

Neuropsychiatric function of housepainters with previous long-term heavy exposure to organic solvents

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Abstract

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Neuropsychiatric effects were examined among 206 men, of whom 135 had been house painters and 71 had been house carpenters, affiliated with their respective trade unions for at least 10 years before 1970. Their lifetime organic solvent exposure was evaluated through the aid of an interview. Relevant potential confounding factors were accounted for in the statistical analysis. Neuropsychiatric symptoms compatible with chronic toxic encephalopathy were more common among the painters than among the carpenters, and these symptoms became increasingly prevalent with increasing cumulative solvent exposure. On only one of 12 psychometric tests, block design, did the painters perform worse than the carpenters, and in this test the painters' performance deteriorated with increasing cumulative exposure. For the majority of the psychometric tests, and for the coordination tests, there were no differences between the painters and carpenters, but the painters with "low" exposure tended to show better, and "heavily" exposed painters worse, results than the carpenters. The 52 painters with the heaviest cumulative exposures and 45 carpenters were examined for psychiatric diagnosis according to DSM-III, with electroencephalography and auditory evoked potential, P-300. Three painters and two carpenters had diagnoses compatible with an organic mental disorder. There were no overall differences between the painters and carpenters, either for the visually examined electroencephalograms or the P-300 latencies.

The excess of neuropsychiatric symptoms among the painters was probably causally linked to solvent exposure. However, these symptoms seemed only rarely, if ever, serious enough to entail a psychiatric diagnosis. Concerning other outcomes, the investigation may not lead to a determination of whether the exposure-response relationship among the painters, with no difference between the entire group of painters and carpenters, is caused by solvent exposure or by selection factors within the group of painters.

Key terms auditory evoked potential-300, carpenters, coordination tests, electroencephalography, epidemiology, occupational exposure, pseudolongitudinal study, psychiatric diagnoses, psychometric tests.

Introduction

In 1856, the French physician August Delpech described a series of 24 patients who had developed severe psychological problems after exposure to carbon disulfide fumes. The patients suffered from insomnia, nightmares, sexual dysfunction, extreme irritability, and uncontrollable rages. Some of them had even committed suicide by jumping out the windows of the rooms where they worked vulcanizing rubber (1).

Around the turn of the century, new solvents such as xylene, benzene, toluene, trichloroethylene, styrene, turpentine, and ethanol were introduced, and cases of central nervous system (CNS) effects, although less serious, were also described among workers with long-term occupational exposure to these solvents (2, 3).

During the 1970s and early 1980s, numerous cross-sectional studies were made in the Nordic countries to establish or refute a link between occupational exposure to solvents and chronic neuropsychiatric problems. The studies covered such groups as housepainters, builders of fiberglass boats, workers in paint factories, and workers exposed to jet fuel (4–9). The outcomes in these studies were symptoms and psychometric tests, and in some cases neurophysiological examinations, computer tomography of the brain, or examination of cerebral blood flow.

Concentration difficulties, deterioration of short-term memory, irritability, depression, alcohol intolerance, headaches, and abnormal fatigue were common symptoms among the subjects that had been heavily exposed for long periods. The psychometric tests revealed disturbances in memory and perception, prolonged reaction times and some loss of coordination (10). Indications of slight effects on the peripheral nervous system were also found in some of the studies (7, 11).

In studies made in the Nordic countries during the same period occupational exposure to solvents was found to be associated with an elevated incidence of early disability retirements due to neuropsychiatric diagnoses (12–16).

The results of the Nordic studies could frequently not be verified in cross-sectional and epidemiologic studies with registers in other countries (17–20). Studies made in Switzerland and Holland revealed excesses of some neuropsychiatric diagnoses, but not others, among disability retirees that had previously been exposed to solvents, and the authors were reluctant to attribute the excesses to solvent exposure (21–23). A study made in the United States found a higher frequency of early retirement due to neuropsychiatric diagnoses among painters than among masons, and thus its findings supported the results of the Nordic studies (24).

These contradictory international research results provided the background for several expert meetings called to discuss priorities for continued research in the area (25, 26). The earlier studies were found to have shortcomings that could lead to both underestimation and overestimation of the risks of exposure to solvents.

The critics argued that the Nordic studies tended to confound the possible effects of solvent exposure with the possible effects of selection to and remaining in a certain profession, particularly that of housepainter, which has been by far the dominant profession associated with heavy exposure to solvents. It was argued that housepainters could be characterized by higher alcohol consumption (21) and lower primary intellectual capacity (27) than workers in similar professions and that the effects observed in the Nordic studies were due to negative social selection into the profession of housepainter. It was also argued that the increases in symptoms and the impaired performance in psychometric tests that had been observed in various cross-sectional studies could have been subacute effects, since the subjects had generally been tested after only one exposure-free night or weekend.

If, on the other hand, exposure to solvents really does lead to chronic neuropsychiatric effects, it can be assumed that the cross-sectional studies of subjects who were still working as painters had underestimated the real risks, since workers who had experienced neuropsychiatric problems had probably often left jobs where they were exposed to solvents. Exposure estimates that were too crude, usually in the form of the number of years in an exposed job, probably also led to a considerable, usually independent, misclassification of the actual exposures and thus to underestimation of the actual effects of exposure and the actual exposure-response relationships.

We have made a clinical examination of housepainters and carpenters who had held these jobs for a long time before 1970, regardless of what jobs or exposures they have today. Each subject's exposure to solvents was carefully charted. Their primary intellectual capacity was assessed by psychometric tests given at conscription. Their alcohol consumption was estimated via questionnaires, laboratory tests, and follow-up in medical registers. Since their current exposure to solvents was low or nonexistent, subacute effects were unlikely.

The aim of the study was to determine whether occupational exposure to solvents increases the risk of chronic damage to the CNS.

Material and methods

Selection of the study group

Cohorts were collected of all the housepainters and carpenters who were born in 1925 or later, who were members of the Stockholm chapters of their unions in 1965, and who had been members for at least ten years before 1971. Information on these criteria was obtained from the membership rosters of the unions. The criteria were met by 767 painters and 1212 carpenters.

The cohort members were followed in four different outcome registers. These were the register of diagnoses at early retirement (RDER), the register of causes of death, the register of diagnoses at discharge from inpatient psychiatric care (PDR) and the alcohol crime register (ACR). Further information on the content of these registers is given in a separate publication (28). The results of the cognitive ability and aptitude tests given to the subjects at military conscription were obtained from the Royal Military Record Office (Krigsarkivet). These tests have been given to all Swedish men born since 1925. The results of the tests are used to place the draftees in suitable military training.

