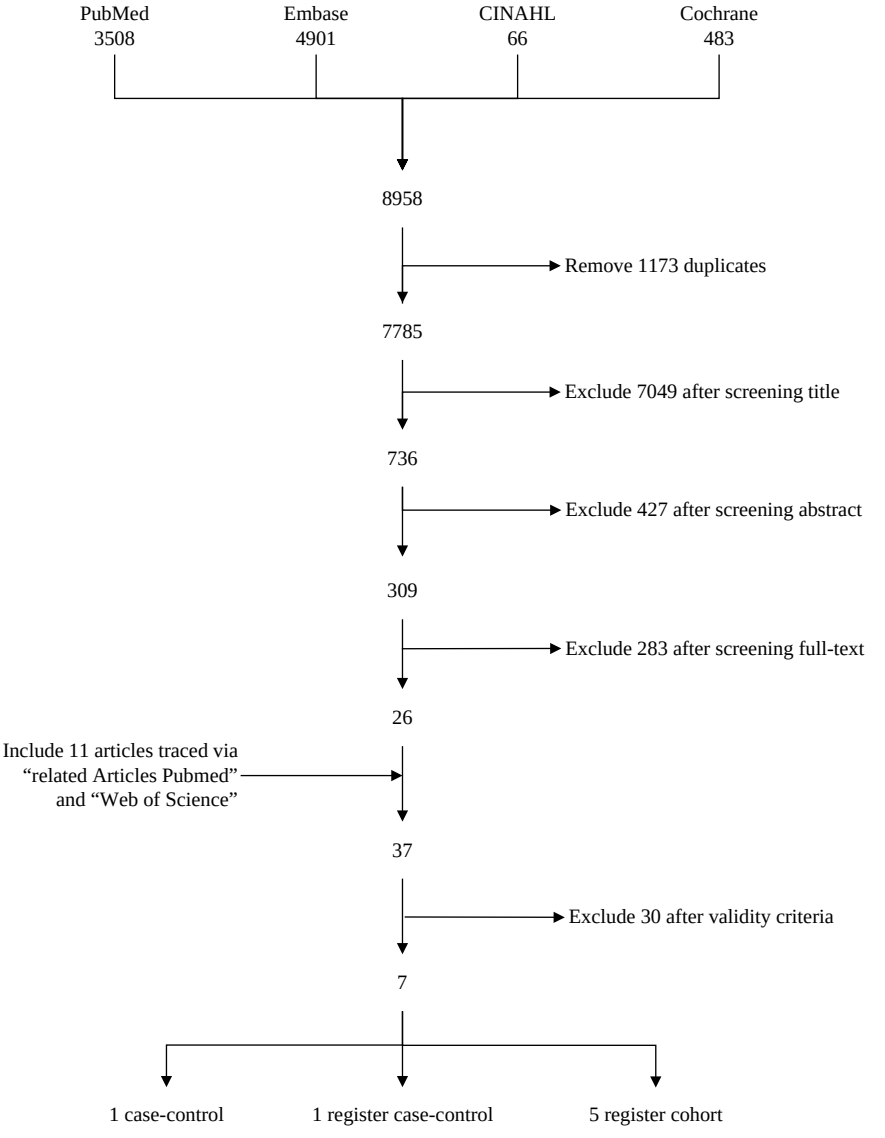

Figure 1. Identification and selection of studies dealing with chemical agents.

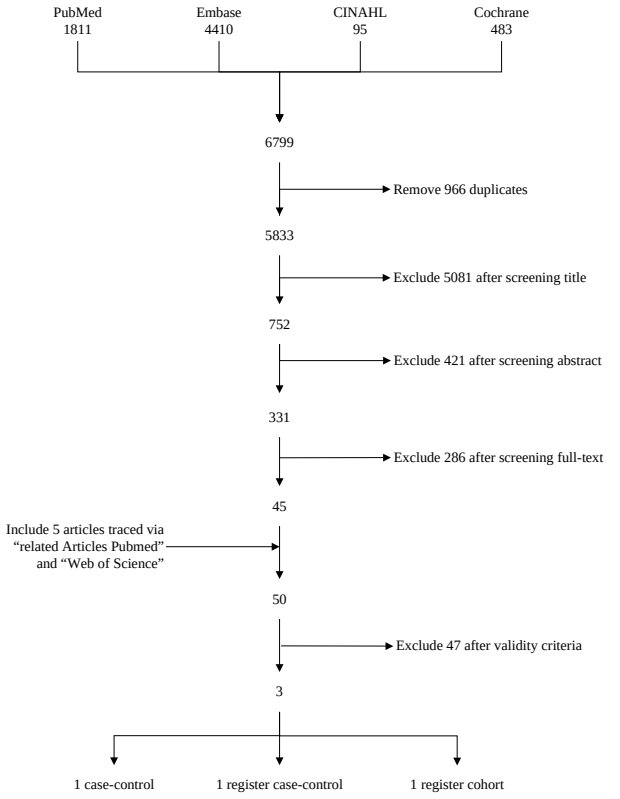

Figure 2. Identification and selection of studies dealing with metals.

remaining relevant articles were cross-linked for references to find other potentially relevant articles.

Study quality assessment

Initially selected studies were appraised according to Armon's classification system, a rating system based on a mixture of criteria developed by professional organizations, in particular the American Academy of Neurology, and developed specifically for ALS risk factor studies (9). This classification system consists of the general methodological criteria (selection of control group, high response rate, blinding, recall bias, quantification of exposure, accounting for confounding and bias and appropriate analytical approach) and some criteria specific for ALS (diagnosis of ALS made according to established criteria and exposure prior to probable biological onset of disease). Levels of evidence range from I (highest) to V (lowest). Risk factor data from studies with Armon ratings of I, II, and III can achieve levels of evidence A ('established risk factor'), B ('probable risk factor'), or C ('possible risk factor'). Risk factor data from level IV or V studies can achieve only an 'unknown risk factor' status.

Assessment was performed independently by two reviewers (NAS, JHV). In case of discordant judgment, consensus was reached after a brief exchange of opinions; if this was not possible, a third reviewer was consulted (KF).

Since the Armon criteria do not include a technical appraisal of exposure assessments, a panel of two occupational hygienists (DH and HK) reviewed the exposure assessment component of the included ALS risk factor studies according to specific criteria (Table I). The criteria used reflected current insights into accuracy and reproducibility of different exposure assessment approaches and their potential for responder bias given a chosen study design. A distinction was made between exposure assessments based on self-reported exposures, self-reported jobs or tasks, assigned exposure by an expert based on job or task information, job exposure matrices (computer based expert systems based on both job and industry information), measurements of external exposure, or internal exposure (e.g. for metals) or a biomarker of exposure (usually a metabolite) of suspected agents (e.g. for pesticides).

Findings produced from exposure assessment methods assigned an EA-rating of 1 are considered uninformative. These exposure assessment methods consist of 1) self-reported exposure, which may lead to non-differential responder bias, 2) registry job history, which is often inaccurate and incomplete, and 3) self-reported job history in an industrial cohort design, which also could lead to bias because other (more objective) sources are available and preferred.

Findings produced from exposure assessment methods assigned an EA-rating of 2 are considered not to be accurate. Examples are: 1) a self-reported job history (with or without mentioning specific tasks) in other study designs which may lead to non-differential responder bias, although this possibility is less likely than with a self-reported exposure; 2) measurements on a single occasion, which can lead to misclassification due to temporal variability or intra-individual variability in case of a biomarker. Single occasion measurements can be performed externally or internally (biomarker). Measuring exposure biomarkers without providing information on external exposure (such as job title information) may result in inaccurate information, because increased internal levels can be due to other sources or, in case of metals, internal degenerative processes rather than external exposure.

Findings produced from exposure assessment methods assigned an EA-rating of 3 are considered valid but not agent-specific; job histories from company records are often accurate but do not necessarily have a link to occupational exposures.

Findings produced from exposure assessment methods assigned an EA-rating of 4 are considered accurate and agent-specific: 1) a job-exposure matrix (JEM) enables linking of occupations to profiles of environmental exposures by providing (semi-)quantitative assessments of exogenous exposures for each occupation, but quality is dependent on quality of job history and assignment at job level

Table I. Exposure assessment (EA) score: system for rating quality of assessment of exposures.

