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Neurologic Evaluation of Workers Previously Diagnosed With Solvent-Induced Toxic Encephalopathy

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Abstract

We examined 52 railroad workers with long-term occupational solvent exposures (average 22 years duration) who had been previously diagnosed by others as having solvent-induced toxic encephalopathy. All described episodes of transient intoxication associated with occupational solvent exposure. Persistent symptoms developed, on average, 16 years after exposure onset and included impaired memory (38), altered mood (21), imbalance (18), and headache (17). Thirteen workers had mild mental status abnormalities, but none fulfilled conventional clinical criteria for encephalopathy or dementia. None had abnormal blink reflex (51) or abnormal electroencephalographic (39) studies. Eight of 47 magnetic

resonance imaging studies showed evidence of scattered ischemic lesions among workers with known diabetes mellitus (2), elevated blood pressure (4), or peripheral vascular disease (2). One magnetic resonance imaging scan showed mild cortical atrophy. In stepwise multiple linear and logistic regression models, no statistically significant (P P P = 0.05) were associated with current use of central nervous system-active medications. Further, lower Mini-Mental Status Examination scores were associated with a history of alcohol abuse (P = 0.01) and lower educational level (P = 0.03). The number of chief symptoms involving memory, mood, balance, or headache differed significantly among workers in different geographic sites (F(3,48) = 2.94, P = 0.04), a finding that was not explained by job title or exposure duration. There also was a significant (P = 0.0001) inverse relationship between initial exposure year (r2 = 0.60) or total years of exposure through 1987 (r2 = 0.56) and interval to major neurologic symptom onset, suggesting that factors other than solvent exposure account in part for worker complaints. We found no objective neurologic evidence supportive of toxic encephalopathy or any other uniform syndrome among these individuals, and most complaints were explained by neuropsychological factors or conditions unrelated to occupational solvent exposure.

Since the initial reports of painters' encephalopathy in the 1970s, the association between neurologic dysfunction and occupational exposure to organic solvents has remained under question. 1-10 The controversy centers on the question of whether occupational exposure to trichloroethylene, trichloroethane, perchloroethylene, mineral spirits, or similar solvents alone or in combination at low doses over long periods of time are capable of causing permanent and irreversible damage to the nervous system. Before initial reports of encephalopathy among Scandinavian painters, there had been little concern about low-dose occupational exposure to organic solvents, despite the recognition that many solvents had neurotoxic potential when present in sufficient amount and that high solvent exposures producing hypoxia and unconsciousness could produce neurologic injuries, including death. In fact, several solvents used as industrial degreasers, including trichloroethylene, were used as anesthetics because they produced reversible unconsciousness at high exposure levels. 11-13 As an anesthetic, trichloroethylene was associated with a syndrome of multiple cranial mononeuropathies, which were later found to be due to a decomposition product, dichloroacetylene. 14-16 Trichloroethylene was replaced as anesthetic agent not because of neurotoxicity but because better anesthetic agents became available. Nevertheless, there was little general concern that chronic low-level or even transient high-level solvent exposures not producing hypoxia were dangerous to the nervous system. 7

Initial reports regarding painters' encephalopathy included case reports and cross-sectional studies that were not adequate to establish whether occupational solvent exposure caused the reported findings. Little attention was given to selection of control workers, measurement of exposure, or evaluation of dose-response relationships. Some reports 17,18 were even revised by participating authors after reanalysis using more appropriate control groups. 19 Subsequent studies were more scientifically rigorous and included masked cross-sectional evaluations to reduce inadvertent bias. 9,20 These studies measured solvent exposures, masked examiners and workers to exposure level information, and controlled for known confounders. Under these conditions, investigators found no clinically significant behavioral or neurologic abnormalities attributable to solvent exposure and no evidence of subclinical dose-response relationships. 20 These studies also identified the importance of exposure measurement. Many reports of solvent encephalopathy used symptoms of acute intoxication as an exposure surrogate because exposure levels were unavailable. 10,18,21 However, the same non-specific symptoms frequently were used as indicators of neurotoxicity. 22 This approach led to circular reasoning, making it impossible to determine the importance of such symptoms in estimating exposure. Unfortunately, a deficiency in many epidemiologic studies is the inability to accurately assess exposure. 23 Of interest, Maizlish and associates demonstrated that exposure estimates based on report of symptoms (eg, lightheadedness or dizziness) did not reflect direct air sample measurements. 9,20 Although the workers they examined had relatively low-level exposures, estimates that were based on reported symptoms, as done in numerous earlier studies, would have overestimated actual exposures. In fact, symptoms of neurasthenia and intoxication were more common among unexposed workers compared with workers in the highest exposure group. 9 To date, the hypothesis that occupational exposure to solvents at low doses over long periods of time causes damage to the nervous system remains unsubstantiated.

To further an exchange of information about this controversy, the Association of Occupational and Environmental Clinics and the National Institute of Occupational Safety and Health sponsored a workshop on solvent exposure among railroad workers. 24 Railroad workers are of interest because of the perception that they have had particularly high solvent exposures, perhaps representing the largest cohort of workers in the United States with such heavy solvent exposure. 25 There was agreement among participants at the workshop that railroad workers with purported solvent-associated occupational illnesses require more rigorous observation and study than accomplished to date. Our experience with one group of railroad workers who were diagnosed by others with toxic encephalopathy follows. On the basis of descriptions of previous examiners, these workers were thought to be representative of railroad workers with solvent-induced encephalopathy.

Methods

Worker Selection and Characteristics

The study was approved by the University of Michigan Medical School Institutional Review Board. Prior to analyses, information linking any individual to the data was removed and data for a random subset of workers were deleted to provide additional anonymity. The study group represents railroad workers referred to us consecutively over approximately 5 years by defense attorneys for independent medical examinations. All workers were involved in litigation against their employer because of alleged occupational solvent exposure producing toxic encephalopathy, and all understood that the examinations were performed in the context of their litigation. All workers had a previous diagnosis of toxic encephalopathy, usually using diagnostic criteria developed at the 1985 World Health Organization (WHO) workshop on organic solvents. 8,26 This 1985 scheme includes a gradation of severity, with the mildest form of encephalopathy (type 1) based on symptoms not necessarily specific though usually referable to the central nervous system (CNS). Mild toxic encephalopathy is defined in two ways, depending on the presence of sustained change in mood or personality change (type 2A) or an intellectual impairment demonstrated on neuropsychological testing (type 2B). Severe toxic encephalopathy (type 3) is described as having features of a chronic dementia. For workers whose type of encephalopathy was not specified previously, we applied the WHO terminology.

The characteristics of the group are shown in Table 1. All exposure information was historical, based on the individual worker's description, and verified by review of occupational records when available. Each worker was assigned the job classification that reflected his primary assignment during the period of highest exposure. Several different job classifications provided different exposure opportunities, although exposure experiences were similar because of common work environments. A typical history included daily spraying of solvent from a pressurized tank onto a locomotive, and direct application of solvent from an open bucket onto parts. All workers denied use of respiratory or dermal protection. Typically, chemicals were described by their common or trade names. Those most frequently reported were trichloroethylene, trichloroethane, and perchloroethylene, alone or (usually) in combination. Less frequently mentioned were carbon tetrachloride, xylol, mineral spirits, kerosene, toluene, and unidentified solvent mixtures.

The duration of occupational solvent exposure averaged 22 years (range 10 to 39 years), and all workers reported exposures of at least 10 years duration, fulfilling partial criteria for long-term exposure as reported by others. 27 The highest-level exposures occurred before the mid-1980s, after which exposure was minimal because of changing work practices. Because of limited solvent exposures after the mid-1980s, the opportunity for solvent exposure from the presence of solvents in the workplace therefore differed from that reported, averaging 7

years less. On the basis of this calculation, 43 workers still fulfilled duration criteria for long-term exposure. All workers regularly experienced symptoms at work that they attributed to acute solvent intoxication. Symptoms included transient headache, dizziness or lightheadedness, "drunkenness," and balance problems. No worker reported accidents, injuries, or loss of consciousness related to acute solvent intoxication.

