

Has the Scandinavian solvent syndrome controversy been solved?

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HOGSTEDT C. Has the Scandinavian solvent syndrome controversy been solved? *Scand J Work Environ Health* 1994;20 special issue:59—64. This article discusses the “Scandinavian solvent syndrome” and reviews epidemiologic studies on occupational solvent exposure and two related outcomes. High cumulative exposure to organic solvents in the 1960—1970s was related to early retirement from neuropsychiatric disorders, but solvent exposure alone was an unlikely cause of more severe dementia conditions. Heavy alcohol consumption seemed to modify the effect on solvent-related brain disorders strongly, but no reports exist of alcohol consumption as a confounding factor. Many cross-sectional and experimental studies support functional impairment from high solvent exposure. The mists and myths around the “Scandinavian solvent syndrome” can now be cleared up: it was not a uniform syndrome, it might be reversible in many cases, it is not confined to the Scandinavian countries, the risk of more severe dementia is substantial for combined high solvent exposure and excessive alcohol consumption, and many solvent-exposed workers receive early retirement due to solvent-related neuropsychiatric disorders.

KEY TERMS — alcoholism, epidemiology, neuropsychiatric function, organic solvents, review.

The more recent history of what has been called the “Scandinavian solvent syndrome” can be traced back to the beginning and middle of the 1970s. Several series of case reports were published from the Scandinavian countries (1, 2) on solvent-exposed cases with a symptomatology that could be summarized as a psychoorganic or neurasthenic syndrome. The typical symptoms to be reported were memory disturbances, excessive tiredness, personality changes (including depression), irritability and affect lability, sometimes intellectual reduction, and problems in maintaining a job and other social functions.

The interest in a possible causal relationship grew when several cross-sectional studies, mostly from Scandinavian countries, reported excess neuropsychiatric symptoms and impaired neuropsychological performance among house painters, car painters, jet-fuel exposed workers, and styrene-exposed workers, to name a few. (See reference 3.) Several Scandinavian investigators also found an excess of disability pensions due to neuropsychiatric disorders in solvent-exposed occupational groups (4—7).

Case reports of similar types and the psychoorganic syndrome in relation to high exposure to organic solvents had been described many decades earlier in the literature on psychiatric and occupational medicine (8—12). Already in 1955 the case reports had

been supported by an epidemiologic study from Switzerland (13). These authors concluded that “the clinical examinations showed a relatively high frequency of subjective complaints, of alterations of the vegetative nervous system and of neurological and psychiatric symptoms. There is a relationship between the frequency of those nervous alterations and the degree of exposure to trichloroethylene [p 142].”

Why did the rediscovery of these occupational disorders cause so much debate and questioning? Was it assumed that improvements in the work conditions during the 1960s and the 1970s should have diminished solvent exposure in the industrialized countries to levels that did not produce effects? Were the effects mainly expected from carbon disulfide and trichloroethylene exposure? Was there suspicion that liberal Scandinavian compensation laws might accept such a relationship between the prevailing solvent exposure and these symptoms while the scientific basis was insufficient?

The controversy seems to have been sharpened by the Danish practice to classify — and reclassify — these neuropsychiatric symptoms as presenile dementia (14). In many countries dementia indicated a progressive, nonreversible process of a much more severe type than what had been found among the working populations studied. There was, however, no uniform psychiatric practice for classifying less severe brain disorders at the time. It was not until the American Psychiatric Association published its *Diagnostic and Statistical Manual of Mental Disorders (DSM—III)* in 1980 that a more uniform classification was broadly accepted for clinical, research, and administrative use. Neither that diagnostic system nor the revised version from 1987 (15) has been widely

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used and could therefore not have been applied in retrospective studies. Furthermore, it would not have excluded dementia as a possible classification of the clinical pictures identified among some painters and other solvent-exposed workers. DSM—III—R defines the criteria for mild dementia as: "although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgement [p 107]." The criteria for moderate dementia imply that independent living is hazardous and for severe dementia that continual supervision is required. Most of the reported cases had, however, less pronounced intellectual reduction than normally associated with dementia diagnoses.