EA-score	Method of Exposure assessment	Design	Interpretation
1	Self-reported exposure Registry job history	(Hospital-based) case-control Industrial cohort	Uninformative
	Self-reported job history	Industrial cohort	
2	Self-reported job history Self-reported job history and task Environmental monitoring single occasion Biomonitoring single occasion	(Hospital-based) case-control Community-based cohort	Findings not completely valid
3	Company job history	Industrial cohort Nested case-control	Findings valid, but not agent-specific
4	Job Exposure Matrix (JEM) Case-by-case assessment by expert(s) Biomonitoring repeated occasions Environmental monitoring repeated occasions	(Hospital-based) case-control Community-based cohort Industrial cohort Nested case-control	Findings are valid and agent-specific

may result in exposure misclassification for an individual subject; 2) a case-by-case assessment by expert(s) is accurate and may perform even better than a JEM, especially when task information has been collected; 3) repeated sampling of biomarkers or external monitoring is agent-specific and will lead to less underestimation of an exposure-response relationship because of the reduced influence of temporal or intra-individual variability.

Data extraction

Studies meeting both criteria for methodological and exposure assessment components were included. Sufficient methodology was classified as ratings of I, II, III or IV according to Armon's classification system (9). Level V studies were excluded because they represent studies with uncontrolled data, e.g. case series, chance observations, expert opinions that are not based on verifiable data, or studies where the risk factor studies most probably occurred after biological disease onset. Sufficient quality of exposure assessment was classified as Exposure assessment scores of 3 or 4.

Because of the heterogeneity of studies, a formal meta-analysis could not be performed. For each chemical agent and metal, reported risk estimates together with their corresponding confidence intervals were provided.

Results

Literature search

The search strategy produced 8958 studies involving chemical agents and 6799 studies on metals. Details of inclusion and exclusion are provided in Figures 1 and 2. Subsequent screening of title, abstract and full-text articles according to the selection criteria, 37 studies dealing with chemical agents and 50 dealing with metals were selected for rating of methodology and exposure assessment as shown in Table II.

Study characteristics and quality assessment

Only seven (18%) studies dealing with chemicals and three (6%) studies dealing with metals were included in the study based on our combined criteria of an Armon score of IV or better as well as an EA-score of 3 or better (Table II). The characteristics of these studies are presented in Table III. All selected studies were classified as Armon III and IV, predominantly due to problems in study design. In all but one (12) study, registers were used (the maximum Armon classification for this type of study is III, because (mortality and morbidity) registers are a less accurate method for determining outcome than examination of patients or charts). In one case-control study (12), issues such as testing of multiple hypotheses, lack of blinding and insufficient response rates resulted in a rating of III according to Armon's classification system[9], even though it had been rigorously designed and was population based. The characteristics and assessments of the excluded 30 studies dealing with chemical agents and 47 studies dealing with metals are presented in E-Tables III–IV.

Data extraction

Characteristics, quality assessment and reported data for each study listed according to chemical agent and metal are presented in E-Tables V–VI. An overview is given in Figure 3. Since studies showed considerable heterogeneity both in design and

Table II. Class of methodological evidence and exposure assessment quality of studies.

A. Dealing with exposure to chemical agents as a risk factor for ALS

	EA-score					
	0	1	2	3	4	All
No. with Armon I	0	0	0	0	0	0
No. with Armon II	0	0	0	0	0	0
No. with Armon III	0	0	1	0	1	2
No. with Armon IV	2	15	12	1	5	35
No. with Armon V	0	0	0	0	0	0
Total No. of studies	2	15	13	1	6	37

B. Dealing with exposure to metals as a risk factor for ALS

	EA-score					
	0	1	2	3	4	All
No. with Armon I	0	0	0	**0**	**0**	0
No. with Armon II	0	0	0	**0**	**0**	0
No. with Armon III	1	0	2	**0**	**1**	4
No. with Armon IV	2	6	36	**0**	**2**	46
No. with Armon V	0	0	0	**0**	**0**	0
Total No. of studies	3	6	38	**0**	**3**	50

Studies meeting the following validity criteria were selected and are shown in Bold: 1) Armon rating of I, II, III, or IV and b) Exposure assessment score of 3 or 4.

quality, a formal meta-analysis could not be performed. Different association measures (ranging from mortality odds ratio (MOR) to standardized mortality ratio (SMR)) were reported.

Associated chemicals

Figure 3 shows the reported risk estimates and corresponding 95% CIs reported by studies dealing with chemicals. Valid information was available for chemical agents categorized as A) organic solvents, B) occupations potentially exposed to solvents, C) agricultural chemicals, D) occupations potentially exposed to pesticides, and E) other chemical agents. Data for benzene and other aromatic hydrocarbons, any solvent, any pesticides and oils were reported in more than one study. For solvents, risk estimates reported in three studies were slightly increased (in the range 1.1–1.2) and significant in one out of three. For the subcategory of solvents including benzene and other aromatic hydrocarbons, increased risk was reported five times (risk estimates in the range 1.1–6.9), although not significant. For pesticides, a significantly increased risk was reported

Table III. Characteristics of included studies.

Author, year	Patients (no.)	Controls (no.)	Armon	EA-score
A. Chemical agents				
Case-control				
McGuire 1997 (10)	174	348	III	4
Register case-control[b]				
Gait 2003 (13)	22	206	IV	4
Register cohort [a]				
Burns 2001 (27)	19	6760	IV	4
Lewis 2000 (16)	19	34560	IV	3
Park 2005 (10)	6347	2501541	IV	4
Steenland 2006 (14)	11	16906	IV	4
Welp 1996 (15)	7	35443	IV	4
B. Metals				
Case-control				
McGuire 1997 (10)	174	348	III	4
Register case-control[b]				
Gait 2003 (13)	22	206	IV	4
Register cohort[a]				
Vinceti 2000 (12)	3	2065	IV	4

[a] Industrial cohorts were used in Lewis 2000, Steenland 2006, Welp 1996; Open population cohorts were used in Park 2005, and Vinceti 2000.

[b] Nested case-control within industrial cohort was applied in Gait 2003.

twice: one study (12) reported a risk estimate of 2.5 (95% CI 1.2–5.1) based on 16 exposed patients with ALS; another study (13) reported a risk estimate of 1.2. For oils, one study reported a decreased (0.7) and three studies an increased risk estimate (ranging from 1.2 to 1.8); this was significantly increased in one study. Data from all other individual chemical agents were reported in only one study (12,13); significant associations were found for exposure to cleaning solvents or degreasers, alcohols or ketones, insecticides, fertilizers, as well as for occupations potentially exposed to solvents (hairdressers and cosmetologists) or pesticides (farm-related occupations) (Figure 3).

Associated metals

Figure 3 shows the reported risk estimates and corresponding 95% CIs reported by studies dealing with metals. Valid information was available for A) lead, B) mercury, C) aluminum, D) cadmium, E) chromium, F) manganese, G) selenium, and H) metals not otherwise specified. One study (14) reported a significantly increased ALS risk for individuals exposed to selenium (risk estimate 5.72, 95% CI 1.46–15.57), based on three exposed patients with ALS. Results for unspecified metals, reported in two studies (12,15), were conflicting and not significant. Only one study reported on the effects of other specific metals (lead, mercury, aluminum, cadmium, chromium, manganese), revealing no significant associations (12).

Discussion

This comprehensive review of the literature shows that evidence for specific chemical agents and metals as risk factors for ALS is scarce and often generated from poor exposure assessment methods. Only seven out of 37 studies dealing with chemical agents and three out of 50 studies dealing with metals had sufficient methodological and exposure assessment quality. Risk estimates for most individual chemical agents and metals were reported in only one study. Moreover, studies differed in design and methods of analysis and used different association measures, thus making it impossible to produce a formal meta-analysis of the sparsely available data per exposure to chemical agent or metal investigated in more than one study. For pesticides, significantly increased risk estimates were reported in two studies. An increased ALS risk was reported for exposure to cleaning solvents or degreasers, alcohols or ketones, insecticides, fertilizers, selenium, as well as for occupations potentially exposed to solvents (hairdressers and cosmetologists) or pesticides (farm-related occupations) in one study only; to assess these potential risk factors, these findings should be replicated by future association studies. Reviews on risk factor studies of exogenous exposure to chemical agents and metals in ALS have been narrative in nature or semi-systematic (9,10). The present study selected according to an a priori set of criteria regarding