Numerous conditions unrelated to solvent exposure existed that could contribute to neurologic symptoms or signs. Four workers had adult onset diabetes mellitus. Additional potentially confounding conditions included high blood pressure (17), liver disease (1), and chronic pain other than headache (10). Six workers reported prior alcohol abuse, and one of the six reported prior polysubstance abuse. Thirty-one workers had been prescribed medications with potential CNS effects, including antidepressant (23), antianxiety (6), combined antidepressant and antianxiety (4), narcotic analgesic (4), and stimulant (2) medications. In addition, 32 workers were receiving at least one among a variety of antihypertensive, anticholesterol, antidiabetic, cardiac, cardiovascular, corticosteroid, and headache medications. Fourteen workers were using no prescription medications at the time of our evaluation; three of them previously had taken antidepressant medications.

Neurologic Evaluation

A standard clinical neurologic examination had been performed on all workers. 9 Evaluation included medical and occupational histories and review of past and current use of medications, alcohol, and chemicals used in hobbies. Workers identified their chief (primary) complaints. Other neurologic symptoms not volunteered were elicited in a structured review of nervous system symptoms. Records were reviewed to confirm the presence of medical conditions that could adversely affect the nervous system. Previous medical examinations and laboratory results, including magnetic resonance imaging (MRI) and electroencephalographic (EEG) reports, also were reviewed, as were available education records.

Examination results included review of a structured mental status examination based on cognitive domains such as general intellect, orientation to time and place, simple receptive and expressive language, communication, attention and concentration, immediate working memory, logical thinking, and following commands. A Mini-Mental State Examination (MMSE) score had been calculated for each worker. 28 The remainder of the neurologic examination results included assessment of cranial nerves; motor function (station and gait, coordination, alternate motion rate, and strength in proximal and distal muscles); sensory function, including fine touch, vibration (128-Hz), pin-pain, temperature, dual simultaneous stimulation, and Romberg test; and reflexes (muscle stretch reflexes and primitive reflexes, including palmomental, snout, grasp, Chaddock,

and Babinski). Orthostatic blood pressure measurements and response to volitional hyperventilation had been recorded when indicated.

Assessment of Encephalopathy and Affect

Several definitions of encephalopathy were used, including those developed at the 1985 WHO solvent conference. 26 We designated workers with any CNS symptoms with type 1, 2, or 3 encephalopathy. Workers with predominant neurobehavioral deficits were designated with type 2 (mild toxic encephalopathy). This was subdivided into type 2A (mood or personality change) and 2B (intellectual or cognitive impairment). The latter designation requires neuropsychological testing but, for the purposes of this study, was defined as any abnormality on mental status testing. This distinction made little difference in the overall classification because all workers with cognitive complaints and abnormal mental status had previous neuropsychological testing identifying at least some absolute abnormality. A few workers who were classified with type 1 encephalopathy because they had normal mental status testing could have been classified with type 2B encephalopathy by using the criterion of any abnormality on neuropsychological testing. This is one of the difficulties of using the WHO classification scheme. Workers demonstrating features of dementia were designated type 3 encephalopathy or severe chronic encephalopathy. 8 Because of limitations of the WHO criteria, including reliance on non-specific symptoms and failure to incorporate neurologic findings in the definition of encephalopathy, we also assigned a traditional definition of encephalopathy on the basis of symptoms and neurologic signs of impairment.

Additional definitions of clinical encephalopathy required the presence of symptoms and signs consistent with diffuse cortical dysfunction among symptoms, mental status testing, and motor/reflex examinations. Appropriate symptoms (worker or family member report) included any of the following: memory loss, impaired cognition, irritability, short attention span, or impaired behavior (disinhibition). Abnormal mental status testing required disturbance of at least two of the following: personal orientation to self and environment, simple calculations, short-term memory, digit span, comprehension, similarity testing, multiple step command, or summary MMSE score. An abnormal motor/reflex examination required at least two of the following: postural tremor, slowed coordination, abnormal alternate motion rate, asterixis, dysarthria, akathesia, ataxia, increased tone, increased muscle stretch reflexes, primitive reflexes, or myoclonus. Probable clinical encephalopathy required appropriate symptoms and at least two mental status and two motor/reflex examination abnormalities. Workers who did not fulfill the criteria but who had appropriate symptoms and at least one mental status or motor/reflex examination abnormality were labeled possible clinical encephalopathy. Confirmed encephalopathy required appropriate abnormalities on neuropsychometric testing. This was defined operationally on

the basis of the results of the clinical and neuropsychological evaluations and will be reported separately. The neurologic examination was used to identify workers with possible abnormal affect, defined as appropriate symptoms of depressed mood, suicidal ideation, terminal sleep disturbance, or feelings of hopelessness. Definite abnormal affect required neuropsychological evaluation and also will be reported separately.

Nerve Conduction and Blink Reflex Studies

Sensory and motor nerve conduction studies had been performed on unilateral sural, peroneal motor, median sensory and motor, and ulnar sensory nerves, as reported previously. 29 Bilateral blink reflexes were recorded from the orbicularis oculi muscles in response to percutaneous electrical stimulation of the supraorbital nerve. Response measures included R1 and R2 latencies, measured as the shortest latency recorded from 4 to 8 acceptable responses. A uniform stimulation protocol delivered stimuli randomly without cueing, thereby reducing anticipation.

Assessment of Neuropathy

Subclinical or clinical neuropathy was established by using a combination of abnormalities from the categories of symptoms, signs, and electrodiagnostic testing as consistent with standard clinical practice. 30,31Clinical neuropathy was defined as the presence of abnormalities consistent with a sensory or sensorimotor polyneuropathy in at least two of the following: physical symptoms, peripheral sensation, or decreased gastrocnemius-soleus reflexes compared with quadriceps reflexes. Appropriate symptoms include report of symmetrical stocking or stocking-glove distribution numbness, tingling, or sensory loss. Workers with a single appropriate abnormality among symptoms, sensation, or reflexes were labeled possible clinical neuropathy. Confirmed clinical neuropathy required abnormal electrodiagnostic testing consisting of at least one abnormal nerve conduction measure in two peripheral nerves. 29

Statistical Analysis

The frequency of symptoms, clinical signs, and neurologic diagnoses were tabulated. When possible, the likely cause of individual problems was identified and recorded. Exposure duration (reported and based on exposure opportunity), latent interval from exposure onset to development of first persistent symptom, geographic work location, and job title during time of predominant exposure were recorded, as were confounders that could potentially influence the neurologic examination (age, years of education, history of alcohol abuse, and use of CNS-active medications). Stepwise multiple linear regression models were used to identify the contribution of demographic variables (eg, age, education, body mass index), potential confounding factors (eg, past history of alcohol abuse, current use of CNS-active medications), and exposure duration to the frequency

of chief complaints (symptoms of abnormal mood, memory, balance, headaches), the frequency of abnormal neurologic signs (eg, mental status, cranial nerves, tandem gait, Romberg), and performance on a cognitive screening measure (MMSE). These models were then used to assess for the presence of dose-response relationships between exposure duration and the number of symptoms suggestive of encephalopathy or signs of impairment. The level of significance for including a term was P P > 0.10. To further explore the relationship between demographic variables, confounders, and exposure duration and the presence or absence of specific symptoms or signs, logistic regression models were calculated using the dichotomous data. Correlations between continuous variables were assessed by using Pearson's coefficients, and non-parametric correlations were assessed with Spearman's coefficients. Given the multiple comparisons generated, a conservative significance level of 0.01 was used. Potential differences in exposure duration, reported symptoms, and signs of impairment between workers in different job categories or in different geographic locations were examined using analysis of variance.