From this group, painters and carpenters were chosen for the clinical examinations. The following requirements were set:

1. They had resided in Stockholm County on 31 December 1986.
2. They took their military conscription tests in 1949, 1951 (painters only), 1953, 1957, or 1961, and the results of these tests were available. Painters tested in 1951 were added after a third of the study group had been examined. To improve the exposure-response analyses, we found it desirable to have a group of painters twice as large as the group of carpenters. The earlier goal had been to have 1.5 times as many painters as carpenters. For these test years, two of the conscription tests were identical: an instruction test and a test of verbal ability. The combined results of the conscription tests were not to equal stanine 1 (an extremely poor score), since this test result very probably did not reflect a maximum performance on the test occasion.
3. They were not identified in the registers as having a diagnosed illness that could be assumed to affect the description of symptoms or the results of psychometric tests seriously but was not suspected of being caused by exposure to solvents. We compiled a list of such exclu-

sion diagnoses from the list of all diagnoses reported to the two registers in the entire cohorts. In the classification we were not aware of whether a subject was a painter or a carpenter. The list covered diagnoses such as malignant tumors, psychoses, cerebrovascular disease. Out of the 150 painters and 195 carpenters remaining (figure 1) four carpenters were excluded due to repeated care for psychosis according to the RDP (one case of schizophrenia and one case of other psychosis), chronic endocarditis (one case), and other diseases of the retina and the optical nerve (one case) according to the RDER. One painter was excluded since he had died in 1987.

4. Since the carpenters in the cohort outnumbered the painters and since twice as many painters as carpenters were wanted in the group, about half of the carpenters were excluded at random. Among the carpenters excluded at random were two cases of neurosis according to the RDP and one was a case of angina pectoris according to the RDER.

Altogether 149 painters and 85 carpenters, all men, were called to the examination.

Clinical examination

Stage I

The study group was called in random order for a physical examination. Two subjects were called for each Monday, Tuesday Wednesday, and Thursday during the examination period. Along with their appointment, they were sent a questionnaire which they were to fill out and leave with the receiving nurse. The persons giving the examinations did not see the questionnaire, nor did they know which subjects were painters and which were carpenters.

A total of 135 painters and 71 carpenters showed up for their examinations, corresponding to 91 and 84%, respectively, of those called. The examination occurred in 1988–1989. Table 1 shows the register distribution of the painters and carpenters who came or did not come to the examination. The diagnoses found among the painters who were called to the examination but did not attend it were two cases of alcoholism and one case of neurosis according to the RDP. Among the carpenters who did not show up for the examination was one case of neurosis according to the RDP and one case of obesity according to the RDER. Among the painters actually

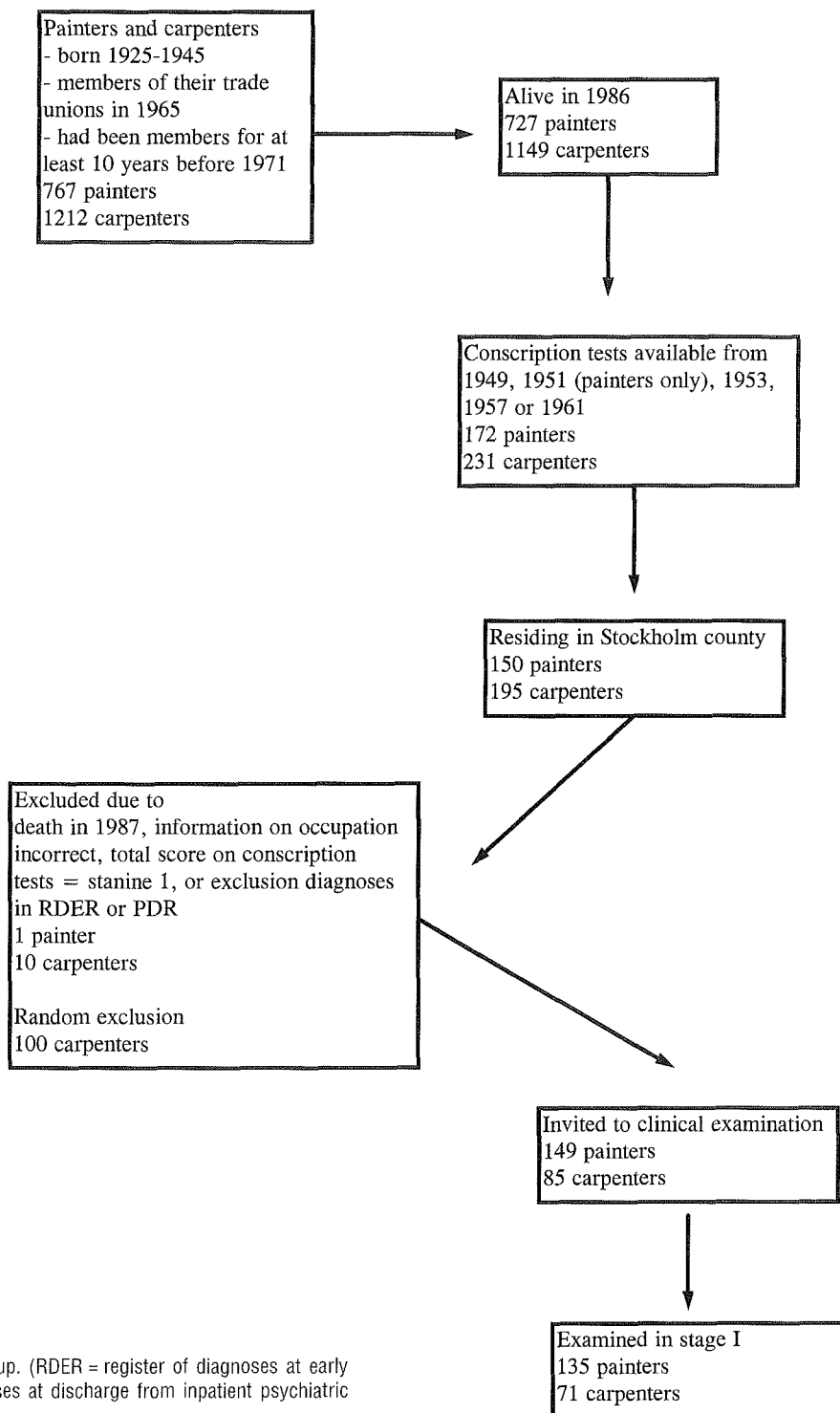


Figure 1. Selection of the study group. (RDER = register of diagnoses at early retirement, PDR = register of diagnoses at discharge from inpatient psychiatric care)

examined there were three cases of musculoskeletal disease and one case of vertigo according to the RDER. It seems likely that psychiatric morbidity was overrepresented among those who did not participate in the study compared with those who did. Those who did not wish to participate were telephoned and asked why. Of the 8 painters and 11 carpenters who could be reached, one

painter and four carpenters reported illness (leukemia, diabetes, traffic accident, stomach ulcer, and high blood pressure) as a reason for not participating. Seven painters and seven carpenters said they did not have time or did not wish to participate.