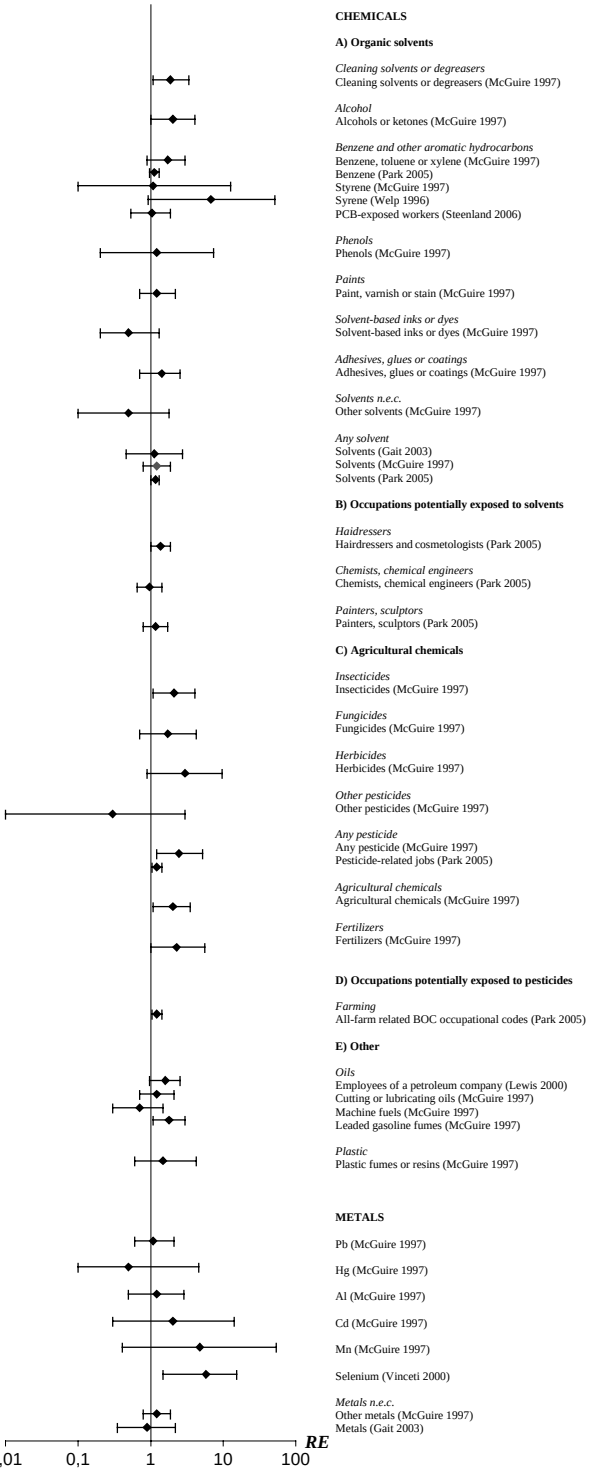

Figure 3. Forest plots of risk estimates from studies of exposure to chemical agents and metals and the risk of ALS. Risk estimates (RE) reported were odds ratios (OR), standardized mortality ratio (SMR), proportionate mortality ratio (PMR), and standardized incidence ratio (SIR). Details about risk estimates together with study characteristics are presented in E-appendices 5 and 6. This figure shows the risk estimates and 95% CI for each individual study per agent. Note: due to heterogeneity, a meta-analysis could not be performed and is not shown in this figure.

methodological class of evidence. Moreover, criteria for the quality of the method of exposure assessment were developed and applied.

The strength of evidence was limited by methodological limitations and heterogeneity: studies were classified as having a relatively low level of evidence – class III or IV according to Armon's classification system. Only one study reached a class III level of evidence (12).

Moreover, in more than 80% of the studies a level 0, 1 or 2 EA-rating was assigned indicating several limitations in exposure assessment. Interestingly, some class III studies had a low level EA-rating score, resulting in an overall poor assessment and exclusion of those studies (E-Tables). Overall, many of the earlier studies on ALS and occupational exposure can be regarded as hypothesis-generating. Exposure assessment was predominantly characterized by subjective approaches. Aetiological studies, exploring predefined hypotheses on the role of occupational or environmental exposures, obtained self-reports of exposure or categorization of job titles which are prone to bias and are not reproducible. Alternatively, many studies applied single-occasion biomonitoring without information on external exposure, which is susceptible to temporal variability and may in addition reflect internal processes rather than external exposure.

It is only since 1995 that case-control studies have contained exposure assessment components of sufficient quality to be included in a weight of evidence analysis. Interestingly, several studies applied a job-exposure matrix, which enables the linking of occupations to profiles of environmental exposures by providing (semi-)quantitative assessments of exogenous exposures for each occupation; others applied case-by-case assessments, or were based on company job histories, which produce accurate and objective data. A few industry-specific studies have been performed exploring relations between a limited number of more specific potential determinants of ALS, resulting in more solid exposure assessment than is possible in open population studies on a range of agents (15–18).

Objectively scoring the quality of method of exposure assessment of each individual study emphasizes that a high-quality method is necessary to produce valid and reproducible information on exogenous exposure. Nevertheless, the current Armon criteria only assess epidemiological criteria and do not mention any technical requirements. Since the overall quality assessment depends on both sets of criteria, we propose applying this combined assessment method in future meta-analyses and systematic reviews on association studies between exogenous risk factors and ALS. A majority of the initially included studies (30 dealing with chemical agents and 47 dealing with metals) did not meet the quality criteria. However, it must be noted that not all of these studies reflect poor quality. Initial inclusion criteria were liberal in order to screen all available indirect evidence; thus, EA-rating was low in some well-designed studies not initially designed to detect a (causal) relationship between exogenous exposures to chemical agents and metals but which focused on occupation (as a proxy for exposure to chemical agents and metals) (19,20).

Pesticides were agents with significantly increased risk estimates reported in more than one study, albeit in class IV studies. Some have suggested that an increased prevalence of ALS among Gulf War veterans and farmers may imply a link between exposure to environmental toxins, such as organophosphate pesticides and chemical nerve agents, and ALS (21,22). In addition, a potentially increased ALS risk for soccer players due to exposure to high levels of toxic herbicides or fertilizers used to maintain football grounds has also been proposed (23). Besides the significantly increased risk estimates reported for pesticides in two studies (12,13), this review also showed a significantly increased risk estimate for insecticides (12), fertilizers (12), other agricultural chemicals (12), and farm-related occupations (13). Moreover, these findings corroborate the hypothesis that exposure to pesticides and consequent mitochondrial dysfunction plays a role in the pathogenesis of ALS and other neurodegenerative disorders (24–26).

Studies with higher quality exposure assessment methods must be performed in order to provide valid information on environmental risk factors for ALS. Occupation can serve as a surrogate for a variety of environmental exposures (27). A job-exposure matrix can be relatively easily applied to large study populations, such as emerging international collaborative projects (28,29). Validity is dependent on quality of job history and job levels may not be sufficiently specific, and so smaller studies, in which exposure is assessed per case by expert(s), may produce more valid data, but may not have sufficient power to demonstrate associations by themselves. Moreover, more industry-based studies should be performed.

In conclusion, this systematic review of the literature revealed exposure to pesticides as a potential environmental risk factor for ALS, but additional well-designed studies in which exogenous exposure of the subjects is adequately assessed are clearly needed to replicate and shed more light on these findings. Hopefully, this will eventually lead to the identification of exogenous risk factors for this devastating disease.