The controversy has basically concerned whether it is scientifically sound to accept long-term occupational exposure to legally accepted levels of commonly used organic solvents as a cause of increased risk — reversible or irreversible — of functional impairments (after the acute and subacute phase) or even more severe psychiatric illnesses due to brain damage.

A sufficient number of studies has now been published to make it possible to discuss potential risk increases for two different sets of outcomes, (i) the risk of being retired early due to neuropsychiatric disorders and (ii) the risk of becoming a hospitalized psychiatric patient, especially due to disorders related to organic brain damage.

So far no follow-up study has been published with a clinical base-line examination of unexposed workers and a reexamination many years later, after some of the workers have become exposed to solvents. Such a design might be thought of as optimal if there is good control of preexposure intellectual and psychological capacity, careful exposure assessment, and uniform, observer-blinded examinations — but it would also be very expensive. A "pseudolongitudinal" design has, however, been applied by Mikkelsen and his co-workers (16), and it will also be reviewed.

Does long-term organic solvent exposure increase the risk of disability pension due to neuropsychiatric diagnoses?

In 1986 the four studies published on individuals considered for a disability pension because of some type of mental disorder were reviewed (17). All four studies were from Scandinavia and demonstrated a roughly doubled risk for painters and some other solvent-exposed workers to develop an occupationally incapacitating neuropsychiatric disorder before the age of retirement. The majority of the design deficiencies seemed to work in the direction of diluting the risk estimates, making it more difficult to detect true risks.

In 1989—1992 five more studies were published on the risk of disability pension due to neuropsychi-

atric disorders. In a Swiss cohort study 1916 painters and 1948 electricians were identified through the 1970 census and followed to 1984 (18). For four categories of neuropsychiatric diseases there were 20 pensions granted to painters and 10 to electricians, giving an age-standardized risk ratio of 1.8. Among the 20 painters, alcoholism was the main cause of disability for four men and a contributing case for eight. Among the 10 electricians, alcohol was a contributing cause for one man only. Alcoholism as a contributing factor has been discussed later.

In a study from the United States, the Social Security Administration's records of white male recipients of disability compensation were used in a case-referent study on this topic (19). The cases were defined as men with any of several neuropsychiatric diseases, and the referents as men with other disabling conditions. The men were considered exposed if they had worked as painters prior to disability and unexposed if they had worked as bricklayers. The painters had a significant excess of neuropsychiatric disability with an adjusted odds ratio of 1.4.

In a Dutch case-referent study the subjects were selected from the Painters' and Construction Workers' Organization and included 252 men awarded disability benefits due to neuropsychiatric disorders. The referents consisted of a random sample of 822 men from the trade union (20, 21). For exposure, a specific painter's index was calculated, and it was strongly associated positively with the risk for neuropsychiatric disorders. The odds ratios were at least doubled.

In 1990 a nested case-referent study of disability pensions among Norwegian seamen, with special reference to neuropsychiatric disorders and exposure to solvents, was published (22). Employment on chemical and oil tankers was regarded as solvent-exposed, substantiated by separate industrial hygiene reports. The study included 68 cases of disability pension due to neurosis, psychosis, or diseases of the nervous system as either the primary or secondary diagnosis and four times as many referents. For all types of diagnoses the tanker seamen had a much higher risk of disability pension compared with the seamen on dry cargo ships, but a particularly high, dose-exposure related ratio was found for neuropsychiatric diagnoses.

The number of early retirements in 1971—1984 was compared between the 767 house painters and the 1212 house carpenters who were born in 1925 or later, were members of the Stockholm branches of the respective trade unions in 1965, and had been members for at least 10 years before 1970 (23). The total incidence of early retirement was higher for the painters [46 cases, relative risk (RR) 1.3] and the incidence for neuropsychiatric disorders, as the first diagnosis, was higher for the painters than for the carpenters (15 cases, RR 6.5). Alcoholism was the most common neuropsychiatric disorder diagnosed. It showed the highest relative risk (9 cases, RR 8.0). See the later discussion on the possibility of alco-

holism as a confounding factor. Four of the painters had a first diagnosis that was considered relevant for a solvent-induced disorder compared with one among the carpenters [RR 3.5, 95% confidence interval (95% CI) 0.7—16].