All the subjects were given both oral and written instructions not to mention their job, and they were

Table 1. Results of register searches for all painters and carpenters invited to stage I of the examination. (RDP = Register of Diagnoses at Inpatient Psychiatric Care, RDER = Register of Diagnoses at Early Retirement, ACR = Alcohol Crime Register)

Occupation	RDP	RDER	ACR	Any register
Painters				
Participated (N = 135)	2	4	3	8
Did not participate (N = 14)	3	—	2	3
Carpenters				
Participated (N = 71)	—	—	5	5
Did not participate (N = 14)	1	1	1	2

checked for tell-tale signs (paint flecks were washed off, etc) before the examination began.

The examination program began with blood tests. Then the subject repeated two of the psychometric tests taken at the time of conscription into military service and filled out the Profile of Mood States (POMS). One of the subjects, selected at random, then went to an occupational hygienist for an individual assessment of exposure, while the other went to a physician for a medical examination, including an interview regarding symptoms and computerized coordination tests. After about 75 min the subjects exchanged places, so that the second was with the occupational hygienist and the first was with the physician. They then had lunch. The afternoon was spent on a battery of psychometric tests, for which the subjects were placed at random with the two examining psychologists. The examination program, including lunch, lasted about 8 h.

Stage II

About a year later, the painters with the highest cumulative exposure to solvents, as judged by preliminary estimates, and a group of carpenters with the same age distribution were called to the second stage of the examination. This stage included neurophysiological examinations and interviews for psychiatric diagnosis and personality assessment. These examinations took approximately 4 h. Of the 58 painters and 53 carpenters called, 52 painters and 45 carpenters participated. The reason generally given for not participating was lack of interest in being tested further. The painters and carpenters who did not participate in stage II did not differ from those who did with regard to frequency of neuropsychiatric symptoms, but among those who did not participate (both painters and carpenters) there was a slight tendency to have had poorer results on the psychometric tests. The neurophysiological examinations were made without the examiner being aware of the subject's profession. In the interviews that formed the basis for the psychiatric diagnoses, however, the examiner knew the subject's profession.

Stage III

Of those who had participated in stage II, 15 painters and 15 carpenters individually matched for age (with no more than two years' difference) were examined with magnetic resonance tomography (MRT) of the brain. The painters chosen were those from stage II who had the highest cumulative exposures. All those chosen participated in the examination. The results were assessed without knowledge of the subjects' professions.

Exposure

Each subject was interviewed by an experienced occupational hygienist (GN) about work conditions during his career, with particular emphasis on exposure to solvents. Contact with solvents during free time was also covered. Prior to the interview, each subject was sent a brief questionnaire on education, time spent in previous jobs, and present employment. The questionnaire was filled out and brought to the interview. The primary purpose of the questionnaire was to prepare the subject for the interview with the occupational hygienist.

Interview

Procedure

The interview questions were formulated after a review of the exposure assessments previously published in the literature (29, 30, 10) and on the basis of prior experience in estimating past solvent exposures (31) and familiarity with painters' work conditions. The interviews were not highly structured; the questions were answered in any order the subject chose. Although the interviews with the painters emphasized jobs that involved contact with solvents, there were also questions on other work conditions, such as dust, noise, and awkward work positions. The problems the painters had when using water-based lacquers were also discussed.

Variables relevant to exposure

The painters' contact with solvents has changed over the years. Until the mid-1950s, they used mostly paints containing linseed oil and turpentine, as well as varnish and cellulose lacquers. In the latter part of the 1950s and in the 1960s they used mostly alkyd-based paints with white spirit as solvent. Water-based paints were becoming increasingly common, especially in new buildings. By the mid-1970s, water-based paints were used in most new construction, and about 10 years later they were also common in renovation and maintenance. White spirit was the solvent most widely used in house painting. A few painters had sometimes used paints containing toluene or xylene, however. Longer periods of such exposure were noted.

Paints based on linseed oil, which were widely used up until the 1950s, contain solvents that are less volatile than those used in white spirit-based paints. A paint-type factor of 0.5 is therefore used for this kind of painting. The paint-type factor used for painting with paints based on toluene or xylene is the ratio between the exposure limit for white spirit and that for toluene or xylene during the period in question (table 2).

At the interview, a list was made of the jobs the subject had held, and their duration and worktime per day were estimated. For each job, the proportion of worktime involving contact with solvents was estimated. Overtime and extra jobs were noted. The average distribution (as the percentage) of worktime spent indoors and outdoors was estimated. The proportions of worktime spent painting with a roller or brush, or spray painting, were estimated (as the percentage); solvent exposure while spray painting was assumed to be twice as high as while painting with a roller or brush. Proper use of a respirator was assumed to halve the exposure. These assumptions were based on earlier estimates (29, 30) and on the interviewer's own judgment. The time spent painting outdoors with solvent-based paints was extremely limited, and was therefore not noted. For each painter the time actually spent painting was finally summarized in painting months. One painting month was equal to painting with a roller or brush for 176 h (22 workdays of 8 h).

We have been able to compare the interview information on time spent in different tasks in different jobs for 10 painters during a period from the late 1970s until the late 1980s with information collected to calculate wages when the jobs were performed. There was good agreement between the two sources of information.

As a measure of brief, intense exposure, any feelings of lightheadedness connected with painting were also discussed.

A painter's exposure to solvents is determined partly by ventilation conditions while the paint is being applied and while it is drying. The interview contained questions on whether work was usually done with the windows open, and whether it was possible to establish a draft. These conditions were about the same for all the painters, however, and did not seem to have had much effect on the actual exposures; they were therefore omitted from the final exposure index.

The interview also contained questions on the amount of paint used in different painting techniques and on whether the subject worked alone or was exposed to the solvents of other painters (secondary exposure). The size of the surfaces painted was also mentioned. This information was not used, however, in the construction of the exposure index, since the painters often did not remember these circumstances very well.

About the only time the carpenters were directly exposed to solvents was when they were using glue, and

Table 2. Occupational exposure limits (OEL) for white spirit in force during different periods and the corresponding OEL factor for white spirit and paint-type factors for toluene and xylene.