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References

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. N Engl J Med. 2001;344:1688–700.
2. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. Lancet. 2007;369:2031–41.
3. Simpson CL, Al-Chalabi A. Amyotrophic lateral sclerosis as a complex genetic disease. Biochim Biophys Acta. 2006; 1762:973–85.
4. Shaw CE, Al-Chalabi A, Leigh N. Progress in the pathogenesis of amyotrophic lateral sclerosis. Curr Neurol Neurosci Rep. 2001;1:69–76.
5. Slowik A, Tomik B, Wolkow PP, Partyka D, Turaj W, Malecki MT, et al. Paraoxonase gene polymorphisms and sporadic ALS. Neurology. 2006;67:766–70.
6. Saeed M, Siddique N, Hung WY, Usacheva E, Liu E, Sufit RL, et al. Paraoxonase cluster polymorphisms are associated with sporadic ALS. Neurology. 2006;67:771–6.
7. Cronin S, Greenway MJ, Prehn JH, Hardiman O. Paraoxonase promoter and intronic variants modify risk of sporadic amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2007;78:984–6.
8. Haley RW. Gulf war syndrome: narrowing the possibilities. Lancet Neurol. 2003;2:272–3.
9. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. Neuroepidemiology. 2003;22: 217–28.
10. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. Environ Health Perspect. 2005;113:1250–6.
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–12.
12. McGuire V, Longstreth WT Jr, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. Am J Epidemiol. 1997;145:1076–88.
13. Park RM, Schulte PA, Bowman JD, Walker JT, Bondy SC, Yost MG, et al. Potential occupational risks for neurodegenerative diseases. Am J Ind Med. 2005;48:63–77.
14. Vinceti M, Nacci G, Rocchi E, Cassinadri T, Vivoli R, Marchesi C, et al. Mortality in a population with long-term exposure to inorganic selenium via drinking water. J Clin Epidemiol. 2000;53:1062–8.
15. Gait R, Maginnis C, Lewis S, Pickering N, Antoniak M, Hubbard R, et al. Occupational exposure to metals and solvents and the risk of motor neuron disease: a case-control study. Neuroepidemiology. 2003;22:353–6.
16. Steenland K, Hein MJ, Cassinelli II RT, Prince MM, Nilsen NB, Whelan EA, et al. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. Epidemiology. 2006;17:8–13.
17. Welp E, Kogevinas M, Andersen A, Bellander T, Biocca M, Coggon D, et al. Exposure to styrene and mortality from nervous system diseases and mental disorders. Am J Epidemiol. 1996;144:623–33.
18. Lewis RJ, Schnatter AR, Katz AM, Thompson FS, Murray N, Jorgensen G, et al. Updated mortality among diverse operating segments of a petroleum company. Occup Environ Med. 2000;57:595–604.
19. Chancellor AM, Slattery JM, Fraser H, Warlow CP. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry. 1993;56:1200–6.
20. Longnecker MP, Kamel F, Umbach DM, Munsat TL, Shefner JM, Lansdell LW, et al. Dietary intake of calcium, magnesium and antioxidants in relation to risk of amyotrophic lateral sclerosis. Neuroepidemiology. 2000;19:210–6.
21. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003;61:750–6.
22. Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. Neurology. 2003; 61:742–9.
23. Al-Chalabi A, Leigh PN. Trouble on the pitch: are professional football players at increased risk of developing amyotrophic lateral sclerosis? Brain. 2005;128:451–3.
24. Jenner P, Olanow CW. Understanding cell death in Parkinson's disease. Ann Neurol. 1998;44:S72–84.
25. Beal MF. Mitochondria take centre stage in ageing and neurodegeneration. Ann Neurol. 2005;58:495–505.
26. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease withx exposure to pesticides, farming, well water, and rural living. Neurology. 1998;50:1346–50.
27. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Amyotrophic lateral sclerosis and occupational history: a pilot case-control study. Arch Neurol. 1996;53:730–3.
28. Beghi E. 127th ENMC International Workshop: implementation of a European registry of ALS. Naarden, The Netherlands, 8–10 October 2004. Neuromuscul Disord. 2006; 16:46–53.
29. Chang, T.M.S. Monograph on Artificial Cells: Biotechnology, Nanotechnology, Blood Substitutes, Regenerative Medicine, Bioencapsulation, Cell/Stem Cell Therapy. World Science Publishers, Singapore; 2007.

E-Table 1. Search terms in Medline, EMBASE, CINAHL, Cochrane: Chemical Agents.

Medline

ALS
"motor neuron disease" [MeSH Terms] OR "motor neurone disease" OR "motor neurone diseases" OR "motor neuron disease" OR "motor neuron diseases" OR "lateral sclerosis" OR ALS OR MND OR "progressive spinal muscular atrophy" OR "motor neuropathy" OR "motor neuropathies"

Chemicals
"Specialty Uses of Chemicals" [MeSH Terms] OR "Organic Chemicals" [MeSH Terms] OR "Inorganic Chemicals" [MeSH Terms] OR "Toxic Actions" [MeSH Terms] OR chemical* OR solvent* OR pesticide* OR fungicide* OR herbicide* OR insecticide* OR toxic* OR toxif* OR toxik* OR toxin* OR "macromolecular substances" [MeSH Terms] OR plastic* OR impregnat* OR apat OR "Tars" [MeSH Terms] OR tar OR tars OR "Petroleum" [MeSH Terms] OR petroleum* OR pitch OR "paint" [MeSH Terms] OR paint* OR varnish* OR fume* OR vapour* OR vapor* OR "ink" [MeSH Terms] OR ink* OR thinner* OR adhesive* OR glue* OR mucilage* OR "sticky paste" OR gum* OR latex* OR alcohol* OR ethanol* OR ketone* OR toluene* OR benzene* OR xylene* OR oil* OR "Fuel Oils" [MeSH Terms] OR fuel* OR phenol* OR styrene* OR "Manure" [MeSH Terms] OR manure* OR "Minerals" [MeSH Terms] OR mineral* OR ore OR "taconite" [Substance Name] OR "manganese poisoning" [MeSH Terms] OR "dust" [MeSH Terms Terms] OR dust*

EMBASE
ALS
'motor neuron disease'/syn OR 'lateral sclerosis' OR als OR mnd OR 'progressive spinal muscular atrophy'/syn OR 'motor neuropathy'/syn OR 'motor neuropathies' AND [humans]/lim AND [embase]/lim

Chemicals
'environmental, industrial and domestic chemicals'/syn OR 'general and inorganic chemicals'/exp OR chemical* OR solvent* OR 'solvent'/syn OR 'chemical pest control'/syn OR pesticide* OR 'pesticide'/syn OR fungicide* OR 'fungicide'/syn OR herbicide* OR 'herbicide'/syn OR insecticide* OR 'insecticide'/syn OR 'malathion'/syn OR toxi* OR 'toxin'/syn OR 'abrin'/syn OR 'plastic industry'/syn OR plastic* OR 'plastic'/syn OR impregnat* OR apat OR tar* OR 'tar'/syn OR 'chemical industry'/syn OR 'petrochemical industry'/syn OR petroleum* OR 'petroleum'/syn OR 'pitch'/syn OR 'paint industry'/syn OR paint* OR 'paint'/syn OR varnish* OR thinner* OR 'thinner'/syn OR 'gases, fumes, vapors and related phenomena'/exp OR fume* OR vapor* OR 'vapor'/syn OR vapour* OR ink* OR 'ink'/syn OR adhesive* OR 'adhesive'/syn OR 'glue sniffing'/syn OR glue* OR 'glue'/syn OR mucilage* OR 'mucilage'/syn OR 'sticky paste'/syn OR gum* OR 'latex'/syn OR alcohol* OR 'alcohol'/syn OR ethanol* OR ketone* OR 'ketone'/syn OR 'aromatic hydrocarbon'/syn OR benzene* OR 'benzene'/syn OR toluene* OR 'toluene'/syn OR styrene* OR 'styrene'/syn OR xylene* OR 'xylene'/syn OR oil* OR 'oil'/syn OR 'fuel and fuel related phenomena'/exp OR fuel* OR phenol* OR 'phenol'/syn OR manure* OR 'manure'/syn OR mineral* OR 'mineral'/syn OR 'ore'/syn OR 'dust and dust related phenomena'/exp OR dust* OR 'dust'/syn

CINAHL
ALS
((als) in TI) or ((als) in AB) or ((lateral sclerosis) in TI) or ((lateral sclerosis) in AB) or ((motor neuron diseases) in TI) or ((motor neuron diseases) in AB) or ((motor neurone disease) in AB) or ((motor neurone disease) in TI) or ((motor neuron disease) in TI) or ((motor neuron disease) in AB) or ((motor neuropathies) in TI) or ((motor neuropathies) in AB) or ((motor neuropathy) in TI) or ((motor neuropathy) in AB) or ((progressive spinal muscular atrophy) in TI) or ((progressive spinal muscular atrophy) in AB) or ((mnd) in TI) or ((mnd) in AB)

Chemicals
(alcohol*) or (latex*) or (gum*) or (sticky paste) or (mucilage*) or (glue*) or (adhesive*) or (thinner*) or (ink*) or (vapor*) or (vapour*) or (fume*) or (varnish*) or (paint*) or (pitch) or (petroleum*) or (tar*) or (apat) or (impregnat*) or (plastic*) or (dust*) or (insecticide*) or (ore) or (herbicide*) or (mineral*) or (fungicide*) or (manure*) or (pesticide*) or (styrene*) or (solvent*) or (phenol*) or (toxi*) or (fuel*) or (oil*) or (xylene*) or (chemical*) or (benzene*) or (toluene*) or (ketone*) or (ethanol*)

Cochrane
(lateral sclerosis) or (motor neuron disease) or (motor neurone disease) or (progressive spinal muscular atrophy)

E-Table II. Search terms in Medline, EMBASE, CINAHL, Cochrane: Metals.