Results

Neurologic Evaluation

Complaints reported by individual workers are summarized in Table 2. The most common chief complaints included difficulty with memory or concentration, impaired mood, abnormal balance, or headache; 46 workers listed at least one of these as a chief complaint. When all complaints were considered, including those elicited in the review of symptoms, all but two workers reported at least one of the above symptoms. Slightly less than one-half of the workers (46%) complained of abnormal memory and impaired mood.

The results of the neurologic examination are summarized in Table 3. Eighteen workers had a normal neurologic examination, and 34 workers had at least one abnormality. Abnormalities of mental status were the most prevalent findings identified. Thirteen workers had mental status signs, including abnormalities of general intellect, attention, short-term memory, and abstract thinking. Six of the 13 workers had a single mental status abnormality. Three workers had poor reading skills in association with a poor general fund of information. All three were high school graduates, but they reported poor grades, failed courses, or repeated courses or years, suggesting a long-standing problem and limited educational achievement. Two of the three had clinical evidence of an underlying depressive disorder, and the third was taking a narcotic analgesic for a chronic pain syndrome. Of the remaining 10 workers, seven had concurrent evidence of depression or an anxiety disorder and had been prescribed CNS-active (psychotropic) medications. An additional worker had evidence of a functional disorder, giving inconsistent results and performing better on more difficult, compared with easier, tasks. The remaining worker had inconsistent performance and a school

record of poor educational performance with an IQ measurement in the low 70s when in high school.

Cranial nerve abnormalities included retinopathy (1) in a worker with diabetes mellitus, anisocoria (1), and a tonic (Adie's) pupil (1). Two workers had unilateral localized weakness, one in the distribution of a nerve root and the other in the distribution of a division of the brachial plexus. Three workers had a mild postural tremor. The tremor was most prominent in a worker who was prescribed lithium, from which tremor is a common side effect. Fourteen workers had abnormal gait, all identified on tandem walking. Six of the 14 had an abnormal Romberg or distal sensory loss explaining the gait disorder. Three others had astasia-abasia with intermittent and exaggerated findings inconsistent with an organic gait disorder. All but one of the 14 used medications that potentially interfered with balance. Twelve workers had sensory loss, which was symmetric in seven, with mild stocking or stocking-glove impairment of vibration and pin-pain sensations. The remaining five workers with focal sensory abnormalities demonstrated dermatomal (1), single nerve (2), nerve branch (1), or non-physiologic (1) distributions. None of the seven workers with symmetric sensory loss had impaired joint-position sensation or astereognosis. One of the seven had hypoactive ankle reflexes. Palmomental reflexes were recorded in 16 workers. No other primitive reflexes were recorded. On the basis of the subjective evaluation of affect, which included review of individual histories and direct observation, 32 workers had symptoms and signs consistent with possible depressed mood.

Assessment of Encephalopathy and Neuropathy

On the basis of WHO criteria, 10 workers had type 1 and 42 workers had type 2 encephalopathy; no worker had type 3 (Table 4). Of those with type 2 encephalopathy, 21 fulfilled criteria for type 2A, 8 for type 2B, and 13 for both 2A and 2B. Under conventional clinical criteria, 27 workers had possible encephalopathy based on the presence of appropriate symptoms, but no worker fulfilled criteria for probable clinical encephalopathy based on the presence of appropriate symptoms and combined mental status and motor or reflex abnormalities. Of the 27 workers with possible clinical encephalopathy, 12 had no mental status abnormalities and eight had a single abnormality recorded on mental status testing. Ten of the 27 workers had no motor or reflex abnormalities, and 14 had only one motor or reflex abnormality, most typically a palmomental reflex. The remaining three workers with motor or reflex abnormalities had palmomental reflexes and mild sustension tremor (1), palmomental reflexes and abnormal tandem gait (1), and mild sustension tremor and abnormal tandem gait (1). Comparison of symptoms of encephalopathy and neurologic findings consistent with encephalopathy after separating workers on the basis of their WHO classification is shown in Table 5. Workers classified as having WHO type 1 encephalopathy had

fewer mental status signs on standard neurologic examination than remaining workers, and there was a significant increase in the number of mental status abnormalities (P = 0.0001) and a decrease in the MMSE score (P = 0.002) among workers classified as WHO type 1, 2A, 2B, and 2A, B. No similar relationship was identified for the number of motor or reflex abnormalities suggestive of encephalopathy and the WHO classifications (P = 0.5478).

Thirty-nine workers had conventional EEG examinations, all producing normal results. Forty-eight workers had cranial MRI studies. Eight of the 48 studies were abnormal, but only one demonstrated cerebral atrophy, described as mild or equivocal. The other seven abnormal MRI studies demonstrated evidence suggestive of scattered ischemic lesions. These included two workers with diabetes mellitus, four with elevated blood pressure (three diagnosed with and treated for hypertension), and one with vascular disease. No worker had abnormal blink reflex studies.

Six workers had clinically evident polyneuropathy (clinical neuropathy). Three of the six fulfilled electrodiagnostic criteria for confirmed clinical neuropathy. Two of the three workers with confirmed clinical neuropathy had diabetes mellitus. Diabetes is one of the most common causes of polyneuropathy, and these two workers had nerve conduction findings consistent with diabetic neuropathy. The third worker had findings characteristic of a diabetic neuropathy as well as a family history of diabetes but had never been tested for diabetes. Twelve other workers had focal electrodiagnostic abnormalities consistent with local trauma, including six with median mononeuropathy at the wrist, six with ulnar mononeuropathy, and one with residual abnormalities from a prior radiculopathy.

Differential Diagnoses

On the basis of the clinical examination and test results, a differential diagnosis had been developed for all workers, providing when possible a conventional clinical explanation (diagnosis) for the individual primary complaints (Table 6). For most workers, a common explanation existed that frequently had been identified by the worker's personal physician. Frequently, workers with memory complaints provided examples of their difficulties that were characteristic of normal memory variation rather than a pathologic disorder of cognition. Examples included forgetting names of familiar people, forgetting where they had placed their tools, needing lists when shopping, and being unable to remember specifics of their trip after driving to and from work. Interpretation of such complaints was complicated by use of medications known to interfere with cognitive function. Many workers also were using medications known to influence coordination and balance. Workers frequently denied knowledge of such potential relationships or other medication side effects. Memory complaints frequently

occurred in association with depressed mood or history of increased anxiety, making it difficult to separate the role of psychological factors in their complaints.

Overall Assessment and Dose-Response Relationships

Stepwise multiple linear regression models were used to assess for the presence of a dose-response relationship between the number of exposure years and the total number of symptoms or signs or impairments, while controlling for the possible confounding effects of age, educational level, body mass index, history of alcohol abuse, and current use of CNS-active medications.(Table 7) No statistically significant (P P P = 0.046). Workers currently using CNS-active medications were also somewhat more likely to demonstrate signs of impairment on neurologic examination compared with remaining workers.

After dichotomizing responses for individual symptoms and signs (present/absent), logistic regression models were used to assess dose-response effects of exposure while controlling for possible confounders. There were no significant relationships between exposure duration and the presence of symptoms such as memory loss ([chi]2 = 3.45, P = 0.75) or balance complaints ([chi]2 = 9.43, P = 0.15). Complaints of mood changes were significantly related to current use of CNS medications ([chi]2 = 13.72, P = 0.03), and complaints of headaches were inversely related to workers' educational level ([chi]2 = 18.29, P = 0.006). In terms of neurologic signs, there were no significant relationships between exposure duration and confounding variables and the presence of neurologic signs, such as abnormal mental status ([chi]2 = 6.89, P = 0.33), abnormal cranial nerves ([chi]2 = 3.88, P = 0.69), abnormal sensation ([chi]2 = 8.83, P = 0.18), abnormal Romberg ([chi]2 = 11.79, P = 0.07), or abnormal Palmomental reflex ([chi]2 = 6.12, P = 0.41).

