Apparently ethanol is an Organic Solvent

Organic Solvents and Multiple Sclerosis: A Synthesis of the Current Evidence

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To evaluate the possible relation between exposure to organic solvents and the development of multiple sclerosis, we carried out a best-evidence synthesis of the available information. We found 13 studies with varying methodology that included information on solvent exposure. In 10 of the studies, there were indications of an increased risk of multiple sclerosis in relation to solvent exposure. We made three selections of studies for both pooled analyses and meta-analyses. The relative risk point estimates that we obtained varied from 1.7 to 2.6. Our evaluation is consistent with the hypothesis that organic solvents may be a cause of multiple sclerosis. (Epidemiology 1996;7: 429–433)

Keywords: meta-analysis, organic solvents, multiple sclerosis, exposure.

The causes of multiple sclerosis (MS) remain unknown despite intensive research. There is evidence for both genetic[1] and environmental factors.[2,3] A number of epidemiologic studies of MS have targeted occupational exposures, including organic solvent exposure. Our aim in this paper is to review all currently available studies on MS and solvent exposure.

Methods

We knew some of the pertinent studies of MS and solvent exposure from our work in the field, and we also carried out a literature search for the period 1966–1994 in the MEDLARS database. We reviewed all available studies for a best-evidence synthesis, a technique first proposed by Slavin.[4] This method combines the detailed analysis of critical issues and study characteristics of traditional narrative reviews with the quantification and systematic literature search methods of meta-analysis.

We evaluated studies in terms of (a) how many of the cases in the catchment area were likely to have been enrolled, (b) the adequacy of diagnostic criteria, (c) the choice of controls in case-control studies with respect to their representativeness of the source population for the cases, (d) the methodology of exposure assessment and (e) dose-response analysis, (f) control of confounding, and (g) assessment of effect modification (Table 1).

First, we included all available studies, representing a total of 1,079 cases (selection 1). We then excluded studies based on prevalence comparisons and analyzed the seven case-control studies that presented an effect estimate, representing a total of 890 cases (selection 2). Finally, we selected the three case-control studies that had the most similar design, included exposure assessment, and had a reasonably large size; these studies comprised 312 cases (selection 3).

For each of the three selections of studies, we calculated a pooled Mantel-Haenszel relative risk[5,6] ($RR_{MH\text{-}pool}$) and a "meta" RR (RR_{meta}), using a formula that enabled us to pool studies of different design as far as they provide an estimate of the same underlying relative risk.[7] The RR_{MHpool} estimates have the advantage of including study-specific data on the number of individuals. On the other hand, the RR_{meta} estimates are based on data after adjustment for confounding, where such procedures were performed.

Results

We found 13 published studies concerning solvent exposure and MS (9 case-control studies, 1 proportional mortality study, 2 prevalence comparisons, and 1 ecologic study) (Table 2).

Prevalence Comparison Studies

The first published study addressing the question of MS and solvent exposure was a prevalence survey from Italy in 1982.[8] The authors compared the prevalence of MS among workers in the shoe and leather industry in Florence with the prevalence of MS among the economically active and among the general population of the

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TABLE 1. Weighting* of Studies for Pooled Analyses and Meta-analyses with Regard to Solvent Exposure

Author	Appropriateness of Analysis				Cases/Controls			Exposure
	Dose-Response Analysis	Control of Confounding	Assessment of Effect Modification	Adequate Interview Procedure	Clear Case Definition	Good Case Coverage	Appropriate Control Selection	Good Exposure Assessment
Case-control studies								
Flodin *et al*[11]	+	+	+	+	(+)	+	+	+
Juntunen *et al*[12]	−	+	−	+	+	+	+	+
Koch-Henriksen[13]	(+)	+	−	+	+	+	+	(+)
Souberbielle *et al*[14]	−	+	−	+	+	+	+	−
Hopkins *et al*[15]	−	+	−	+	+	+	+	−
Grönning *et al*[16]	+	+	+	+	+	+	(+)	+
Landtblom *et al*[17]	−	+	−	+	(+)	+	+	+
Nelson *et al*[18]	+	+	−	+	+	+	−	+
Casetta *et al*[19]	−	−	−	+	+	+	+	−
Prevalence comparisons								
Amaducci *et al*[8]	0	0	0	0	+	+	0	0
Giuliani *et al*[9,10]	0	0	0	0	+	+	0	0

* + = yes; − = no; (+) = yes with some reservation; 0 = not relevant.

city, respectively. The prevalence ratio was 4.9 relative to each control group. Another prevalence study, presented in 1988,[9,10] reported a prevalence ratio of 3.1 for shoe and leather workers.