Time period	White spirit (OEL, mg · m ⁻³)	White spirit (OEL factor)	Paint-type factor	
			Toluene	Xylene
—1973	1200	2.4	1.6	2.7
1974—1978	600	1.2	1.7	1.4
1979—	500	1.0	1.7	1.4

their exposure was therefore estimated in gluing months. Exposure during ordinary gluing was assumed to be equal to exposure while painting with a roller or brush. Spraying glue was regarded as equivalent to spraying paint.

Exposure estimates

White spirit was by far the dominant solvent in the exposed group. Review of old monitoring records, most of them from the 1970s, showed that exposure levels during actual painting time were usually near the exposure limit for white spirit that was then in force. In measurements that reflected the painters' exposure during the entire workday, exposure averaged about half the exposure limit. The few monitoring reports we obtained that were made prior to 1970 all showed exposures exceeding the exposure limit, some of them markedly (Nise et al, to be published).

On the average, the subjects in our study painted for somewhat less than half their worktime. Their exposure during actual painting time was assumed to reflect the changes in the exposure limit over the years. For each period, therefore, the number of painting months was multiplied by an "exposure-limit factor" equal to the ratio between the exposure limit for white spirit that was in force at that time and the exposure limit in force at the time of the study (table 2). The exposure measure thus obtained was called the "exposure-limit month." Relevant exposure to other solvents was weighted by the ratio between the exposure limits (in milligrams per cubic meter) for white spirit and the solvent in question.

Cumulative solvent exposure

For each subject, the total cumulative solvent exposure in a lifetime was calculated as the total number of estimated exposure-limit months. The exposure-limit months (ELM) were accumulated over each job according to the following formulas:

$$ELM_i = t_i \times (j \times k \times l \times m)$$

$$CSE_n = \sum_i ELM_i$$

i = exposure-specific job period, t_i = number of painting months during the i :th job period, j = application method (1 = roller or brush; 2 = spray), k = respirator (proper use

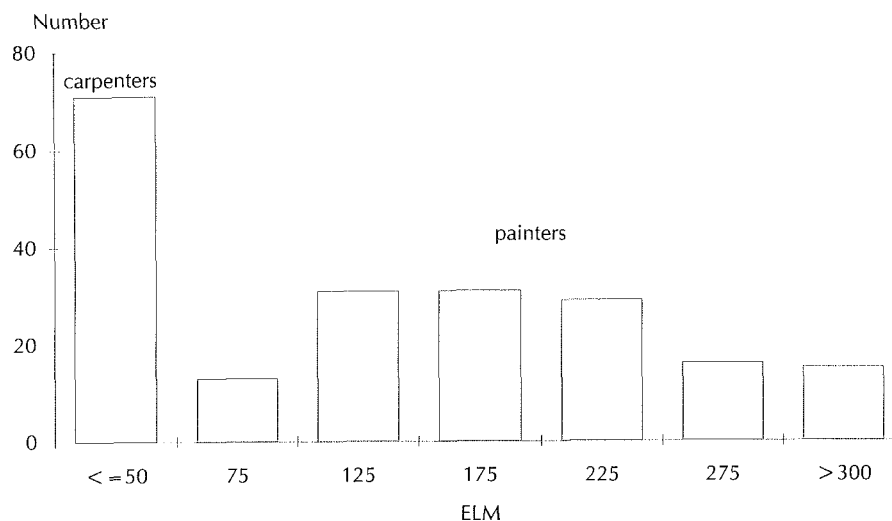


Figure 2. Distribution of the subjects according to their cumulative solvent exposure, as measured in exposure-limit months (ELM).

= 0.5) l = factor for paint type (linseed oil = 0.5; white spirit = 1, toluene and xylene, see table 2), m = occupational exposure limit factor for white spirit (see table 2), and n = n :th subject.

Among the painters, the cumulative solvent exposure ranged from 55 to 438 exposure-limit months (figure 2). For the statistical analyses, the painters were divided into three exposure categories. The upper limit for "low" exposure was set at the 25th percentile. Painters with exposures between the 25th and 75th percentiles were put in the "intermediate" exposure group, and those with exposures above the 75th percentile were placed in the "high" exposure group.

The median exposure for the carpenters was 0 exposure-limit months, with a range from 0 to 46; 38 of the carpenters, whose contact with solvents had been non-existent or very sporadic, were regarded as unexposed.

Solvent exposure during the most-exposed year

Solvent exposure during the most-exposed year was the total of exposure-limit months for the year with the most intense exposure to solvents. If exposure was the same for several years in a row, the middle year was chosen. If equal numbers of exposure-limit months occurred in non-consecutive years, the earliest was chosen.

Solvent exposure during the last year

The last year of exposure refers to the number of exposure-limit months in the year prior to our examination. In the interview 66 of the painters reported that they were no longer exposed to solvents. They worked exclusively with water-based paints or had changed to an unexposed job or were unexposed for some other reason. Of the 66 painters 19 had been unexposed during 1 year, 14 for 2–4 years, 13 for 5–9 years, and 20 for ≥ 10 years.

Exposure with lightheadedness

Exposures leading to lightheadedness were reported by 85% of the painters. Most of these cases had occurred during the 1960s, although they had also occurred both earlier and later. Frequent lightheadedness ($N = 65$) refers to ≥ 30 occasions of definitely unpleasant feelings, and loss of consciousness, memory blackout, or near-accident on at least one occasion. Painters who had had no such experiences, painters who had experienced < 30 incidents of lightheadedness with only slight problems, and painters who had felt marked symptoms on only a few occasions were placed in a group with slight effects ($N = 70$). Although one carpenter reported having had feelings of lightheadedness, all of the carpenters were placed in the reference group.

The variation in the different exposure estimates is shown in table 3. For all the exposure estimates, the carpenters were placed in their own exposure group, which constituted a reference category. Most of the painters had been exposed the most heavily during the 1960s since the use of solvent-based paints dropped considerably thereafter. Only 0–14% (median 2%) of the total number of exposure-limit months were accumulated during the five years immediately prior to the study (figure 3). The current jobs of the painters and carpenters who participated in the study, and the current jobs of the painters distributed by exposure group as determined by cumulative solvent exposure, are shown in table 4.