Medline

ALS
'motor neuron disease' [MeSH Terms] OR 'motor neurone disease' OR 'motor neurone diseases' OR 'motor neuron disease' OR 'motor neuron diseases' OR 'lateral sclerosis' OR ALS OR MND OR 'progressive spinal muscular atrophy' OR 'motor neuropathy' OR 'motor neuropathies'

Metals
'metals, heavy' [MeSH Terms] OR 'metals, light' [MeSH Terms] OR elements [MeSH Terms] OR metal OR metals OR metals [MeSH Terms] OR 'Heavy Metal Poisoning, Nervous System' [MeSH Terms] OR metallurgy [MeSH Terms] OR aluminium OR aluminum [MeSH Terms] OR aluminum* OR magnesium [MeSH Terms] OR magnesium* OR selenium [MeSH Terms] OR selenium* OR manganese [MeSH Terms] OR manganes* OR calcium [MeSH Terms] OR calcium* OR arsenic [MeSH Terms] OR arsenic* OR silicon* OR lead [MeSH Terms] OR lead* OR mercury [MeSH Terms] OR mercur* OR cadmium [MeSH Terms] OR

EMBASE

ALS
'motor neuron disease'/syn OR 'lateral sclerosis' OR als OR mnd OR 'progressive spinal muscular atrophy'/syn OR 'motor neuropathy'/syn OR 'motor neuropathies' AND [humans]/lim AND [embase]/lim

Metals
'heavy metal'/syn OR 'metal'/syn OR metal* OR 'element'/syn OR element* OR 'heavy metal poisoning'/syn OR aluminum/syn OR aluminum* OR aluminium OR magnesium/syn OR magnesium* OR selenium/syn OR selenium* OR manganese/syn OR manganes* OR calcium/syn OR calcium* OR arsenic/syn OR arsenic* OR silicon/syn OR silicon* OR lead/syn OR lead* OR mercury/syn OR mercur* OR cadmium/syn OR iron/syn OR iron* OR silver/syn OR silver* OR chromium/syn OR chromate* OR cobalt/syn OR cobalt* OR nickel/syn OR nickel* OR 'welding'/syn OR weld*:ti OR weld*:ab AND [embase]/lim AND [humans]/lim

CINAHL

ALS
((motor neuron disease) in AB) or ((motor neuron disease) in TI) or ((motor neurone disease) in AB) or ((motor neurone disease) in TI) or ((motor neuron diseases) in AB) or ((motor neuron diseases) in TI) or ((lateral sclerosis) in AB) or ((lateral sclerosis) in TI)) or ((als) in AB) or ((als) in TI) or ((mnd) in AB) or ((mnd) in TI)) or ((progressive spinal muscular atrophy) in AB) or ((progressive spinal muscular atrophy) in TI) or ((motor neuropathy) in AB) or ((motor neuropathy) in TI) or ((motor neuropathies) in AB) or ((motor neuropathies) in TI)

Metals
element* or metal* or aluminum* or aluminium or magnesium* or selenium* or manganes* or calcium* or arsenic* or silicon* or lead* or mercur* or cadmium* or iron* or silver* or chromium* or cobalt* or nickel* or chromate* or ((weld*) in AB) or ((weld*) in TI)

Cochrane
(lateral sclerosis) or (motor neuron disease) or (motor neurone disease) or (progressive spinal muscular atrophy)

E-Table III. Study characteristics and quality assessment of studies dealing with chemical agents and ALS.

	Study population			
Author, Year	Patients (no.)	Controls (no.)	Level of evidence Armon	EA-score
Case-control				
Chio 1991	512	512	IV	2
Chancellor 1993	103	103	III	2
Gunnarsson 1992	92	372	IV	2
Li 1990	560	220	IV	2
Deapen 1986	518	518	IV	1
Kondo 1981 (A+B)	712+158	637+158	IV	2
Mitchell 1995	128	256	IV	2
Granieri 1988	72	216	IV	2
Graham 1997	70	70	IV	2
Strickland 1996/2	25	50	IV	2
Morahan 2006	179	179	IV	1
Norris 1989	54	54	IV	1
Savettieri 1991	46	92	IV	1
Sienko 1990	6	12	IV	2
Yoshida 1989	31	22	IV	0
Roelofs-Iverson 1984	145	177	IV	2
Den Hartog-Jager 1987	100	100	IV	1
Kalfakis 1991	316	360	IV	2
Gregoire 1991	35	35	IV	2
Register-based case-control				
Gunnarsson 1991	1375	1434	IV	1
Hawkes 1989?	33	131	IV	1
Register-based cohort				
Argyriou 2005	133	835,000, Gen. Popul.	IV	1
Chen 1999	953	953	IV	1
Govoni 2005	91	Gen. Popul.	IV	1
Gunnarson 1996	168	Gen. Popul.	IV	1
Mandrioli 2003	143	Gen. Popul.	IV	1
Martyn 1989	2	3830	IV	0
Schulte 1996	635	Gen. Popul.	IV	1
Thomas 1990	2	~1000	IV	1
Weisskopf 2005	937	12,000,000	IV	1

Gen. Popul.: General Population
EA: Exposure assessment

1. Argyriou AA, Polychronopoulos P, Papapetropoulos S, et al. Clinical and epidemiological features of motor neuron disease in south-western Greece. Acta Neurol Scand 2005; 111(2):108–113.
2. Chancellor AM, Slattery JM, Fraser H, Warlow CP. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry 1993; 56(11):1200–1206.
3. Chen R, Dick F, Seaton A. Health effects of solvent exposure among dockyard painters: mortality and neuropsychological symptoms. Occup Environ Med 1999; 56(6):383–387.
4. Chio A, Meineri P, Tribolo A, Schiffer D. Risk factors in motor neuron disease: a case-control study. Neuroepidemiology 1991; 10(4):174–184.
5. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 1986; 123(5):790–799.
6. den Hartog Jager WA, Hanlo PW, Ansink BJ, Vermeulen MB. Results of a questionnaire in 100 ALS patients and 100 control cases. Clin Neurol Neurosurg 1987; 89(1):37–41.
7. Govoni V, Granieri E, Fallica E, Casetta I. Amyotrophic lateral sclerosis, rural environment and agricultural work in the Local Health District of Ferrara, Italy, in the years 1964–1998. J Neurol 2005; 252(11):1322–1327.
8. Graham AJ, Macdonald AM, Hawkes CH. British motor neuron disease twin study. J Neurol Neurosurg Psychiatry 1997; 62(6):562–569.
9. Granieri E, Carreras M, Tola R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964–1982. Neurology 1988; 38(10):1604–1608.
10. Gregoire N, Serratrice G. [Risk factors in amyotrophic lateral sclerosis. Initial results apropos of 35 cases]. Rev Neurol (Paris) 1991; 147(11):706–713.
11. Gunnarsson LG, Bodin L, Soderfeldt B, Axelson O. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. Br J Ind Med 1992; 49(11):791–798.
12. Gunnarsson LG, Lindberg G, Soderfeldt B, Axelson O. Amyotrophic lateral sclerosis in Sweden in relation to occupation. Acta Neurol Scand 1991; 83(6):394–398.
13. Gunnarsson LG, Lygner PE, Veiga-Cabo J, de Pedro-Cuesta J. An epidemic-like cluster of motor neuron disease in a Swedish county during the period 1973–1984. Neuroepidemiology 1996; 15(3):142–152.