Case-Control Studies

The first case-control study, conducted in Sweden, appeared in 1988[11] and found an increased odds ratio (OR) for solvent exposure in men, especially in combination with welding. In 1989, Juntunen *et al*[12] published a study that investigated solvent exposure among twins with MS and their healthy twin siblings. They found a negative association. In contrast, Koch-Henriksen,[13] in a matched case-control study, found an OR of 2.0 [95% confidence interval (CI) = 0.8–4.7]. Souberbielle *et al*[14] reported a case-control study that listed the professions of cases and controls but did not present any estimation of actual solvent exposure. No predominance of occupations with a likely solvent exposure was found among the cases. Hopkins *et al*,[15] in a case-control study, investigated complete occupational histories, but there was little correlation between MS and "exposure to various chemicals, radiation or potentially toxic gases." Specific figures for organic solvent exposure were not presented. Grönning *et al*,[16] in a case-control study from Norway, found an increased OR of 1.6 (95% CI = 0.8–2.9), and Landtblom *et al*,[17] in a case-control study, also reported a positive effect, particularly in men (OR = 3.3; 95% CI = 1.1–9.5). Also, in a case-control study of automobile plant workers, Nelson *et al*[18] found an association between exposure to organic solvents and chronic neurologic disease, MS in particular, although the numbers were small. Recently, Casetta *et al*[19] reported an OR of 4.0 (95% CI = 1.4–11.1).

TABLE 2. Studies of Multiple Sclerosis and Solvent Exposure

Author and Year	Place	Study Design	RR	95% CI	Number of Cases
Case-control studies					
Flodin *et al*,[11] 1988	Sweden		1.9	0.9–3.7	82
Juntunen *et al*,[12] 1989	Finland	Co-twin study	0.2	0.02–1.7	21
Koch-Henriksen,[13] 1989	Denmark	Matched	2.0	0.8–4.7	187
Souberbielle *et al*,[14] 1990	France		Not calculable		230
Hopkins *et al*,[15] 1991	USA	Matched	Not calculable		16
Grönning *et al*,[16] 1993	Norway		1.6	0.8–2.9	139
Landtblom *et al*,[17] 1993	Sweden		2.8	1.3–5.5	91
Nelson *et al*,[18] 1994	USA	Matched	2.7	0.6–13.0	20
Casetta *et al*,[19] 1994	Italy		4.0	1.4–11.1	104
Various study designs					
Amaducci *et al*,[8] 1982	Italy	Prevalence comparison	4.9	2.1–11.0	81
Giuliani *et al*,[9,10] 1988	Italy	Prevalence comparison	3.1	2.0–4.8	108
Milham,[20] 1983	USA	Proportional mortality study	(PMR* = 233)		
Lauer,[21] 1989	Europe	Ecologic study	(r_s† = 0.4)		84
Total cases					1,163

* Proportional mortality ratio for automobile mechanics; see text.
† r_s for chemical industry in Denmark; see text.

Proportional Mortality Studies

Milham[20] reported occupational mortality data from Washington state for 1959–1979, which showed a higher than expected MS mortality in automobile mechanics and draftsmen, two occupations with solvent exposure. For the larger diagnostic group, "inflammatory diseases of the nervous system," which contains MS cases, Milham found an elevated proportional mortality ratio for airplane mechanics, who are likely to be exposed to solvents.

Ecologic Studies

Lauer[21] published an ecologic study in 1989 examining the association between the risk of MS and the proportion of workers in different industries in four European countries. For the chemical industry, in which exposure to organic solvents is comparatively common, there was a positive correlation in only one of the four countries.