Individual correlations were examined between symptoms, signs, and MMSE scores and criterion variables, such as exposure duration, body mass index, demographic characteristics, and potential confounders. At the 0.01 significance level, three variables (mood complaints, balance complaints, and tandem gait abnormalities) were significantly correlated with CNS-active medication use. There were no significant relationships with exposure duration. At a 0.05 level of significance, the MMSE scores correlated significantly with exposure duration. Paradoxically, a high MMSE score (better performance) was associated with longer exposure duration. The stepwise multiple linear regression model generated to evaluate a possible dose-response relationship between the number of exposure years and MMSE scores after controlling for age, education, gender, history of alcohol abuse, and use of current CNS medications identified no dose-response relationship with exposure years. However, there was a significant relationship between MMSE and past history of alcohol abuse and educational level (P = 0.012), accounting

for 13.0% of the total variance. Workers with a history of alcohol abuse and with lower educational levels were more likely to obtain lower MMSE scores.

There were no significant differences in exposure duration between workers with different job classifications using analysis of variance models (F (3,48) = 0.59, P = 0.62). Moreover, there were no significant differences between workers in different job classes and the total number of symptoms reported (F (3,48) = 2.42, P = 0.08), number of signs of impairment (F (3,48) = 1.51, P = 0.23), and MMSE scores (F (3,48) = 0.70, P = 0.56). However, workers in different geographic locations had significant differences in reported exposure duration (F (3,48) = 4.49, P = 0.007). In particular, workers at one of the geographic locations (site A) had significantly longer potential exposure than did workers at remaining sites. There was also a significant difference in the total number of reported chief complaints among problems with memory, mood, balance, or headache symptoms between workers in different geographic sites (F (3,48) = 2.94, P = 0.04). Workers at site B reported the fewest number of symptoms (mean = 1.5 +/- 0.7), and workers at site C reported the greatest number (mean = 2.4 +/- 1.2). There were no significant differences in neurologic signs (F (3,48) = 0.86, P = 0.47) or MMSE scores (F (3,48) = 1.07, P = 0.37) among the four geographic sites.

Interval From Onset of Occupational Exposure to Onset of Symptoms

Unexpectedly, there existed a significant (P = 0.0001) inverse relationship between total years of exposure and interval to symptom onset. On average, the first persistent chief symptom developed 15 years (1 to 33 years) after exposure onset. However, there was an inverse relationship between the initial exposure year (r2 = 0.61;Fig. 1) or the total years of exposure through 1987 (r2 = 0.56) and the interval to the onset of the first major neurologic symptom. In other words, workers with the longest exposure opportunity (as estimated by the year of first occupational exposure or the number of years with potential exposure through 1987) developed symptoms after a longer latent interval than did workers with a shorter exposure opportunity. For example, workers who began work before 1970 developed symptoms, on average, 22 years later, whereas workers who began work in the 1970s to 1980s developed symptoms 13 years later (P

Discussion

In the more than 20 years since the first reports of painters' encephalopathy, subsequent studies have produced disparate results, with the bulk of evidence failing to support a consistent association between occupational solvent exposure and encephalopathy. However, interpretation of the evidence requires more than just a tabulation of the positive and negative studies; it should be based on an understanding of the methods used to evaluate the possible association between occupational solvent exposure and encephalopathy. 23,32 Case

reports do not provide reliable evidence of causal associations because they involve individuals who are selected on the basis of both disease and exposure. The selection criteria are often undefined, and it cannot be determined how such selected individuals relate to the underlying population from which they are selected. However, case reports provide an important starting point for further scientific research into whether the purported associations exist and whether they are causal.

Properly conducted cross-sectional studies provide more reliable evidence of associations between exposures and disease, but they are inherently limited by an inability to determine the temporal sequence between exposure and disease. This is a critical issue in the literature on solvents and encephalopathy because of the concern that people who enter solvent-exposed jobs may have different preexposure cognitive abilities than do workers in other trades, with whom they are often compared. 19 As a result, associations between deficits of cognitive ability and solvent exposure may result from deficits that existed before the exposure occurred rather than after exposure. Cross-sectional studies can provide useful evidence that associations exist, but they must be followed by more rigorous studies to ensure that such associations are causal.

Cohort and case-control studies often provide more reliable evidence of causality. Cohort studies based on historical exposure information (recorded before subjects are diagnosed with encephalopathy) can reliably establish that exposure preceded disease. Of six cohort studies, four 33-36 failed to find associations between occupational solvent exposure and encephalopathy, one was confounded by alcohol consumption, 37 and one found a twofold risk of presenile dementia among painters compared with bricklayers. 38 These studies leave considerable doubt about the causal interpretation of the associations that have been reported in cross-sectional studies.

Case-control studies have examined the relationship between solvent exposures and various neurologic and psychiatric disorders, including CNS dysfunction, 39 neuropsychiatric disability, 40-44 neuropsychiatric disorders, 45 psychiatric illness or disease, 46,47 alcoholism or neuropsychiatric disorders other than neuroses, 48 presenile dementia, 49,50 Alzheimer's disease, 51,52 and multiple sclerosis. 53 These studies have found either no association or weak associations between solvent exposure and these disorders. A major concern in many of these studies is a lack of exposure information. Because of the difficulties inherent in recalling distant past exposures, these studies have been based on the memory of the subjects to establish exposure or on inferred exposure on the basis of job titles, without measurements to confirm either the identity of the solvents or the actual exposure circumstances. In addition, control of confounding variables, such as preexposure educational attainment and alcohol and drug use,

has been limited. As a result, case-control studies do not provide convincing support for the conclusion that solvent exposure causes neurologic and psychiatric disorders.

If painters' encephalopathy is not an established disorder, then why has it become so controversial, and how are the symptoms experienced by the workers in our study explained? The answer to the first question is that much of the debate reflects social and legal, not medical, issues. All of the workers reported here were litigants against their employer. For the most part, their diagnosis of toxic encephalopathy was not established by a neurologist, the medical specialist who typically examines patients suspected of having encephalopathy. In contrast, most neurologists, including those who frequently care for patients with encephalopathy, have never examined a patient with encephalopathy thought to be related to occupational solvent exposure. In fact, despite the implications of a diagnosis of encephalopathy, only 13 of the 52 workers had been referred to a neurologist for any reason. Four of the 13 workers had a diagnosis of encephalopathy confirmed by the neurologist, with diagnoses of probable Alzheimer's disease versus small vessel ischemia (1), multiple chemical sensitivity syndrome (1), anxiety and depression associated with solvent exposure (1), and possible presenile dementia (1). All four workers had normal EEG studies. Two of the four had MRI evidence of scattered ischemic lesion. Of these two workers, one had diabetes mellitus and one had elevated blood pressure; both provided a history of alcohol abuse.

At least some of the controversy reflects the definitions used to describe solvent-induced encephalopathy. The workers in our study were said to fulfill the 1985 WHO definition of toxic encephalopathy, and we agree that these workers fulfilled those criteria. However, although the WHO definition has potential as an epidemiologic instrument for classifying workers, the definition has no diagnostic application in individual cases because it rests heavily on non-specific symptoms and disregards competing diagnoses. For example, behavior can be affected by a variety of factors; only some are neurologic. A person with depression reactive to life experiences but no solvent exposure might typically have memory complaints (one criterion in the WHO definition) and even show signs of intellectual impairment (another WHO criterion) in clinical testing or interview, yet have no neurologically based dysfunction. With a change in life situation, the depression might improve with subsequent improvement in intellectual function. This individual would meet criteria for WHO type 2B encephalopathy, but it would be erroneous to conclude that the cause could be attributed to solvent exposure.

On the basis of our review, the diagnosis of toxic encephalopathy established by others for these 52 workers was based primarily on symptoms and self-report and

did not properly consider other available information, objective signs, or competing diagnoses. All 52 workers had sufficient symptoms to fulfill one of the WHO categories of encephalopathy. Yet none of the 52 workers fulfilled a more conventional clinical classifications of encephalopathy or dementia that includes evidence of appropriate neurologic impairment. Further, explanations independent of occupational solvent exposure existed to account for almost all of the neurologic symptoms and signs listed in Table 6. For example, many symptoms were associated with long-standing problems, such as poor school performance, whereas others reflected common pharmacologic side effects such as imbalance and difficulty concentrating attributable to use of prescription medications.