Potential confounding factors

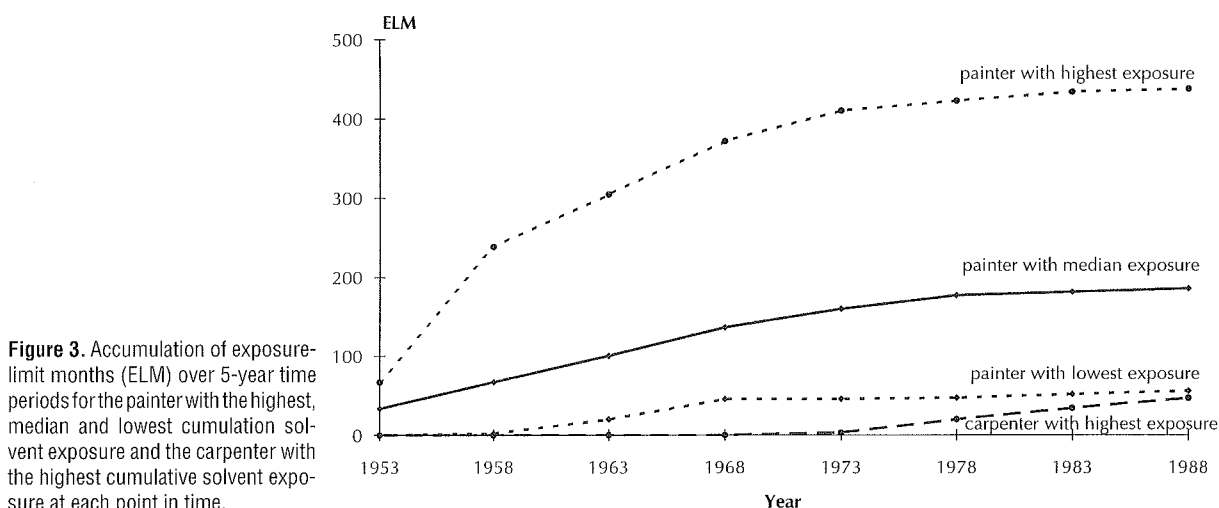
Information was obtained on the potential confounding factors of age, alcohol consumption, primary intellectual capacity, previous neurological illnesses, other diseases with possible effects on the CNS, previous concussions,

Table 3. Exposure levels in the low-, intermediate- and high-exposure categories for cumulative exposure, the most exposed year, and the year prior to the examination. (ELM = exposure-limit month)

Exposure estimate	Exposure category					
	Low		Intermediate		High	
	Number of subjects	ELM range	Number of subjects	ELM range	Number of subjects	ELM range
Cumulative solvent exposure	34	55—131	67	135—245	34	246—438
Most exposed year	35	6.9—9.8	70	10.2—17.8	30	18.6—40
Year prior to examination	66	< 0.1	—	—	69	0.1—4.5

Table 4. Current occupation of study participants, all of whom were either painters or carpenters in 1965. The exposure categories for the painters are calculated as cumulative solvent exposure.

Current occupation	Occupation 1965								Painters' exposure category							
	Carpenter (N ₁₉₆₅ = 71)				Painter (N ₁₉₆₅ = 135)				Low (N ₁₉₆₅ = 34)		Intermediate (N ₁₉₆₅ = 67)		High (N ₁₉₆₅ = 34)			
	Employed		Self-employed		Employed		Self-employed		Employed		Self-employed		Employed		Self-employed	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Same occupation	35	49	13	18	67	50	22	16	16	47	2	6	33	49	15	22
Other occupation	18	25	4	6	30	22	5	4	12	35	4	12	13	19	1	1
Long-term sick leave or early retirement	1	1	—	0	11	8	—	0	—	0	—	0	5	7	—	0

**Figure 3.** Accumulation of exposure-limit months (ELM) over 5-year time periods for the painter with the highest, median and lowest cumulative solvent exposure and the carpenter with the highest cumulative solvent exposure at each point in time.

medicines with effects on the CNS, diseases with possible effects on the peripheral nervous system, handedness, reading or writing difficulties, schooling, vocational training, smoking, diseases of the heart and circulatory system, and exposure to other neurotoxic substances.

Age

For all the analyses, age was dichotomized at 50 years, the median for the entire group. This procedure provided a satisfactory control; average ages in the two age cate-

gories were about the same for the painters and carpenters and for the three exposure groups of painters.

Alcohol consumption

Information on alcohol consumption was obtained as answers to questions in the medical interview on average weekly consumption during the previous year, consumption during the previous week, and consumption on the day before the examination. This information on consumed amounts of beer, wine, and distilled spirits was

converted to grams of alcohol, calculated from the average alcohol content of the beverages in question.

Information on alcohol dependence was obtained via the Malmö-Lund version of the Michigan Alcoholism Screening Test (MAST), which consists of eight yes-no questions on symptoms of alcohol dependence. This test is an effective screening instrument for identifying persons with alcohol dependence (32). The MAST questions were included in the questionnaire sent home to the subjects.

Information on liver effects due to alcohol was obtained by serum analysis for the enzyme gamma glutamyl transferase. Gamma glutamyl transferase is an established indicator of high alcohol consumption (33). Details on our measurements of gamma glutamyl transferase can be found in a separate publication (34). The subjects were also followed in the aforementioned registers for alcohol-related crimes and diagnosed alcoholism [code 291 or 303 of the eighth revision of the International Classification of Diseases (ICD 8)]. These data were used to create measures of both long-term and current alcohol consumption.

Long-term alcohol consumption

The measure for long-term alcohol consumption was constructed by dividing the distributions for average weekly alcohol consumption, the number of "yes" answers on the MAST questionnaire, and the gamma glutamyl transferase values into thirds. The limits for the divisions are shown in table 5. A subject was given 0 points if he was in the lowest third, 1 point if he was in the middle third, and 2 points if he was in the upper third. The three scores were then added together. Individuals who were registered due to an alcohol diagnosis or an alcohol-related crime and who were in the upper third for at least one of the other measures of alcohol dependence, as well as individuals who were not in the registers but were in the upper third for at least two of the other measures, were placed in the high-risk category for alcohol-related CNS effects. Individuals who were in the registers and who were in the middle third for at least one of the other measures, but not in the top third for any of them, as well as individuals who were not in the registers but had a total of 3 or 4 points for the other

measures, without being in the lowest third for any of them, were placed in the category of presumed intermediate risk of alcohol-related CNS effects. The remaining subjects were placed in the low-risk category.

Current alcohol consumption

The measure of current alcohol consumption was based on information about consumption during the previous week, calculated in grams of alcohol, and information on whether the individual had drunk alcohol on the day before the examination. Persons who had consumed alcohol on the day before the examination and persons who had consumed at least 150 g of alcohol during the previous week were placed in a category with presumed high risk of CNS effects due to current alcohol consumption. Persons who had consumed 50 to 149 g of alcohol during the previous week, but had not consumed alcohol on the day before the examination, were placed in a category of presumed intermediate risk of CNS effects due to current alcohol consumption. The remaining subjects were placed in the low-risk category.