TABLE 3. Assessment of Solvent Exposure in 13 Studies of Multiple Sclerosis Patients

Author and Year	Measure of Solvent Exposure
Case-control studies	
Flodin *et al*,[11] 1988	Self-report.* Minimum 1 year occupational exposure. Exposure intensity reported. Latency criterion
Juntunen *et al*,[12] 1989	Self-report. Crude exposure intensity reported
Koch-Henriksen,[13] 1989	Self-report. Three exposure levels
Souberbielle *et al*,[14] 1990	Exposure defined by occupation; see text
Hopkins *et al*,[15] 1991	Self-reported exposure to "hazardous/toxic chemicals"
Grönning *et al*,[16] 1993	Self-report. Minimum 1 year of occupational exposure. Exposure intensity, duration, load reported
Landtblom *et al*,[17] 1993	Self-report. Minimum 1 year of occupational exposure. Exposure intensity reported. Latency criterion
Nelson *et al*,[18] 1994	Semiquantitative exposure indices: industrial hygiene records and air sampling (per plant)
Casetta *et al*,[19] 1994	Self-report. Minimum 8 months of occupational exposure. Three crude exposure levels
Various study designs	
Amaducci *et al*,[8] 1982	Exposure defined by occupation: shoe and leather worker
Giuliani *et al*,[9,10] 1988	Exposure defined by occupation: shoe and leather worker
Milham,[20] 1983	Exposure defined by occupation: different; see text
Lauer,[21] 1989	Exposure defined by branch: chemical industry

* Self-report = by questionnaire and/or interview.

For the leather industry, with less ubiquitous exposure to organic solvents, there were positive correlations in two of the four countries.

Exposure Assessment

In the studies reviewed, the assessments of solvent exposure ranged from crude estimates based on information about work in a certain industry branch[21] or self-reported exposure to "hazardous or toxic chemicals"[15] to semiquantitative indices, calculated from hygiene records and air sampling.[18] Some investigators[11,16,17] provided estimates of the intensity of exposure using a quantitative classification,[22] whereas other studies had more crudely defined exposure categories, such as none, mild, or heavy.[12,13,19] In the majority of the studies, exposure was defined by occupation[8–10,13,20] (Table 3).

Dose-response assessments in three studies[11,16,18] were divergent: one study,[18] using workers with disability as controls, found a dose-response relation; another study[16] found a reverse relation, with the highest OR in patients with fewer symptoms of intoxication, but a positive dose-response relation when based on an exposure index weighted by duration of exposure; a third study[11] showed an increased risk for medium intensity of exposure but not for the high-intensity category of exposure, which included few individuals.

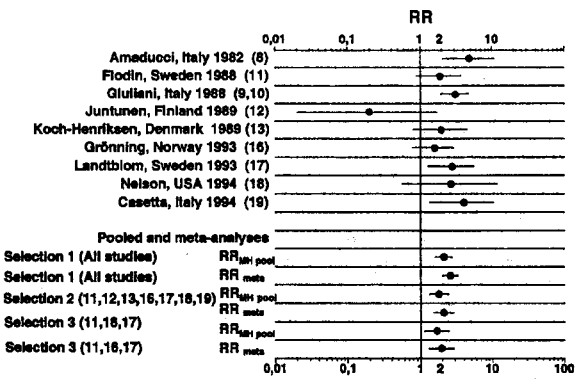

FIGURE 1. Risk estimates of nine studies on multiple sclerosis and exposure to organic solvents and the results of meta-analyses of three subsets of the studies. The horizontal scale is logarithmic.

Pooled Analyses and Meta-Analyses

The plotted RRs (or ORs) for the various studies center around 2, with confidence intervals of differing width (Figure 1). The larger studies show relatively narrow and overlapping confidence intervals. All of our analyses showed an overall RR in the range of 1.7–2.6. The RR_{meta} estimates were higher than the RR_{MHpool} estimates, evidently because the relative risk estimates were greater after adjustment for confounding in some studies (Table 4).