The limited number of signs suggestive of neurologic dysfunction argues against substantial neurotoxic injury of any type in this group of workers. For the most part, abnormalities were either non-specific, isolated findings or variations of normality common in the general population. The most prevalent sign attributed to encephalopathy in the records of these workers was the presence of palmomental reflexes. These primitive reflexes also were the most common abnormality we identified. However, palmomental reflexes exist frequently in asymptomatic, otherwise neurologically intact, adults, as well as in 25% of young adults 54 and in over one third of subjects in the third to ninth decade of life. 55 These prevalences compare favorably with our observation that 16 of the 52 workers (31%) had palmomental reflexes. For comparison, consider the spectrum of neurologic abnormality seen among patients with hypoxic or hepatic encephalopathy. 56-58 Irritability, agitation, and mild confusion develop in the setting of abnormal postural tremor, slowed coordination, and restlessness. As the severity of encephalopathy increases, patients demonstrate progressive personality and cognitive changes and motor abnormalities, including akathesia, asterixis, dysarthria, gross ataxia, paratonia, and appearance of primitive reflexes. Further progression eventually results in coma with hyperreflexia, Babinski and Chaddock signs, decerebrate posturing, altered respiration, and incontinence. These neurologic changes are associated with EEG changes consisting of progressive slowing, disorganization, and amplitude loss. 59 Similarly, neuronal loss produces atrophy recognizable on MRI studies. Nothing suggestive of this wide spectrum of neurologic consequences was recorded for any of the workers we examined, including those who were disabled and unable to work because of encephalopathy.

The process of developing a differential diagnosis is the established method by which clinicians consider possible explanations for a patient's complaints and clinical findings before making a final diagnosis. 60-62 This list of possible diagnoses is reduced to a final diagnosis by evaluating the validity of items in the list, preferably by using diagnostic tests of high specificity and

sensitivity. In the majority of workers described here, the physician diagnosing toxic encephalopathy provided no differential diagnosis and listed no possible explanations other than occupational solvent exposure. Diagnostic evaluations were neither comprehensive nor consistently applied, and the only primary studies performed were either normal (eg, EEG and MRI) or identified non-specific abnormalities (MRI or neuropsychological testing).

Workers did describe symptoms consistent with situational anxiety and depression. Importantly, these symptoms often appeared after workers learned from others that they had evidence of toxic encephalopathy attributable to solvents, information that in itself might explain their emotional reactions. Many of these workers had little understanding about their problem, reporting only that they had been diagnosed with "brain damage." Many expressed anxiety or concern about their future, believing that their condition was progressive and their prognosis dismal. For most, the physician establishing the diagnosis of toxic encephalopathy provided no follow-up after the initial evaluation, and the diagnosis was provided by letter, rather than in person, many months after the visit. Reassurance that they were unlikely to become mentally or physically incapacitated over time because of this problem was not provided. These same workers interpreted such common life events as misplacing their keys or forgetting a neighbor's name as further evidence of their injury. One of the most common causes of apparent dementia is pseudodementia, a treatable form of cognitive impairment that has a psychological, not a neurologic, basis. 63-65 Patients with depressed mood of any cause typically display disinterest and poor concentration, both of which result in memory difficulties.

Additional factors that could influence mood are numerous in this cohort. For example, involuntary job-related relocation could be associated with potential stress on the individual and the family. Workers who had been relocated were more likely to be classified with WHO 2A and 2B encephalopathy ($P = 0.023$) or to have symptoms potentially associated with clinical encephalopathy ($P = 0.03$) than remaining workers. These same two groups did not have significantly different exposure indices (eg, job title, years of exposure) or education.

To identify subclinical evidence of solvent-induced neurotoxicity, we explored potential dose-response relationships among symptoms, signs, job title, employment duration, and duration of exposure opportunity as surrogate measures for actual exposure. None of these accounted for differences in frequency of chief complaints or signs. We also found no evidence of a dose-response solvent effect on nerve conduction study measures, a finding identical to our previous report on a smaller sample of workers drawn from the same database. 29 The absence of polyneuropathy or a subclinical dose-response effect on nerve conduction studies is further evidence supporting a lack of neurotoxicity in

railroad workers with occupational solvent exposure. The peripheral nervous system is easily evaluated, 66 and peripheral measures are unaffected by educational, emotional, and motivational influences-confounders that make portions of the central nervous systems examination difficult. The absence of any dose-response relationships also suggests that factors other than solvent exposure account in part for worker complaints. Unexpectedly, we did find differences associated with location of work that were not explained by job title or exposure duration. Separation into geographic groups by worksite identified some differences in symptom frequency but not in exposure history. The differences in chief symptoms by geographic location are another form of evidence that psychological factors are important in symptom development and perpetuation in this sample of workers.

The latent period from onset of solvent exposure to development of persistent symptoms was variable and inconsistent with development of toxic-induced disorder. Rather than being clustered around a uniform latent interval, the inverse relationship between the initial exposure year and the interval to symptom onset shown in Fig. 1 is atypical of a neurotoxic or pharmacologic effect. More likely, this latency is suggestive of the findings expected if attention had been drawn to non-specific symptoms at a given period of time, such as in relationship to removal of solvent from the workplace. Indeed, several workers mentioned a meeting at which attorneys described the type of symptoms that could result from exposure. Further, the observation that symptoms differed by location despite uniform exposures argues strongly that psychological factors (including group reinforcement), independent of any exposure, explain at least a portion of the concerns.

We found no objective neurologic evidence supportive of toxic encephalopathy or any other typical or uniform syndrome among these workers, and most of their complaints might be explained by neuropsychological factors or conditions unrelated to occupational solvent exposure. Strengths of the present study include review of medical and related records, review of thorough neurologic evaluation results, and application of conventional diagnostic techniques. We found that standard diagnostic evaluations had not been performed previously, and that definitions of encephalopathy had been applied indiscriminately without proper formulation of a differential diagnosis. Undue importance had been given to non-specific symptoms and isolated signs that have no neurologic importance in isolation. Conversely, although we did not identify substantial neurologic problems in this group of workers, we did find evidence of depressed mood and anxiety in many workers. Because all workers had one or more detailed neuropsychological evaluations, the question of whether altered mood can be associated with occupational solvent exposure is being addressed and will be reported separately. Independent of that evaluation, we conclude that the neurologic abnormalities we

identified are, for the most part, explained by factors other than occupational solvent exposure, and that any unexplained abnormalities seem to be mild or equivocal and unlikely to be a source of concern.