Primary intellectual capacity

The primary intellectual capacity was obtained from the results of the two general intelligence tests that all of the subjects had taken at the time of their conscription into military service. The two tests were an instruction test (conscription test A) and a vocabulary test (conscription test C), 40 questions each, multiple-choice, with maximum allotted times of 12 and 7 min, respectively. In the first test, the subject must follow instructions: place an x in the fourth circle in a figure, for example. The vocabulary test consisted of groups of five words each. Four belonged to the same category, such as colors or foods, and the subject had to identify the one word of five that did not belong to that category.

The results of these primary intellectual capacity tests have been presented elsewhere (Michélsen & Lundberg, unpublished manuscript). In summary, they show that performance on both the conscription tests and very probably on the synonyms test (a vocabulary test), evolved differently over time in the different exposure groups, probably because of solvent exposure or some other factors. It thus seems inappropriate to use today's results on these tests as a measure of primary intellectual capacity.

In the present study, the test results from the two tests given at the time of conscription were used as potential confounding factors. The average scores on both tests were very similar among the painters and carpenters in the study group, as well as among all draftees from which our study group was selected. For our analyses, the test results were divided at the median for the entire study group.

Table 5. Measure of long-term alcohol consumption — boundaries of thirds concerning gamma glutamyl transferase serum activity, stated average alcohol consumption per week during the last year, and number of positive responses on the questionnaire of the Michigan Alcoholism Screening Test (MAST).

Boundaries	gamma Glutamyl transferase ($\mu\text{kat} \cdot \text{L}^{-1}$)	Weekly alcohol consumption (g)	Positive responses on MAST
Lower third	0.6	34	2
Upper third	0.8	98	3

Previous neurological illnesses

In the medical interview, the subjects were asked whether they had ever been hospitalized for a CNS disease with conceivable effects on symptoms or on performance on psychometric tests. The subjects were grouped into those who reported such a disease and those who did not. The reported diseases were meningitis, encephalitis, cerebral hemorrhage, and cerebral infarction. For example, epilepsy and polyneuritis were specifically asked about, but these diseases were not reported by any subject.

Other diseases with possible effects on the central nervous system

The subjects were asked about other diseases with conceivable effects on symptoms or on performance in psychometric tests. Seven cases of diabetes were reported, five among the painters and two among the carpenters. One carpenter had insulin treatment, while the others were on antidiabetic medicines or only advised to follow a proper diet. One carpenter reported depressed thyroid function and was being treated with thyroid hormones.

Most of the statistical analyses were performed also with the subjects reporting these diseases excluded, but the results did not change. Thus they were included in all the analyses.

Previous concussions

The subjects were divided into those who reported that they had had a concussion, regardless of how long they were unconscious, and those who had not.

Medicines with effects on the central nervous system

In the medical interview each subject was asked about current and previous consumption of neuroleptics, antidepressants, tranquilizers or sleeping pills for a prolonged period, and the subjects were divided into those who reported such consumption and those who did not.

Diseases with possible effects on the peripheral nervous system

Diseases with conceivable effects on the peripheral nervous system were used as a potential confounding factor in the analyses of vibration thresholds. These diagnoses included diabetes, alcoholism, and vibration injury to the hands (white fingers).

Handedness

Handedness is an expression of some aspects of brain organization. Left-handedness may be a possible risk

factor for disturbances of an individual's cognitive and emotional function (34). The Edinburgh Handedness Inventory (35) was used to determine handedness. The group was divided into those who were definitely right-handed (93 painters and 57 carpenters) and others (42 painters and 14 carpenters).

Reading and writing difficulties

Reading and writing difficulties are relevant to cognitive function, and also indirectly to the psychological health of the individual (36). The occurrence of reading or writing problems was judged from the interview with the psychologist. Reading and writing problems were considered to exist if, during the interview, the subject stated that he had reading or writing problems or had had such problems in school. The other subjects were assumed to have no reading or writing problems.

Schooling

The subjects were divided into those who had had eight years of schooling or less and those who had attended school for nine years or more.

Vocational training

The subjects were divided into those who received vocational training at a school and those who learned their jobs as apprentices.

Smoking

Smoking has been treated as a potential confounding factor in studies of some outcomes, such as the results of the Profile of Mood States (POMS). For the analyses, the subjects were divided into the following three groups: those who currently smoked every day or occasionally, those who did not currently smoke but who had previously smoked regularly, and those who had never smoked or had previously smoked only occasionally.

Diseases of the heart and circulatory system

Previous or current heart or circulatory diseases were asked about in the medical interview. The heart and the carotid artery were auscultated and any murmur or arrhythmia was noted.

The carotid, radial, and femoral arteries, as well as the dorsal artery of the foot and the tibial posterior artery, were palpated, and a note was made if the pulse was weak or impalpable. Blood pressure was measured by a cuff around the left arm after the subject had been lying down for about 5 min.

From this information, numerous variables were constructed as a measure of possible arteriosclerosis. In a

preliminary analysis, none of these variables was found to be noticeably correlated to any of the results of the study. Only a few individuals had serious illness, and they were distributed fairly evenly among the exposure groups. Measures of heart and circulatory diseases were therefore not used as potential confounding factors in the data analyses.

Exposure to other neurotoxic substances

Fourteen of the painters had used paints containing lead pigments during the 1950s and 1960s for particular, usually seasonal, jobs. The painter who had used the most lead paint had used it for about two years. No painter had used lead paint during the 20 years prior to the examination. No other neurotoxic exposures had occurred among either the painters or the carpenters. Exposure to neurotoxic substances other than solvents was therefore not accounted for in the analyses.

Medicines with effects on the peripheral nervous system

None of the subjects used a medicine suspected of having specific effect on the peripheral nervous system.

Outcomes

Information on symptoms and the results of the psychometric tests were obtained for the entire study group. Parts of the group also received neurophysiological examinations, psychiatric diagnoses, and a brain examination by MRT.

Current and previous symptoms

Information on neuropsychiatric symptoms was obtained from the medical interview and self-assessment questionnaires.

Medical interview

All the subjects were interviewed by the same physician, who used a structured form similar to the one used by Mikkelsen et al (10).

Neuropsychiatric symptoms. During the interview the subject was asked whether he had noticed changes regarding the 14 neuropsychiatric symptoms that have been described in connection with solvent exposure. A change was classified as slight if it had no social consequences or as severe if it had social consequences. All the subjects were asked the following questions describing each symptom: the time it was first noticed, if it appeared

gradually or suddenly, and if it appeared in connection with some memorable event. In the analyses of the individual symptoms, the material was dichotomized into those who had the symptom(s), whether slight or severe, and those who did not.