In short, all published studies indicate that there is an increased risk for workers with long-term exposure to organic solvents to retire early due to neuropsychiatric disorders. The interaction with alcohol has been discussed later.

Studies of hospitalized psychiatric patients

It has been suggested that the increased risk of disability pension due to neuropsychiatric disorders may be caused by acute difficulties to work in solvent exposure and that the effects may be reversible. Studies of patients hospitalized due to different psychiatric disorders, with special emphasis on diagnoses indicating organic brain damage, would elucidate the potential relationship between occupational solvent exposure and more severe disorders than those that may cause early retirement but be less damaging.

A case-referent study among Danish men admitted to a geriatric ward was published in 1985 (24). All of the diagnoses used to select the cases and referents were made during hospitalization. The case group consisted of 207 patients with a broad group of neuropsychiatric diagnoses. One hundred and ten referents were chosen from patients with other diagnoses. Senile and presenile dementia and ischemic cerebral arteriosclerosis were the most common diagnoses. Questionnaires and telephone interviews were used to seek information about the longest held occupation, about employment for more than five years in occupations with risk of solvent exposure, and about alcohol consumption. The workers formerly exposed to solvents had an increased risk ratio of 2—3.

Cherry et al (25) compared occupational exposure to solvents among 309 men with organic dementia, cerebral atrophy, or psychoorganic syndrome admitted to one of 18 Quebec hospitals and individually matched with two sets of referents, one being patients admitted with some other psychiatric diagnosis and the other being patients admitted to a general hospital. Increased risks of about 1.4 were found for those with organic dementia or cerebral atrophy. The excess was concentrated among heavy alcohol drinkers, judged either by associated diagnoses of alcoholism (OR 5.0—5.5) or by recorded alcohol consumption (OR 3.0). However, only minor, nonsignificant differences were found in reported alcohol consumption between the exposed and unexposed workers. The conclusion was that the combined effect of occupational solvent exposure and alcohol intake is probably an important cause of organic brain damage. (See page 62).

Labrèche et al (26) studied 381 men selected from admission lists of two psychiatric hospitals in Mon-

tréal. Two series of referents were selected but only a primary reference group was reported on in this paper. The psychiatric diagnoses were divided into psychotic and nonpsychotic diseases. The odds ratio for nonpsychotic cases was 1.5 after the regression of confounders (90% CI 0.8—3.0). With the psychotic diagnoses the odds ratio was below 1.

A case-referent study was conducted to assess occupational exposure to organic solvents and lead as risk factors for Alzheimer's disease (27). All of the case subjects were diagnosed at a Veterans Administration Hospital in Bedford, Massachusetts. The referents were selected from registration lists of Massachusetts voters and matched by gender, year of birth, and town of residence. Information on occupational history was assessed from a postal questionnaire sent to the spouse or next-of-kin of the study subject. The response rate was poor. A total of 98 case and 162 reference subjects were included in the matched analysis. No apparent association of increased risk of Alzheimer's disease was observed for occupational exposure to organic solvents or lead.

In a case-referent study carried out in Great Britain (28) the relation between exposure to organic solvents and presenile dementia was studied. The cases were all men dying in England and Wales from 1970 up to and including 1979 with presenile dementia as a cause of death on the death certificate. One age-matched referent (2 years) for each case was randomly drawn from other death certificates. The most recent occupation, stated on the death certificate, was used to grade solvent exposure as probable, possible, or no exposure. There were 557 cases and the same number of referents. Thirty-nine referents versus 43 cases had probable or possible occupational exposure to solvents. The authors concluded that the study indicated that exposure to organic solvents has no etiologic role in the development of dementia. However, the exposure classification used in this study should considerably have diluted any true increase in relative risk.