Acknowledgment

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References

1. Chang CM, Yu CW, Fong KY, et al. n-Hexane neuropathy in offset printers. J Neurol Neurosurg Psychiatry. 1993; 56:538-542. ExternalResolverBasic Bibliographic Links

2. Scelsi R, Poggi P, Fera L, Gonella G. Industrial neuropathy due to n-hexane: clinical and morphological findings in three cases. Clin Toxicol. 1981; 18:1387-1393. ExternalResolverBasic Bibliographic Links

3. Herskowitz A, Ishii N, Schaumburg HH. n-Hexane neuropathy. A syndrome occurring as a result of industrial exposure. N Engl J Med. 1971; 285:82-85. ExternalResolverBasic Bibliographic Links

4. Paulson GW, Waylonis GW. Polyneuropathy due to n-hexane. Arch Intern Med. 1976; 136:880-882. ExternalResolverBasic Bibliographic Links

5. Iida M. Neurophysiological studies in n-hexane polyneuropathy in the sandal factory. Electroencephalogr Clin Neurophysiol. 1982; 36(suppl):671-681. ExternalResolverBasic

6. Spencer PS, Schaumburg HH, Raleigh RL, Terhaar CJ. Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch Neurol. 1975; 32:219-222. ExternalResolverBasic Bibliographic Links

7. Spencer PS, Schaumburg HH. Organic solvent neurotoxicity: facts and research needs. Scand J Work Environ Health. 1985; 11(suppl 1):53-60. ExternalResolverBasic Bibliographic Links

8. Baker EL, Fine LJ. Solvent neurotoxicity: the current evidence. J Occup Med. 1986; 28:126-129. ExternalResolverBasic Request Permissions Bibliographic Links

9. Maizlish NA, Fine LJ, Albers JW, Whitehead L, Langolf GD. A neurological evaluation of workers exposed to mixtures of organic solvents. Br J Ind Med. 1987; 44:14-25. ExternalResolverBasic Bibliographic Links

10. Bleecker ML, Bolla KI, Agnew J, Schwartz BS. Dose-related subclinical

neurobehavioral effects of chronic exposure to low levels of organic solvents. Am J Ind Med. 1991; 19:715-728. ExternalResolverBasic Bibliographic Links

11. Waters EM, Gerstner HB, Huff JE. Trichloroethylene. I. An overview. J Toxicol Environ Health. 1977; 2:671-701. ExternalResolverBasic Bibliographic Links

12. Leech PN. The use of trichloroethylene for general anesthesia. JAMA. 1936;13C-130. ExternalResolverBasic

13. Rosenberg NL. Neurotoxicity of organic solvents. In: Rosenberg NL, ed. Occupational and Environmental Neurology. Boston: Butterworth-Heinemann; 1995: 71-113.

14. Buxton PH, Hayward M. Polyneuritis cranialis associated with industrial trichloroethylene poisoning. J Neurol Neurosurg Psychiatry. 1967; 30:511-518. ExternalResolverBasic Bibliographic Links

15. Humphrey JH, McClelland M. Cranial-nerve palsies with herpes following general anaesthesia. Br Med J. 1944; 4:315-318. ExternalResolverBasic

16. Feldman RG, Mayer RM, Taub A. Evidence for peripheral neurotoxic effect of trichloroethylene. Neurology. 1970; 20:599-606.

17. Arlien-Soborg P, Henriksen L, Gade A, Gyldensted C, Paulson OB. Cerebral blood flow in chronic toxic encephalopathy in house painters exposed to organic solvents. Acta Neurol Scand. 1982; 66:34-41. ExternalResolverBasic Bibliographic Links

18. Arlien-Soborg P, Bruhn P, Gyldensted C, Melgaard B. Chronic painters' syndrome. Chronic toxic encephalopathy in house painters. Acta Neurol Scand. 1979; 60:149-156. ExternalResolverBasic Bibliographic Links

19. Gade A, Mortensen L, Bruhn P. "Chronic painter's syndrome." A reanalysis of psychological test data in a group of diagnosed cases, based on comparisons with matched controls. Acta Neurol Scand. 1988; 77:293-306. ExternalResolverBasic Bibliographic Links

20. Maizlish NA, Langolf GD, Whitehead LW, et al. Behavioural evaluation of workers exposed to mixtures of organic solvents. Br J Ind Med. 1985; 42:579-590.

21. Baker EL Jr, Smith TJ, Landrigan PJ. The neurotoxicity of industrial

solvents: a review of the literature. Am J Ind Med. 1985; 8:207-217. ExternalResolverBasic Bibliographic Links

22. Linz DH, Morton WE, Wiens AN, Coull BM, Maricle RA. Organic solvent-induced encephalopathy in industrial painters. J Occup Med. 1986; 28:119-125.

23. Taubes G. Epidemiology faces its limits. Science. 1995; 269:164-169. ExternalResolverBasic Bibliographic Links

24. Workshop on solvent exposure among railroad workers. Organized by the Association of Occupational Environmental Clinics; Sponsored by NIOSH; November 6-7, 1996; Washington, D.C.

25. Frumkin H, Ducatman A, Kirkland K. Solvent exposure in the railroad industry (letter). J Occup Environ Med. 1997; 39:926-930. Ovid Full Text Request Permissions Bibliographic Links

26. World Health Organization. Chronic Effects of Organic Solvents on the Central Nervous System and Diagnostic Criteria. Copenhagen: WHO and Nordic Council of Ministers; 1985.

27. Edling C, Ekberg K, Ahlborg G Jr, Alexandersson R. Long term follow up of workers exposed to solvent. Br J Ind Med. 1990; 47:75-82.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189-198. ExternalResolverBasic Bibliographic Links

29. Albers JW, Wald JJ, Werner RA, Franzblau A, Berent S. Absence of polyneuropathy among workers previously diagnosed with solvent-induced toxic encephalopathy. J Occup Environ Med. 1999; 41:500-509. Ovid Full Text Request Permissions Bibliographic Links

30. Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetes. Muscle Nerve. 1988; 11:21-32.

31. Dyck PJ, Litchy WJ, Lehman KA, Hokanson JL, Low PA, O'Brien PC. Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. Neurology. 1995; 45:1115-1121. Ovid Full Text Request Permissions Bibliographic Links

32. Schoenberg VS. Descriptive neuroepidemiology: applications to occupational neurology. Acta Neurol Scand. 1982; 66(suppl 92):1-9. ExternalResolverBasic

33. Guberan E, Usel M, Raymond L, Tissot R, Sweetnam PM. Disability, mortality, and incidence of cancer among Geneva painters and electricians: a historical prospective study. Br J Ind Med. 1989; 46:16-23. ExternalResolverBasic Bibliographic Links

34. Riise T, Kyvik KR, Moen B. A cohort study of disability pensioning among Norwegian painters, construction workers, and workers in food processing. Epidemiology. 1995; 6:132-136. ExternalResolverBasic Request Permissions Bibliographic Links

35. van Vliet C, Swaen GMH, Slangen JJM, de Boorder T. The organic solvent syndrome. A comparison of cases with neuropsychiatric disorders among painters and construction workers. Int Arch Occup Environ Health. 1987; 59:493-501. ExternalResolverBasic Bibliographic Links

36. Williamson AM, Winder C. A prospective cohort study of the chronic effects of solvent exposure. Environ Res. 1993; 62:256-271. ExternalResolverBasic Bibliographic Links

37. Lundberg I, Gustavsson A, Hogberg M, Nise G. Diagnoses of alcohol abuse and other neuropsychiatric disorders among house painters compared with house carpenters. Br J Ind Med. 1992; 49:409-415. ExternalResolverBasic Bibliographic Links

38. Mikkelsen S. A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scand J Soc Med Suppl. 1980; 16:34-43. ExternalResolverBasic Bibliographic Links

39. Cherry NM, Labreche FP, McDonald JC. Organic brain damage and occupational solvent exposure. Br J Ind Med. 1992; 49:776-781. ExternalResolverBasic Bibliographic Links

40. Riise T, Moen BE. A nested case-control study of disability pension among seamen, with special reference to neuropsychiatric disorders and exposure to solvents. Neuroepidemiology. 1990; 9:88-94. ExternalResolverBasic Bibliographic Links

41. van Vliet C, Swaen GM, Volovics A, et al. Exposure-outcome relationships between organic solvent exposure and neuropsychiatric disorders: results from a Dutch case-control study. Am J Ind Med. 1989; 16:707-718. ExternalResolverBasic Bibliographic Links

42. Olsen J, Sabroe S. A case-reference study of neuropsychiatric disorders among workers exposed to solvents in the Danish wood and furniture industry. Scand J Soc Med. 1998; 16:44-49.