TABLE 4. Meta-analysis of Three Selections of Studies on Multiple Sclerosis and Solvent Exposure

	Selection 1: All Studies with a Calculated Risk Estimate	Selection 2: Studies with Defined Exposures	Selection 3: Most Similar Studies with Defined Exposures
Number of studies	9	7	3
References	8–13, 16–19	11–13, 16–19	11, 16, 17
RR_{MHpool}* (95% CI)	2.1 (1.6–2.7)	1.8 (1.3–2.4)	1.7 (1.1–2.4)
RR_{meta}† (95% CI)	2.6 (2.0–3.3)	2.1 (1.5–2.9)	2.0 (1.6–2.5)

* RR_{MHpool} = Mantel-Haenszel calculation of ORs or RRs.
† RR_{meta} = calculated by formula; see text.[7]

Discussion

There are many known or suspected relations between organic solvents and human disease. Examples are peripheral neuropathy, benzene-induced hemopathy, leukemia, Hodgkin's disease, chronic glomerulonephritis, cirrhosis,[23] halothane-induced hepatitis,[24] and histiocytic lymphoma and lymphosarcoma.[25] Several studies show altered function of the immune system

on both cellular and molecular levels.[23,26,27] Toxic effects of chronic exposure to solvents have been demonstrated at the central nervous system level, predominantly leading to degenerative changes and reproductive hazards.[23]

Three case-control studies had fewer than 30 cases, limiting their informativeness.[12,15,18] Case selection is a possible limitation in the two studies from our group, as we included cases with possible MS, some of whom may have had other disorders.[11,17] The choice of hospital controls may be a problem in the study by Grönning *et al*,[16] since they may not have been representative of the study population that produced the cases. The small effects seen by Nelson *et al*[18] may stem from the selection of population controls from the same plants as the cases, a matching which was not controlled in their analysis. The excess risk from solvents may be more evident in male MS patients[11,17]; Juntunen *et al*[12] studied mainly female patients, an approach that perhaps explains their smaller effect estimates.

The proportional mortality study from the United States indicated an increased mortality from MS in automobile mechanics and draftsmen, and from "inflammatory diseases of the nervous system" in airplane mechanics.[20] These occupations may entail exposure to solvents. Nevertheless, in groups such as painters and several other occupations with known solvent exposure, the proportional mortality ratios were not increased and, in fact, were sometimes lower than expected. Several occupations without solvent exposure showed elevated proportional mortality ratios. This study[20] therefore provides only equivocal support for an association between solvent exposure and MS.

Exposure assessment varied widely among the studies. If autoimmune mechanisms are involved in the pathogenesis of MS, a dose-effect model may not apply. If so, the quantification of solvent exposure may not be crucial, and studies with a weak exposure assessment may nevertheless be worth considering. Table 3 gives the reported means of assessing the solvent exposure in the different studies. Timing of exposure in relation to onset of disease was reported in only two of the studies, with an assumed induction time of 5 years.[11,17]

Some authors have criticized meta-analysis, especially outside the context of randomized clinical trials, because it may simply combine erroneous results from many studies.[28,29] There are also doubts about weighting schemes in meta-analyses, since weighting adds subjective bias to the result, wastes information, and hides sources of heterogeneity.[29]

We acknowledge reluctance to pool the results of prevalence comparisons with those of case-control studies, as we did in selection 1 (Table 4). Selection 2 contains only case-control studies, but they differ in quality and design. There is only minor heterogeneity (the Finnish co-twin study[12]). We believe selection 3 to be the most appropriate. Regardless of the weighting procedure, the results of the different analyses are similar, mitigating the methodologic concerns.

The association between solvent exposure and MS may involve differences in individual susceptibility, either from genetic differences or from a promoting effect through damage to the blood-brain barrier. Increased intrathecal albumin concentrations as a sign of blood-brain barrier damage have been demonstrated in solvent-exposed individuals, although not consistently.[27,30–32] Migration studies reveal that MS is initiated early in life.[33–35] This finding does not rule out the possibility that exposure to solvents later in life may precipitate the clinical onset of MS or cause latent disease to become active.

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