14. Hawkes CH, Cavanagh JB, Fox AJ. Motoneuron disease: A disorder secondary to solvent exposure? Lancet 1989; 1(8629):73–76.
15. Kalfakis N, Vassilopoulos D, Voumvourakis C, Ndjeveleka M, Papageorgiou C. Amyotrophic lateral sclerosis in southern Greece: an epidemiologic study. Neuroepidemiology 1991; 10(4):170–173.
16. Kondo K, Tsubaki T. Case-control studies of motor neuron disease: association with mechanical injuries. Arch Neurol 1981; 38(4):220–226.
17. Li TM, Alberman E, Swash M. Clinical features and associations of 560 cases of motor neuron disease. J Neurol Neurosurg Psychiatry 1990; 53(12):1043–1045.
18. Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. Neurology 2003; 60(4):683–689.
19. Martyn CN. Motoneuron disease and exposure to solvents. Lancet 1989; 1(8634):394.
20. Mitchell JD, Davies RB, Al-Hamad A, Gatrell AC, Batterby G. MND risk factors: an epidemiological study in the north west of England. J Neurol Sci 1995; 129 Suppl:61–64.
21. Morahan JM, Pamphlett R. Amyotrophic lateral sclerosis and exposure to environmental toxins: an Australian case-control study. Neuroepidemiology 2006; 27(3):130–135.
27. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Amyotrophic lateral sclerosis and occupational history. A pilot case-control study. Arch Neurol 1996; 53(8):730–733.
28. Thomas TL, Kang HK. Mortality and morbidity among Army Chemical Corps Vietnam veterans: a preliminary report. Am J Ind Med 1990; 18(6):665–673.
29. Weisskopf MG, McCullough ML, Morozova N, Calle EE, Thun MJ, Ascherio A. Prospective study of occupation and amyotrophic lateral sclerosis mortality.
22. Norris FH, Padia LA. Toxic and pet exposures in amyotrophic lateral sclerosis. Arch Neurol 1989; 46(9):945.
23. Roelofs-Iverson RA, Mulder DW, Elveback LR, Kurland LT, Molgaard CA. ALS and heavy metals: a pilot case-control study. Neurology 1984; 34(3):393–395.
24. Savettieri G, Salemi G, Arcara A, Cassata M, Castiglione MG, Fierro B. A casecontrol study of amyotrophic lateral sclerosis. Neuroepidemiology 1991; 10(5–6):242–245.
25. Schulte PA, Burnett CA, Boeniger MF, Johnson J. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 1996; 86(9):1281–1288.
26. Sienko DG, Davis JP, Taylor JA, Brooks BR. Amyotrophic lateral sclerosis. A case-control study following detection of a cluster in a small Wisconsin community. Arch Neurol 1990; 47(1):38–41. Am J Epidemiol 2005; 162(12):1146–1152.
30. Yoshida Y, Hamada R, Kamitsuchibashi H, et al. Determination of urine thiocyanate in patients with amyotrophic lateral sclerosis. Acta Neurol Scand 1989; 80(5):444–450.

E-Table IV. Study characteristics and quality assessment of studies dealing with metals and ALS.

Author, year	Study population		Level of evidence Armon	EA-score
	Patients (no.)	Controls (no.)		
Case-control				
Armon 1991	74	201	IV	2
Bergomi 2002	22	40	IV	2
Chancellor 1993	103	103	III	2
Chio 1991	512	512	IV	2
Conradi 1980	16	22	IV	2
Deapen 1986	518	518	IV	1
Deibel 1997	31	17	IV	2
Den Hartog-Jager 1987	100	100	IV	1
Felmus 1976	25	25	IV	2
Felmus 1982	7	7	IV	2
Graham 1997	70	70	IV	2
Granieri 1988	72	216	IV	2
Gresham 1986	66	66	IV	2
Gunnarsson 1992	92	372	IV	2
Ihara 2005	25	16	IV	2
Ince 1994	38	22	IV	2
Kamel 2002	109	256	III	2
Kapaki 1997	28	38	IV	2
Kasarkis 1995	5	5	IV	2
Kihira 1990	5	5	IV	2
Kondo A 1981	712	637	IV	2
Longnecker 2000	107	262	III	0
Markesberry 1995	38	22	IV	2
Mitchell 1984	20	14	IV	2
Mitchell 1986	5	5	IV	2
Mitchell 1995	128	256	IV	2
Miyata 1983	7	6	IV	2
Morahan 2006	179	179	IV	1
Nagata 1985	25	37	IV	2
Norris 1989	54	54	IV	1
Oishi 1990	11	11	IV	2
Pamphlett 1998	22	20	IV	2
Pamphlett 2001	20	20	IV	2
Pierce-Ruhland 1980	21	21	IV	2
Pierce-Ruhland 1981	80	78	IV	2
Provinciali 1990	77	80	IV	2
Roelofs-Iverson 1984	145	177	IV	2
Sienko 1990	6	12	IV	2
Stober 1983	9	15	IV	2
Strickland 1996/2	25	50	IV	2
Tandon 1994	15	17	IV	2
Tandon 1995	12	10	IV	2
Vinceti 1997	16	39	IV	2
Register-based case-control				
Gunnarsson 1991	1375	1434	IV	1
Register-based cohort				
Bharucha 1983	~	~	IV	1
Guidetti 1996	79	416034	IV	0
Scarpa 1988	51	596025	IV	0

EA-score: Exposure assessment score

1. Armon C, Kurland LT, Daube JR, O'Brien PC. Epidemiologic correlates of sporadic amyotrophic lateral sclerosis. Neurology 1991; 41(7):1077–1084.
2. Bergomi M, Vinceti M, Nacci G, et al. Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case-control study. Environ Res 2002; 89(2):116–123.
3. Bharucha NE, Schoenberg BS, Raven RH, Pickle LW, Byar DP, Mason TJ. Geographic distribution of motor neuron disease and correlation with possible etiologic factors. Neurology 1983; 33(7):911–915.
4. Chancellor AM, Slattery JM, Fraser H, Warlow CP. Risk factors for motor neuro disease: a case-control study based on patients from the Scottish Motor.
Neuron Disease Register. J Neurol Neurosurg Psychiatry 1993; 56(11):1200–1206.
5. Chio A, Meineri P, Tribolo A, Schiffer D. Risk factors in motor neuron disease: a case-control study. Neuroepidemiology 1991; 10(4):174–184.
6. Conradi S, Ronnevi LO, Nise G, Vesterberg O. Abnormal distribution of lead in amyotrophic lateral sclerosis–reestimation of lead in the cerebrospinal fluid J Neurol Sci 1980; 48(3):413–418.
7. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 1986; 123(5):790–799.
8. Deibel MA, Ehmann WD, Candy JM, Ince PG, Shaw PJ, Markesbery WR. Aluminum in motor neuron disease spinal cord. TRACE ELEM ELECTROCYTES 1997; 14(1):51–54.
9. den Hartog Jager WA, Hanlo PW, Ansink BJ, Vermeulen MB. Results of a questionnaire in 100 ALS patients and 100 control cases. Clin Neurol Neurosurg 1987; 89(1):37–41.
10. Felmus MT, Patten BM, Swanke L. Antecedent events in amyotrophic lateral sclerosis. Neurology 1976; 26(2):167–172.
11. Felmus MT, Rasool CG, Bradley WG. Calcium content of RBCs from patients with amyotrophic lateral sclerosis. Arch Neurol 1982; 39(7):454.
12. Graham AJ, Macdonald AM, Hawkes CH. British motor neuron disease twin study. J Neurol Neurosurg Psychiatry 1997; 62(6):562–569.
13. Granieri E, Carreras M, Tola R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964–1982. Neurology 1988; 38(10):1604–1608.
14. Gresham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and occupational heavy metal exposure: a case-control study. Neuroepidemiology 1986; 5(1):29–38.
15. Guidetti D, Bondavalli M, Sabadini R, et al. Epidemiological survey of amyotrophic lateral sclerosis in the province of Reggio Emilia, Italy: influence of environmental exposure to lead. Neuroepidemiology 1996; 15(6):301–312.
16. Gunnarsson LG, Lindberg G, Soderfeldt B, Axelson O. Amyotrophic lateral sclerosis in Sweden in relation to occupation. Acta Neurol Scand 1991; 83(6):394–398.
17. Gunnarsson LG, Bodin L, Soderfeldt B, Axelson O. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. Br J Ind Med 1992; 49(11):791–798.
18. Ihara Y, Nobukuni K, Takata H, Hayabara T. Oxidative stress and metal content in blood and cerebrospinal fluid of amyotrophic lateral sclerosis patients with and without a Cu, Zn-superoxide dismutase mutation. Neurol Res 2005; 27(1):105–108.
19. Ince PG, Shaw PJ, Candy JM, et al. Iron, selenium and glutathione peroxidase activity are elevated in sporadic motor neuron disease. Neurosci Lett 1994; 182(1):87–90.
20. Kamel F, Umbach DM, Munsat TL, Shefner JM, Hu H, Sandler DP. Lead exposure and amyotrophic lateral sclerosis. Epidemiology 2002; 13(3):311–319.
21. Kapaki E, Zournas C, Kanias G, Zambelis T, Kakami A, Papageorgiou C. Essential trace element alterations in amyotrophic lateral sclerosis. J Neurol Sci 1997; 147(2):171–175.
22. Kasarskis EJ, Tandon L, Lovell MA, Ehmann WD. Aluminum, calcium, and iron in the spinal cord of patients with sporadic amyotrophic lateral sclerosis using laser microprobe mass spectroscopy: a preliminary study. J Neurol Sci 1990; 130(2):203–208.
23. Kihira T, Mukoyama M, Ando K, Yase Y, Yasui M. Determination of manganese concentrations in the spinal cords from amyotrophic lateral sclerosis patients by inductively coupled plasma emission spectroscopy. J Neurol Sci 1990; 98(2–3):251–258.
24. Kondo K, Tsubaki T. Case-control studies of motor neuron disease: association with mechanical injuries. Arch Neurol 1981; 38(4):220–226.
25. Longnecker MP, Kamel F, Umbach DM, et al. Dietary intake of calcium, magnesium and antioxidants in relation to risk of amyotrophic lateral sclerosis. Neuroepidemiology 2000; 19(4):210–216.
26. Markesbery WR, Ehmann WD, Candy JM, et al. Neutron activation analysis of trace elements in motor neuron disease spinal cord. Neurodegeneration 1995; 4(4):383–390.
27. Mitchell JD, Davies RB, Al-Hamad A, Gatrell AC, Batterby G. MND risk factors an epidemiological study in the north west of England. J Neurol Sci 1995129 Suppl:61–64.
28. Mitchell JD, East BW, Harris IA, Prescott RJ, Pentland B. Trace elements in the spinal cord and other tissues in motor neuron disease. J Neurol Neurosurg Psychiatry 1986; 49(2):211–215.
29. Mitchell JD, Harris IA, East BW, Pentland B. Trace elements in cerebrospinal fluid in motor neurone disease. Br Med J (Clin Res Ed) 1984; 288(6433):1791–1792.
30. Miyata S, Nakamura S, Nagata H, Kameyama M. Increased manganese level in spinal cords of amyotrophic lateral sclerosis determined by radiochemical neutron activation analysis. J Neurol Sci 1983; 61(2):283–293.
31. Morahan JM, Pamphlett R. Amyotrophic lateral sclerosis and exposure to environmental toxins: an Australian case control study Neuroepidemiology 2006; 27(3):130–135.
32. Nagata H, Miyata S, Nakamura S, Kameyama M, Katsui Y. Heavy metal concentrations in blood cells in patients with amyotrophic lateral sclerosis Neurol Sci 1985; 67(2):173–178.
33. Norris FH, Padia LA. Toxic and pet exposures in amyotrophic lateral sclerosis. Arch Neurol 1989; 46(9):945.
34. Oishi M, Takasu T, Tateno M. Hair trace elements in amyotrophic lateral scleros TRACE ELEM MED 1990; 7(4):182–185.
35. Pamphlett R, McQuilty R, Zarkos K. Blood levels of toxic and essential metals in motor neuron disease. Neurotoxicology 2001; 22(3):401–410.
36. Pamphlett R, Waley P. Mercury in human spinal motor neurons. Acta Neuropath (Berl) 1998; 96(5):515–519.
37. Pierce-Ruhland R, Patten BM. Repeat study of antecedent events in motor neuron disease. Ann Clin Res 1981; 13(2):102–107.
38. Pierce-Ruhland R, Patten BM. Muscle metals in motor neuron disease. Ann Neurol 1980; 8(2):193–195.