A recent meta-analysis of 11 case-referent studies on Alzheimer's disease did not give any suggestion of an association with solvent exposure (29). These nonpositive results for the most severe dementia are in good agreement with the findings of follow-up studies of solvent-exposed patients from departments of occupational medicine in Finland, Denmark, and Sweden, where no indications were obtained regarding the development of such severe dementias (30—33). Severe dementia has not even been established among solvent abusers according to a critical review (34).

Pseudolongitudinal study of neurobehavioral effects among Danish painters and bricklayers

In 1988, Mikkelsen et al (16) reported a follow-up study on painters and bricklayers. The study popu-

lation was established from male subjects with membership in 1971 in a Copenhagen local union of house painters or bricklayers, born 1916–1940 and with exclusion of those awarded any sort of pension before 1976. The participant rates for the painters and bricklayers were 88 and 83%, respectively, of the invited subjects; 85 painters and 85 bricklayers participated.

A clinical overall assessment was done by a psychologist without knowledge of the occupational status of the person being examined. According to the authors this overall assessment “interprets and combines numerous pieces of information into a single measure of acquired mental impairment, and was performed according to the general practice and guidelines used for the clinical assessment of dementia at the neuropsychological division. The greater the discrepancy between the expected and the observed general performance, the higher the degree of dementia. Performance in specific tests was evaluated considering both quantitative and qualitative aspects as well as the validity of the test. Clinical signs of demented behavior and degree, history and relevance of symptoms of mental impairment were evaluated in relation to test performance and were used in the interpretation of test results and final assessment of the degree of the dementia [p 27].”

An individual solvent-exposure index in units of liters per day times years was based on a very elaborate interview on work practices and categories including an estimate of the average number of liters of paint used on a workday when painting with a brush, roller, or a spray gun. The degree of dementia and dyscoordination increased significantly with increasing solvent exposure. A similar, but nonsignificant association was found for the relation between performance in psychometric tests and solvent exposure. Painters with low exposure performed equal or better than the bricklayers.

Computerized tomographic examinations of the brain were performed on a subsample stratified according to degree of dementia since the original intention was to study the association between questionnaire symptoms of dementia, the clinical assessment of dementia, and cerebral atrophy. However, the same data were also used in an effort to evaluate the relationship between solvent exposure and cerebral atrophy. The results seemed to indicate an increasing degree of cerebral atrophy with increasing solvent exposure.

The degree of the dementia concept used and the degree of dyscoordination and cerebral atrophy were positively associated with each other, a finding suggesting that they might reflect different aspects of a common underlying factor, organic brain damage. The results of Mikkelsen and his co-workers indicate causality between long-term high solvent exposure and increased risk of chronic encephalopathy in their study population.

In the mid-1980s, independently of Mikkelsen and his co-workers, my co-workers and I started to plan a similar study which has been described (35), carried out, and soon will be submitted for publication.

Is alcoholism a confounding factor?

Several studies from different countries have found an excess of alcoholism diagnoses among painters when this group was compared with other skilled construction workers, but there has usually not been any indications of higher alcohol consumption among the solvent-exposed workers (36). The interpretation of the finding of excess alcoholism has varied. It has been suggested that the alcoholism diagnoses are misdiagnoses of solvent-induced changes. Another suggestion has been that painters consume more alcohol than workers in allied trades because of social and cultural differences and that excess alcohol consumption is a truly confounding exposure. It is also possible that there might be an interaction between solvent exposure and alcohol intake that may increase the number of alcohol diagnoses.

A Swedish study was designed to examine whether diagnoses of alcoholism were more common among house painters than among another group of construction workers — namely, house carpenters (23). Cohorts of 1212 house carpenters, born in 1925 or later, and 767 house painters were followed in 1985–1986 in the following four registers: the register of diagnoses at early retirement, the register of diagnoses at discharge from in-patient psychiatric care, the alcohol crime register (containing all crimes linked to the handling or consumption of alcohol), and the death register. In this study there was an excess risk for alcoholism among painters, as compared with carpenters. However, the excess risk was confined to those found in several registers due to an alcohol diagnosis. It was not present among those found in only one register.