In a summary index the subject could be classed as lacking symptoms associated with solvent exposure, as having slight symptoms of organically based functional decline of the CNS, as having clear symptoms of organically based functional decline of the CNS, or as having CNS symptoms due to something else. The subjects in the last group were distinguished from those with a suspected organic basis by their sudden appearance, usually in conjunction with a life crisis such as a divorce or the death of a close relative.

After initial analyses of the relation between exposure and the individual categories in the summary index, the index was dichotomized: those who had no symptoms and those who were considered to have CNS symptoms with a nonorganic basis were classed as lacking signs of organically based CNS damage, while the others were considered to have such signs.

Symptoms not included in the summary index or neuropsychiatric symptoms. During the medical interview, the subjects were also questioned about headaches and balance problems. Any reported symptoms were noted.

Earlier neuropsychiatric symptoms. To obtain information on whether previous psychiatric problems had been reversible, the examining physician asked the subject whether he had previously had any psychiatric disease and, if so, whether he was hospitalized for it and if he had previously taken psychoactive drugs for any longer period. In the questionnaire sent to the subjects, they were also asked whether they had ever been examined for suspected damage to the brain due to chemical exposure.

Self-assessment questionnaires

Mood. POMS (37) has been recommended by the World Health Organization (WHO) (38) for epidemiologic studies of mood changes resulting from exposure to organic solvents. The questionnaire consists of 65 words describing feelings and moods, which are summarized in six factors. For all the questions, the subject reports his mood during the previous week on a scale of 1 to 5.

POMS was translated into Swedish by Swedish college teachers of English, and then back into English by persons with American English as their native language and Swedish as their second language, and then back again to Swedish, in several rounds, in order to achieve the best possible agreement with the original.

The questionnaire was given to each subject in the first half-hour of the day he was examined. The result for

each factor on the form was the total point sum for the words in that factor. For the computer analysis, the material was divided at the 75th percentile of the point sum for each factor among the carpenters.

Insomnia. A Swedish self-assessment form was used for insomnia. The form has been used in studies of the effects of shift work in various types of jobs (39). The form includes 17 questions on sleep and wakefulness. The questions are answered on a five-point scale or with information on sleeping times. The questions on the form are grouped into indices of sleep quality, recovery, and sleep apnea.

This form was included in the questionnaire that was sent to the subjects. They filled it out and brought it to the initial medical examination, where it was checked and completed if necessary. For the analyses, the results were divided, within each factor as well as for each question, at the 75th percentile of the results of the carpenters, so that those with more sleeping problems were put into a problem group.

Other symptoms. The questionnaire that was sent to the subjects also included questions on other symptoms that have been associated with solvent exposure: deterioration of the sense of hearing, taste or smell, lower alcohol tolerance, balance problems and dizziness, and gastrointestinal symptoms. These questions were answered by yes or no.

Coordination and clinical status

The physician also made a clinical examination of neurological status and a detailed examination of each subject's coordination capacity.

Physical coordination was tested by ordinary qualitative methods and also by a computer-based test system (CATSYS), with which ordinary clinical examination methods yield quantified results.

Clinical status

For each subsection of the clinical examination, the results were divided into a group with normal results and one with results with some form of deviation. The examinations and the assessments followed the procedures described by Mikkelsen et al (10).

Knee-heel test. The subject lay on an examination table and was asked to lift one leg and place his heel on his other knee. He was then asked to move the heel downward, keeping it pressed to the skin, and then to move it back up to the kneecap again. Coordination of movements, whether the heel touched the patella, and any instability in holding the heel against the patella or in moving it along the skin were noted.

Finger-nose test. The subject lay with his arms at his sides. He closed his eyes, and then touched his nose with his left and right index finger alternately, about five times. The coordination of the movements and the accuracy in touching the tip of the nose were noted.

Romberg's test. The subject stood with his feet together and his eyes closed. It was observed whether he stood still, swayed, or had any difficulty maintaining his balance.

Walking forward and backward. With his eyes open the subject walked forward and backward along a line taped on the floor for 3 m. It was noted whether the forward motion was natural, hesitant, atactic, or in some other way deviant. The number of missteps was also noted; two or more forward and three or more backward were regarded as abnormal.

Tremor. It was noted whether the person showed a tremor when his hands were resting on a support or when his fingers were stretched. Any occurrence of intention tremor was also noted.

Tuning-fork test for vibration sensitivity. The subject closed his eyes. A vibrating tuning fork was held against the dorsal side of the distal interphalangeal joint of the index finger and the big toe and against the outer ankle, on both the right and left sides. The vibrations of the tuning fork were stopped by the examiner. The result was registered as normal if the subject could correctly tell when the vibrations stopped.

Computerized coordination tests

The CATSYS (computerized coordination ability test system) was also used (40) for measuring coordination. CATSYS consists of a touch-sensitive screen and a broad response key attached to a personal computer. The system was set up on a table in front of the subject. All the tests were done with the dominant hand. Three tests were administered with CATSYS.

Screen-nose point test. With his eyes open the subject placed his finger on a black dot in the middle of the display screen. He was then asked to close his eyes and move the fingertip to the end of his nose and then back to the black dot on the screen. He did this 10 times. The average value and the standard deviation were registered for the distance between the black dot and the fingertip contact.

Hand supination-pronation test. The subject was asked to follow a rhythmic sound from a loudspeaker by lightly beating time on the broad response key, rotating his forearm to use alternately the backs and fronts of the four

fingers. This test was made with both slow (1 Hz) and rapid (3 Hz) rhythms. The slow test lasted 20 s and the fast one was 10 s long. The average value and standard deviation for the times between the stimulus and the response were calculated for each subtest. In a third subtest, the subject followed a rhythm that started at 2 Hz and increased linearly to 7 Hz. This test lasted 10 s. The highest frequency the person could follow was registered.

Finger tapping. The subject held his index finger directly above the response key. He was asked to follow a sound with a slow rhythm (1 Hz) and a sound with a rapid rhythm (4 Hz) by beating time on the key with his finger. The slow rhythm lasted 20 s and the fast one 8 s. The average value and the standard deviation for the time between each stimulus and the response were registered. The test for maximum finger-tapping speed followed the same procedure as the third part of the hand supination-pronation test, except that the maximum stimulus frequency was 8 Hz.