39. Provinciali L, Giovagnoli AR. Antecedent events in amyotrophic lateral sclerosis: do they influence clinical onset and progression? Neuroepidemiology 1990; 9(5):255–262.
40. Roelofs-Iverson RA, Mulder DW, Elveback LR, Kurland LT, Molgaard CA. ALS and heavy metals: a pilot case-control study. Neurology 1984; 34(3):393–395.
41. Scarpa M, Colombo A, Panzetti P, Sorgato P. Epidemiology of amyotrophic lateral sclerosis in the province of Modena, Italy. Influence of environmental exposure to lead. Acta Neurol Scand 1988; 77(6):456–460.
42. Sienko DG, Davis JP, Taylor JA, Brooks BR. Amyotrophic lateral sclerosis. A case-control study following detection of a cluster in a small Wisconsin community. Arch Neurol 1990; 47(1):38–41.
43. Stober T, Stelte W, Kunze K. Lead concentrations in blood, plasma, erythrocytes, and cerebrospinal fluid in amyotrophic lateral sclerosis. J Neurol Sci 1983; 61(1):21–26.
44. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Amyotrophic lateral sclerosis and occupational history. A pilot case-control study. Arch Neurol 1996; 53(8):730 730–733.
45. Tandon L, Kasarskis EJ, Ehmann WD. Elemental imbalance studies by INAA on extraneural tissues from amyotrophic lateral sclerosis patients. J RADIOANAL NUCL CHEM 1995; 195(1):13–19.
46. Tandon L, Ni BF, Ding XX, Ehmann WD, Kasarskis EJ, Markesbery WR. RNAA for arsenic, cadmium, copper, and molybdenum in CNS tissues from subjects with age-related neurodegenerative diseases. J RADIOANAL NUCL CHEM 1994; 179(2):331–339.
47. Vinceti M, Guidetti D, Bergomi M, et al. Lead, cadmium, and selenium in the blood of patients with sporadic amyotrophic lateral sclerosis. Ital J Neurol Sci 1997; 18(2):87–92.

E-Table V. Data from 7 included studies on associations between chemical agents and ALS.

Exposure	Author, year	Design	Region	Patients, (*n*)	Exposed patients, (*n*)	Controls, (*n*)	Exposed controls, (*n*)	Level of evidence, Armon	EA score	Risk estimate	95% CI	Selected risk estimate
A) Organic solvents												
Cleaning solvents or degreasers												
*Cleaning solvents or degreasers	McGuire 1997	2	USA	174	43	348	60	III	4	1.9‖	1.1-3.3	x
Alcohol												
*Alcohols or ketones	McGuire 1997	2	USA	174	21	348	26	III	4	2.0‖	1.0-4.0	x
Benzene, toluene, xylene or styrene and other aromatic hydrocarbons												
Benzene, toluene or xylene	McGuire 1997	2	USA	174	26	348	32	III	4	1.7‖	0.9-3.0	x
Benzene	Park 2005	4	USA	6347	1356	2501541	–	IV	4	1.14‖	0.97-1.33	x
Styrene	McGuire 1997	2	USA	174	21	348	2	III	4	1.1‖	0.1-12.5	x
Styrene (50-199 ppm-years)	Welp 1996	1	Europe	7	7	Gen. Popul.	35443	IV	4	3.14**	0.39-25.5	
Styrene (200-499 ppm-years)	Welp 1996	1	Europe	7	7	Gen. Popul.	35443	IV	4	6.9**	0.92-51.8	x
Styrene ($\geq$500 ppm-years)	Welp 1996	1	Europe	7	7	Gen. Popul.	35443	IV	4	2.47**	0.21-29.11	
Styrene ($\geq$10 years of duration)	Welp 1996	1	Europe	7	7	Gen. Popul.	35443	IV	4	6.69**	0.53-85.08	
PCB-exposed workers	Steenland 2006	3	USA	11	11	Gen. Popul.	17321	IV	4	1.06‡‡	0.53-1.89	x
PCB-exposed workers	Steenland 2006	3	USA	0‡	0	Gen. Popul.	~8660	IV	4	0.00‡‡	0.00-0.68	
PCB-exposed workers	Steenland 2006	3	USA	11‡	11	Gen. Popul.	~8660	IV	4	2.21‡‡	1.11-3.96	
Phenols												
Phenols	McGuire 1997	2	USA	174	2	348	3	III	4	1.2‖	0.2-7.2	x
Paints												
Paint, varnish or stain	McGuire 1997	2	USA	174	23	348	37	III	4	1.2‖	0.7-2.2	x
Solvent-based inks or dyes												
Solvent-based inks or dyes	McGuire 1997	2	USA	174	5	348	20	III	4	0.5‖	0.2-1.3	x
Adhesives, glues or coatings												
Adhesives, glues or coatings	McGuire 1997	2	USA	174	18	348	24	III	4	1.4‖	0.7-2.6	x
Solvents n.e.c.												
Other solvents	McGuire 1997	2	USA	174	3	348	12	III	4	0.5‖	0.1-1.8	x
Any solvent												
Solvents	Gait 2003	4	UK	22‡	10	206	93	IV	4	1.12‖	0.45-2.78	x
Solvents	McGuire 1997	2	USA	174	85	348	155	III	4	1.2‖	0.8-1.9	x
Solvents	McGuire 1997	2	USA	95‡	66	190	120	III	4	1.3‖	0.7-2.3	
Solvents	McGuire 1997	2	USA	79‡	19	158	35	III	4	1.1‖	0.6-2.2	
*Solvents	Park 2005	3	USA	6347	1994	2501541	–	IV	4	1.16‖	1.01-1.34	x
B) Ocupations potentially exposed to solvents												
Hairdressers												
*Hairdressers and cosmetologists	Park 2005	3	USA	6347	?	2501541	–	IV	4	1.38‖	1.00-1.87	x