43. Brackbill RM, Maizlish N, Fischbach T. Risk of neuropsychiatric disability among painters in the United States. Scand J Work Environ Health. 1990; 16:182-188. ExternalResolverBasic Bibliographic Links

44. van Vliet C, Swaen GM, Volovics A, et al. Neuropsychiatric disorders among solvent-exposed workers. First results from a Dutch case-control study. Int Arch Occup Environ Health. 1990; 62:127-132. ExternalResolverBasic Bibliographic Links

45. Axelson O, Hane M, Hogstedt C. A case-referent study on neuropsychiatric disorders among workers exposed to solvents. Scand J Work Environ Health. 1976; 2:14-20. ExternalResolverBasic Bibliographic Links

46. Labreche FP, Cherry NM, McDonald JC. Psychiatric disorders and occupational exposure to solvents. Br J Ind Med. 1992; 49:820-825. ExternalResolverBasic Bibliographic Links

47. Nelson NA, Robins TG, White RF, Garrison RP. A case-control study of chronic neuropsychiatric disease and organic solvent exposure in automobile assembly plant workers. Occup Environ Med. 1994; 51:302-307. ExternalResolverBasic Bibliographic Links

48. Lindstrom K, Riihimaki H, Hanninen K. Occupational solvent exposure and neuropsychiatric disorders. Scand J Work Environ Health. 1984; 10:321-323. ExternalResolverBasic Bibliographic Links

49. O'Flynn RR, Monkman SM, Waldron HA. Organic solvents and presenile dementia: a case referent study using death certificates. Br J Ind Med. 1987; 44:259-262. ExternalResolverBasic Bibliographic Links

50. Palmer K, Inskip H, Martyn C, Coggon D. Dementia and occupational exposure to organic solvents. Occup Environ Med. 1998; 55:712-715. ExternalResolverBasic Bibliographic Links

51. Shalat SL, Seltzer B, Baker EL Jr. Occupational risk factors and Alzheimer's disease: a case-control study. J Occup Med. 1988; 30:934-936. ExternalResolverBasic Request Permissions Bibliographic Links

52. Graves AB, Rosner D, Echeverria D, Mortimer JA, Larson EB. Occupational exposures to solvents and aluminum and estimated risk of Alzheimer's disease. Occup Environ Med. 1998; 55:627-633. ExternalResolverBasic Bibliographic Links

53. Juntunen J, Kinnunen E, Antti-Poika M, Koskenvuo M. Multiple sclerosis and occupational exposure to chemicals: a co-twin control study of a nationwide series of twins. Br J Ind Med. 1989; 46:417-419. ExternalResolverBasic Bibliographic Links

54. Brown DL, Smith TL, Knepper LE. Evaluation of five primitive reflexes in 240 young adults. Neurology. 1998; 51:322. Ovid Full Text Request Permissions Bibliographic Links

55. Jacobs L, Gossman D. Three primitive reflexes in normal adults. Neurology. 1980; 30:184-188. ExternalResolverBasic Request Permissions Bibliographic Links

56. Rothstein JD, Herlong HF. Neurologic manifestations of hepatic disease. In: Riggs JE, ed. Neurologic Manifestations of Systemic Disease. Philadelphia: Saunders; 1989: 563-579.

57. Riordan SM, Williams R. Treatment of hepatic encephalopathy. N Engl J Med. 1997; 337:473-479. ExternalResolverBasic Bibliographic Links

58. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. JAMA. 1985; 253:1420-1426. ExternalResolverBasic Bibliographic Links

59. Markand ON. Electroencephalography in diffuse encephalopathies. J Clin Neurophysiol. 1984; 1:357-407. ExternalResolverBasic Request Permissions Bibliographic Links

60. Richardson WS, Wilson MC, Guyatt GH, Cook DJ, Nishikawa J. Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA. 1999; 281:1214-1219. ExternalResolverBasic Bibliographic Links

61. Sox HC, Blatt MA, Higgins MC, Marton KI. Medical Decision Making. Boston: Butterworth; 1988.

62. Differential Diagnosis. Philadelphia: Lea & Febiger; 1994.

63. Newman S, Klinger L, Venn G, Smith P, Harrison M, Treasure T. Subjective reports of cognition in relation to assessed cognitive performance following coronary artery bypass surgery. J Psychosom Res. 1989; 33:227-233. ExternalResolverBasic

Bibliographic Links

64. Strub RL, Black FW. Neurobehavioral Disorders: A Clinical Approach. Philadelphia: F.A. Davis; 1992: 169-172.

65. Sahakian BJ. Depressive pseudodementia in the elderly. Int J Geriatric Psychiatry. 1991; 6:453-458. ExternalResolverBasic Bibliographic Links

66. Albers JW. Evaluation of the patient with suspected peripheral neuropathy. In: Johnson EW, Pease WS, eds. Practical Electromyography. Baltimore: Williams & Wilkins; 1997: 311-337.

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Table 1

TABLE 1
Characteristics of the 52 Workers at the Time of Evaluation

Characteristic	Mean	Range	*N*
Age (y)	51	37–65	
Male gender			50
Height (M)	1.8	1.6–1.9	
Weight (kg)	88.1	58.9–136.0	
Body mass index (kg/m^2)	27.7	20.3–37.5	
Education (y)	11.5	6–14	
Education < 12 years			12
Exposure history			
Duration of exposure (y)	22	10–39	
Duration exposure opportunity (y)	15	6–35	
Time to symptom onset from first exposure (y)	16	1–43	
Currently working for railroad			20
Solvent-related work disability			21
If solvent-disability, duration (y)	4	1–11	
Job description			
Machinist			18
Electrician			16
Laborer (attendant, carpenter, equipment operator, maintenance)			11
Pipe fitter or boiler maker			7
Condition associated with potential nervous system influence			
History of alcohol abuse			6
Diabetes mellitus			4
High blood pressure (treated)			17
Liver disease (cirrhosis/fatty liver)			1
Psychotropic medication use			31
Antidepressant			23
Antianxiety			6
Narcotic analgesic			4
Central nervous system stimulant			2

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Table 1 . Characteristics of the 52 Workers at the Time of Evaluation

Table 2

TABLE 2
Neurologic Complaints Identified at Time of Evaluation, Including Chief (Primary) Complaints and Those Derived From the Review of Symptoms (n = 52)

	n
Chief complaints	
Memory/concentration difficulty	38
Altered mood	21
Poor balance	18
Persistent or recurrent headache	17
Any of the above chief complaints	46
Combined memory/concentration and mood complaints	19
All complaints, including those derived from review of symptoms	
Any memory/concentration complaint	46
Any mood complaints	37
Any combined memory/concentration and mood complaints	24
None of the above complaints	2

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Table 2 . Neurologic Complaints Identified at Time of Evaluation, Including Chief (Primary) Complaints and Those Derived From the Review of Symptoms (n = 52)

Table 3

TABLE 3
Neurologic Abnormalities (Signs) Identified Among Workers (n = 52)

Test	No.Abnormal
Overall neurologic examination (any abnormality)	34
Clinical mental status	13
General intellect (including orientation and current events)	4
Communication (language)	0
Attention (follow commands; digit repetition)	5
Memory (short-term and working memory)	6
Abstract thinking (similarities, proverb interpretation)	2
Abnormal MMSE* score (<24)	13
Clinically normal mental status but abnormal MMSE score (<24)	8
Cranial nerves	3
Motor	
Strength	
Weakness localized to one muscle or limb	2
Generalized or distal weakness	0
Incoordination	0
Sustension tremor	5
Other tremor, myoclonus, akathesia	0
Gait	
Casual	0
Tandem	14
Sensation	12
Symmetrical sensory loss	7
Vibration	6
Pin-pain	6
Joint-position, temperature, stereognosis	0
Station (Romberg)	6
Reflexes	
Ankle (absent)	1
Babinski	0
Palmomental	16
Other†	19

* MMSE, Mini-Mental Status Examination.
† Hyperreflexia (1), give-away weakness (1), carotid bruit (2), focal atrophy (1), + hyperventilation (3), + Adson's (1), + Tinel (15).

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Table 3 . Neurologic Abnormalities (Signs) Identified Among Workers (n = 52)* MMSE, Mini-Mental Status Examination.+ Hyperreflexia (1), give-away weakness (1), carotid bruit (2), focal atrophy (1), + hyperventilation (3), + Adson's (1), + Tinel (15).