Two explanations of this finding seem likely, first, that a high consumption of alcohol has a tendency to become more excessive among painters than among carpenters and, second, that the damage produced by a high consumption of alcohol is more serious among painters than among carpenters. Both these explanations require an interaction between alcohol and some other factor among the painters. The most likely factor is solvent exposure. Solvent exposure may possibly directly influence alcohol consumption, or solvent exposure may act additively with alcohol to increase the number of neuropsychiatric diagnoses, including alcoholism, among painters.

Discussion

The strength of the association between long-term occupational solvent exposure and early retirement due to neuropsychiatric disorders is not very strong

when compared with the association of other classical occupational disorders. The consistency in different studies from several countries is more impressive, especially considering the weak exposure information, usually merely occupational years, and the inclusion of many psychiatric diagnoses of questionable relevance and precision. Such misclassifications underestimate a truly increased risk.

Some further support for a causal relationship is achieved by the fact that the number of early retirements due to neuropsychiatric disorders among solvent-exposed workers seems to have decreased during the last decade in Sweden as the exposure situation has improved. This phenomenon has mainly been due to a dramatic change from solvent-based paints to water-based paints.

The findings of an excess of alcohol-related diagnoses among solvent workers in some of the studies make the final evaluation somewhat problematic, but the studies by Cherry et al (25, 36) and Lundberg et al (23) seem to imply that reducing solvent exposure would also diminish the influence of alcohol damage. Excessive alcohol consumption seems to work as a modifying factor, and it may make it easier to discover the increased risk of neuropsychiatric disorders, just as cigarette smoking makes it easier to discover the lung cancer effect of asbestos. In conclusion, it seems reasonable to state that long-term occupational exposure to moderately high levels of organic solvents increases the risk of early retirement due to neuropsychiatric disorders.

Concerning more severe brain damage that might necessitate psychiatric treatment in hospitals, the results are somewhat conflicting and the strength of an association is weaker. The exposure assessment has been much more elaborate in some of the hospital studies, as well as the diagnostic work-up, compared with the early retirement studies, but there could still be a dilution of a truly increased risk. Alcoholism was a strongly modifying factor in one of the studies (25). More studies are needed on long-term occupational solvent exposure and the possibility of an increased risk of moderate organic brain damage although it is unlikely that such a potential risk would be of any higher magnitude unless in combination with excess alcohol consumption.

An impressive number of cross-sectional studies on neurobehavioral effects in solvent-exposed groups continues to be published during the 1990s (37–44). Some studies reproduce the initial findings from the Scandinavian countries in the 1970s, while others do not. These discrepancies can usually be explained by low exposure levels, low participation rates, no control of selection forces, and the like. Thus it seems safe to summarize that workers exposed to moderately high concentrations of organic solvents will have an increased risk of neuropsychological symptoms and decreased performances on certain psychological tests when examined within a few days or weeks of their last exposure. From a medical point

of view these findings would, in themselves, question the occupational exposure limits for several organic solvents in many countries, and they are, of course, compatible with an increased risk of long-term functional or organic disturbances. There are also several experimental studies on animals with results that are compatible with such risks (3).

Concluding remarks

It seems reasonable to conclude that the exposure levels for organic solvents that occurred during the 1960s and 1970s in many countries caused an increased risk of impairment of the functional status among workers with high cumulative exposure and that this exposure also caused an increased risk of early retirement due to neuropsychological disorders but that it seems unlikely that this exposure also caused an increased risk of more severe dementia conditions like Alzheimer's disease. Heavy alcohol consumption seems to have a strongly modifying effect on solvent-related mental disorders. There are indications that several of the milder disorders are fully or partly reversible. In spite of many studies from different occupational groups, certain research is still needed to complete the picture of the phenomenon that was called the Scandinavian solvent syndrome but also has been identified in many other countries.

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