E-Table V (*Continued*)

Exposure	Author, year	Design	Region	Patients, (*n*)	Exposed patients, (*n*)	Controls, (*n*)	Exposed controls, (*n*)	Level of evidence, Armon	EA score	Risk estimate	95% CI	Selected risk estimate
Chemists, chemical engineers												
Chemists, chemical engineers	Park 2005	3	USA	6347	?	2501541	–	IV	4	0.97‖	0.64-1.42	x
Painters												
Painters, sculptors	Park 2005	3	USA	6347	?	2501541	–	IV	4	1.18‖	0.78-1.71	x
C) Agricultural chemicals												
Insecticides												
*Insecticides	McGuire 1997	2	USA	174	18	348	18	III	4	2.1‖	1.1-4.1	x
Insecticides	McGuire 1997	2	USA	174	15	348	33	III	4	1.0‖	0.5-1.8	
Insecticides	McGuire 1997	2	USA	95‡	16	190	14	III	4	2.5‖	1.2-5.3	
Fungicides												
Fungicides	McGuire 1997	2	USA	174	4	348	0	III	4			x
Fungicides	McGuire 1997	2	USA	174	10	348	14	III	4	1.7‖	0.7-4.2	
Fungicides	McGuire 1997	2	USA	95‡	4	190	0	III	4			
Herbicides												
Herbicides	McGuire 1997	2	USA	174	7	348	5	III	4	3.0‖	0.9-9.6	x
Herbicides	McGuire 1997	2	USA	174	11	348	15	III	4	1.7‖	0.7-3.9	
Herbicides	McGuire 1997	2	USA	95‡	5	190	4	III	4	2.7‖	0.7-10.7	
2,4-D, very low exposure	Burns 2001	3	USA	3	0	1517	–	IV	4			
2,4-D, low exposure	Burns 2001	3	USA	3	0	1517	–	IV	4			
2,4-D, moderate exposure	Burns 2001	3	USA	3	2	1517	–	IV	4	8.04*		
2,4-D, high exposure	Burns 2001	3	USA	3	1	1517	–	IV	4	4.54*		
2,4-D, total exposure	Burns 2001	3	USA	3	3	1517	–	IV	4	3.45*	1.10-11.11	
Other pesticides												
Other pesticides	McGuire 1997	2	USA	174	1	348	5	III	4	0.3‖	0.0-3.0	x
Other pesticides	McGuire 1997	2	USA	95‡	1	190	2	III	4	0.7‖	0.0-13.4	trend test
Pesticides												
*Any pesticide	McGuire 1997	2	USA	95‡	19	190	16	III	4	2.5‖	1.2-5.1	x
*pesicide-related jobs	Park 2005	3	USA	6347	240	2501541	?	IV	4	1.2‖	1.02-1.41	x
Agricultural chemicals												
*Agricultural chemicals	McGuire 1997	2	USA	174	21	348	28	III	4	2.0‖	1.1-3.5	x
Agricultural chemicals	McGuire 1997	2	USA	79‡	3	158	7	III	4	0.9‖	0.2-3.8	
Agricultural chemicals	McGuire 1997	2	USA	95‡	21	190	21	III	4	2.4‖	1.2-4.8	
D) Occupations potentially exposed to pesticides												
Farming												
*All farm-related, BOC occupation codes 473–477, 479, 483–489	Park 2005	3	USA	6347	245	2501541	–	IV	4	1.2‖	1.02-1.41	x
Farmers, excl horticultural, BOC occupation codes 473	Park 2005	3	USA	6347	198	2501541	–	IV	4	1.23‖	1.03-1.46	

E-Table V (*Continued*)

Exposure	Author, year	Design	Region	Patients, (*n*)	Exposed patients, (*n*)	Controls, (*n*)	Exposed controls, (*n*)	Level of evidence, Armon	EA score	Risk estimate	95% CI	Selected risk estimate
Horticultural specialists	Park 2005	3	USA	6347	?	2501541	–	IV	4	0.00‖	0.00-1.31	
Fertilizers												
*Fertilizers	McGuire 1997	2	USA	174	12	348	12	III	4	2.3‖	1.0-5.5	x
Fertilizers	McGuire 1997	2	USA	95‡	9	190	10	III	4	2.2‖	0.8-6.1	trend
E) Other												
Oils												
Refinery (hydrocarbons)	Jeffrey Lewis 2000	3	Canada	9266‡	7	GP	4.35	IV	3	1.61‡‡	0.65-3.31	
marketing or distribution (finished petroleum products)	Jeffrey Lewis 2000	3	Canada	6800‡	6	GP	3.39	IV	3	1.77‡‡	0.65-3.85	
marine (finished products)	Jeffrey Lewis 2000	3	Canada	1656‡	1	GP	0.83	IV	3	–	–	
exploration, drilling, production or pipeline (crude oil, drilling muds)	Jeffrey Lewis 2000	3	Canada	4432‡	1	GP	1.51	IV	3	–		
Employees of a petroleum company	Jeffrey Lewis 2000	3	Canada	26322‡	18	GP	11.11	IV	3	1.62‡‡	0.96-2.56	x
All employees of a petroleum company	Jeffrey Lewis 2000	3	Canada	8238‡	1	GP	1.4	IV	3		–	
Cutting or lubricating oils	McGuire 1997	2	USA	174	44	348	77	III	4	1.2‖	0.7-2.1	x
Machine fuels	McGuire 1997	2	USA	174	12	348	30	III	4	0.7‖	0.3-1.5	x
*Leaded gasoline fumes	McGuire 1997	2	USA	174	39	348	53	III	4	1.8‖	1.1-3.0	x
Plastic												
Plastic fumes or resins	McGuire 1997	2	USA	174	8	348	10	III	4	1.5‖	0.6-4.2	x

$p < 0.05$
cohort
case-control
mortality cohort
mortality case-control
‡only men
†only women
*RR Risk ratio
‖OR Odds ratio
**SMR Standardized mortality ratio
Studies (n = 7) included according to validity criteria: Armon rating I, II, III, or IV; EA-score 3 or 4 Only one risk estimate per chemical agent per study was selected.

E-Table VI. Data from three included studies on associations between metals and ALS.

Exposure	Author, year	Region	Patients, (*n*)	Exposed patients, (*n*)	Controls, (*n*)	Exposed controls, (*n*)	Level of evidence, Armon	EA score	Risk estimate	95% CI
Lead Pb	McGuire 1997	USA	174	17	348	31	III	4	1.1‖	0.6-2.1
Mercury Hg	McGuire 1997	USA	174	1	348	4	III	4	0.5‖	0.1-4.5
Aluminium Al	McGuire 1997	USA	174	8	348	12	III	4	1.2‖	0.5-2.9
Cadmium Cd	McGuire 1997	USA	174	2	348	2	III	4	2‖	0.3-14.4
Chromium Cr	McGuire 1997	USA	174	0	348	2	III	4	–	–
Manganese Mn	McGuire 1997	USA	174	2	348	1	III	4	4.7‖	0.4-53.3
*Selenium Se	Vinceti 2000	Italy	3	3	Gen. Popul.	–	IV	4	5.72•	1.46-15.57
Metal, not otherwise classified										
Other	McGuire 1997	USA	174	49	348	82	III	4	1.2‖	0.8-1.9
Metals (exposure)	Gait	UK	22	13	206	131	IV	3	0.88‖	0.35-2.22
Metals 0.01–10 yrs	Gait	UK	22	2	206	31	IV	3	0.55‖	0.11-2.79
Metals 10–20 yrs	Gait	UK	22	4	206	31	IV	3	1.17‖	0.32-4.21
Metals 20–30 yrs	Gait	UK	22	4	206	19	IV	3	1.73‖	0.47-6.33
Metals > 30 yrs	Gait	UK	22	2	206	45	IV	3	0.45‖	0.09-2.24

*$p < 0.05$

‖Odds ratio (OR)

•Standardized mortality ratio (SMR)

¶Standardized incidence ratio

Studies ($n = 3$) included according to validity criteria: Armon rating I, II, III, or IV; EA-score 3 or 4.