Table 4

TABLE 4
Assessment of Encephalopathy and Neuropathy

Definition	No. Fulfilling Criteria
Encephalopathy	
World Health Organization	
1	10
2	42
2A	21
2B	8
2A and 2B	13
3	0
Clinical encephalopathy	
Possible encephalopathy (symptoms plus any abnormal mental status or motor/reflex signs)	27
Mental status signs	15
Motor/reflex signs	17
Probable clinical encephalopathy (symptoms plus two mental status and two motor/reflex signs)	0
Neuropathy	
Possible clinical neuropathy	5
Clinical neuropathy	6
Confirmed clinical neuropathy	3

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Table 4 . Assessment of Encephalopathy and Neuropathy

Table 5

TABLE 5

Comparisons of Symptoms and Signs Suggestive of Encephalopathy Identified on the Conventional Neurologic Evaluation Among Workers Separated on the Basis of Their WHO Classification of Encephalopathy*

		Neurologic Evaluation for Encephalopathy Signs (Mean)			Encephalopathy?	
WHO	Symptoms (*n*/*n*)	No. of Mental Status Abnormalities	MMSE Score	No. of Motor/Reflex Abnormalities	Possible (*n*/*n*)	Clinically Evident (*n*)
1	8/10	0	27	0.4	4/10	0
2A	16/21	0.2	25	0.4	9/21	0
2B	6/8	1.3	23	0.8	6/8	0
2A, B	10/13	1.4	24	0.5	10/13	0
3	0/0					

* WHO, World Health Organization; MMSE, Mini-Mental Status Examination.

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Table 6

TABLE 6
Clinical Explanations (Diagnoses) Related to Primary Complaints

Chief Complaints	Diagnosis*
Memory/concentration difficulty (38)	Complaints consistent with normal memory variation (34) Use of *medications* that impaired memory/concentration (20) Potential contribution from depressed mood (18) Fatigue with possible sleep apnea (9) Learning disability/limited education (4)
Altered mood (21)	Use of *medications* associated with altered mood, including anxiety, agitation, depression, abnormal sleep (10) Situational depression (13)
Poor balance, lightheadedness, or dizziness (18)	Use of *medications* associated with dizziness, lightheadedness, unsteadiness, poor coordination (12) Contributing low back or neck pain (6) Mechanical gait problem (4) Cervical spondylosis (1) Meniere's disease or prior labrynthitis (1) Hyperventilation syndrome (5) Benign positional lightheadedness (4) Distal symmetrical sensory loss (3) Orthostatic lightheadedness (4) Inconsistent gait; astasia abasia (1)
Headache (17)	Muscle contraction (14) Vascular (migraine) (2) Mixed, muscle contraction/vascular (5) Recurrent sinusitis (1) Use of *medications* that exacerbate headache (6) Potential contribution from depressed mood (9) Possible sleep apnea (4)
Tremor (3)	Benign postural/physiologic tremor (2) Use of *medication* producing tremor (1)†

* Some workers had multiple explanations for a given complaint.
† Two additional workers had abnormal postural tremor but no complaint of tremor.

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Table 6 . Clinical Explanations (Diagnoses) Related to Primary Complaints* Some workers had multiple explanations for a given complaint.+ Two additional workers had abnormal postural tremor but no complaint of tremor.

Table 7

TABLE 7
Stepwise Multiple Linear Regression Models[a]

	Beta/Partial Correlation	*P* Value
Total no. of symptoms* (adjusted $r^2 = 0.244$)		
CNS medications†	0.51	0.000
Age	−0.24	0.10
Gender	−0.16	0.25
Body mass index	−0.13	0.38
Exposure duration	−0.12	0.39
History of alcohol abuse	0.05	0.71
Educational level	−0.02	0.87
Total no. of signs (adjusted $r^2 = 0.059$)		
CNS medications	0.28	0.046
History of alcohol abuse	0.25	0.08
Gender	−0.19	0.18
Exposure duration	0.14	0.33
Educational level	0.13	0.35
Body mass index	0.08	0.59
Age	−0.04	0.78
Mini-Mental Status Score (adjusted $r^2 = 0.130$)		
History of alcohol abuse	−0.34	0.01
Educational level	0.30	0.03
Exposure duration	0.25	0.08
Body mass index	0.11	0.45
Gender	−0.06	0.67
Age	0.06	0.67
CNS medications	0.01	0.96

[a] CNS, central nervous system.
* Dependent variables.
† Independent variables.

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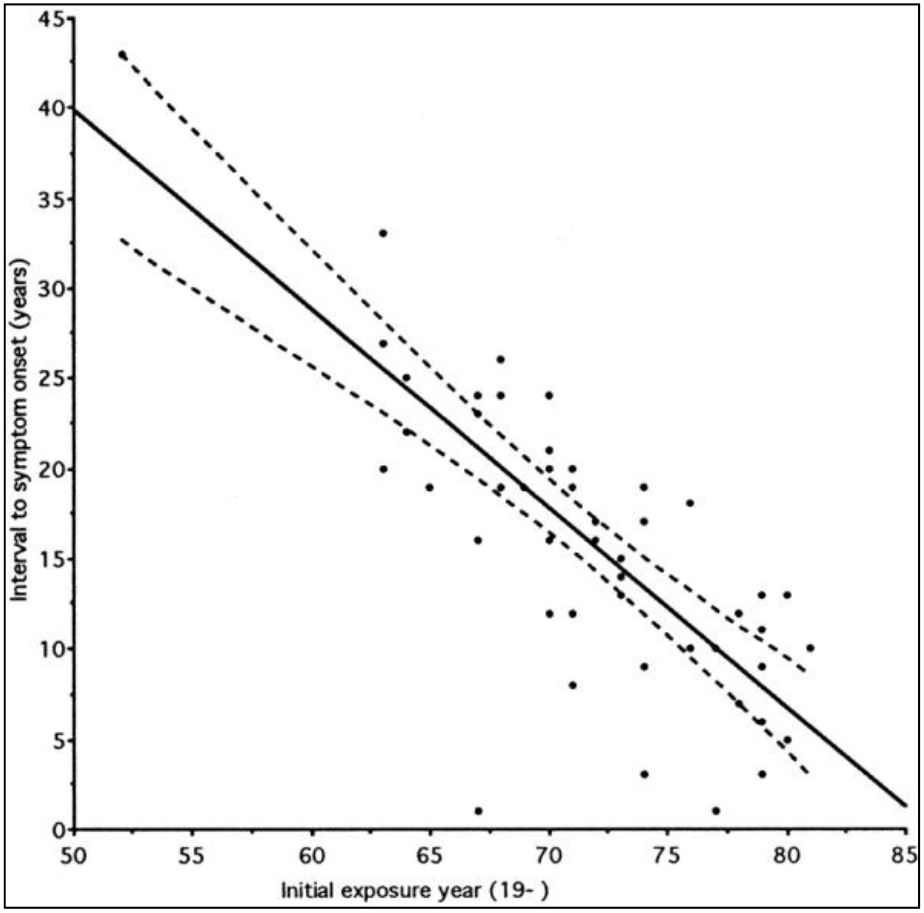
Table 7 . Stepwise Multiple Linear Regression Modelsaa CNS, central nervous system.* Dependent variables.+ Independent variables.

Fig. 1



Neurologic Evaluation of Workers Previously Diagnosed With Solvent-Induced Toxic Encephalopathy.
Albers, James; MD, PhD; Wald, John; Garabrant, David; MD, MPH; Trask, Christine; Berent, Stanley

Journal of Occupational & Environmental Medicine. 42(4):410-423, April 2000.

Fig. 1 . Interval from initial exposure to neurologic symptom onset (years) versus the initial year of occupational exposure to solvents (brackets around regression line indicate 95% confidence bands for true mean of Y.