Psychometric tests

Choice of tests

The choice of psychometric tests for the present study was governed by three considerations. The tests had to

reflect the five areas of psychological function usually represented in studies of neurotoxic effects from organic solvents: verbal ability, visuospatial ability and concept formation, memory, perceptual ability, and psychomotor capacity. The tests also had to be well-known nationally and internationally.

In the choice of tests, consideration was therefore given to the TUFF battery, which has been standard at Swedish occupational medicine clinics for a long time (41, 42). Consideration was also given to the WHO recommendations for an international standard for the study of neurotoxic effects (38). Finally, the choice of tests was governed by the limited time available for the examination. Each test was chosen to fall into one of the five functional areas chosen for study (table 6).

Synonyms. Synonyms, a vocabulary test, was the test used for verbal ability (43). The test consists of 30 items and takes 7 min. The measure of performance was the number of correct answers.

Block design. A subtest of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R), block design, was used to test visuospatial abilities (44). The test consists of nine tasks in which the subject had to use colored blocks to construct a pattern shown on a printed card. The measure of performance was a point total which reflected both speed and aptitude.

Table 6. The psychometric test battery.

Function	Test	Outcomes variables
Verbal ability	Synonyms	Number of correct answers
Visuospatial ability and concept formation	Block design	Sum of tasks solved and time used
	Wisconsin card sorting test	Number of mismatches Number of perseverative errors Number of categories
Memory	Benton	Number of mistakes
	Claeson-Dahl	Weighted score Number of words recognized Number of words memorized
	Corsi block	Number of correctly repeated series (forward) Number of correctly repeated series (backward) Sum for repetition forward and backward
	Digit span	Number of correctly repeated series (forward) Number of correctly repeated series (backward) Sum for repetition forward and backward
	Complex figure	Ability to copy Ability to reproduce from memory
	Digit symbol, memory	Number of digit-symbol combinations correctly reproduced
Perceptual ability	Digit symbol	Number of tasks completed in 90 s
	Trail making A	Time for completion
	Trail making B	Time for completion
	Simple reaction time	Mean of reaction times Mean of standard deviations for reaction times Longest reaction time Shortest reaction time
Psychomotor capacity	Purdue pegboard	Number of movements, dominant hand Number of movements nondominant hand Number of movements, both hands Combination

Wisconsin card sorting test. The Wisconsin card sorting test (WCST) was designed to measure concept formation and the ability to learn and change abstract principles (45). It uses instruction and response cards that show various figures (circles, crosses, squares, triangles) in various numbers and colors. The subject is instructed to sort his response cards (2×64) by color, shape and number, according to different principles laid down by the examiner through instruction cards. The responses can be summarized in several measures. We used the number of mismatches, the number of preservative errors, and the number of categories (learned and followed principles for sorting the cards).

Benton. The Benton test (46) is a memory test using visually presented geometric forms. It consists of 10 tasks, and the measure of performance is the total number of mistakes made in the redrawing of the geometric forms.

Claeson-Dahl. The Claeson-Dahl test (47) is a test of verbal learning ability. A list of 10 two-syllable words is presented orally several times. Each presentation is followed by a brief pause, after which the subjects repeat as many of the words as they can remember. The procedure is repeated at most 10 times, or until the subjects can correctly repeat the 10 words on the list twice. The number of words missed per repetition is multiplied by the ordinal number of the presentation (to a maximum of 10). These products (weighted scores) are added together to yield the performance measure.

A measure of recognition was also obtained. Subjects heard another list of 10 words and then a text in which the words on both lists occurred in random order. They were asked to identify the words in the text that occurred on the original list. The number of correctly identified words was the measure of performance.

Retention was measured by asking the subject to repeat as many of the 10 words as he remembered about 1 h after the first presentation. The number of correctly repeated words was used as the result variable.

Corsi block. A short-term memory test, the Corsi block test, consists of nine blocks glued in random positions on a board (48). The examiner points at several blocks one at a time, and the subject is instructed to point at the blocks in the same order. Series of three to nine blocks are presented, two series per degree of difficulty. The measure of performance is the number of correctly repeated series. The same procedure is then repeated, but this time the subject is asked to point out the blocks in reverse order; these series contain two to eight blocks. The number of correctly reversed series is the second result variable. The third measure of performance consists of the sum of the first two.

Digit span. A test of short-term memory, digit span from WAIS-R (44), was included. Series of three to nine numbers were presented orally, and the subject was asked to repeat them immediately after each presentation. There were two series per degree of difficulty. The test score was the number of correctly repeated series. The procedure was then repeated with series of two to eight numbers, and the subject was asked to repeat them in reverse order. The number of correctly reversed series yields the second test score. The third test score was obtained by adding together the first two.

Complex figures. The complex figures test was used to obtain information about visual memory (49). A complex geometric figure was presented, and the subject was instructed to copy it. He was then asked to draw it from memory. The measure of performance consisted of points (a maximum of 36 points per picture) for how well the subject reproduced the complex figure.

Digit symbol. The part of WAIS-R (44) which tests perceptual ability, the digit symbol test, was also included in the study. The subjects had to join numbers with symbols according to a given key. The test primarily demands speed, but also concentration, alertness, and some manual dexterity are needed. The performance measure was the number of tasks correctly completed within 90 s.

Digit symbol memory. Digit symbol was also used as a simple test of short-term memory. After the subjects had taken the digit symbol test, they were asked to draw the symbols from memory and combine them with the appropriate numbers. The number of correctly drawn and numbered symbols was used as the outcome variable.

Trail making. A component of the Halstead-Reitan test battery (48), trail making, was also used. The test, which has two parts, is primarily a test of perceptual ability and speed. Part A is mostly visual searching and motor speed, and part B requires mental coordination as well. For both parts, the measure of performance is the time taken for completion.

Simple reaction time. Simple reaction time was tested by the method included in CATSYS. The subject held a button in his dominant hand and was told to push the button as quickly as possible whenever a light flashed from the light diodes. There were 64 light signals at random intervals over a 6-min period, in accordance with WHO recommendations (50). The average value and the standard deviation for the reaction time, as well as the longest and shortest reaction time, were noted.

Purdue pegboard. The Purdue pegboard test (51) measures psychomotor capacity and manual dexterity for the

right and left hands and for both hands together. The three outcome variables are the number of pins placed in the board during half a minute. A fourth performance measure is the number of pins, washers, and collars that the subject moves alternately with the right and the left hand during a brief period of time.

Test procedure

The data were collected by two psychologists who had been specially trained for the task. The subjects were divided between them at random on the day of the examination and were tested individually. The procedure took about 3.5 h. It began with a brief interview about some potential confounding factors for the relationship between solvent exposure and the test results. (See the section on potential confounding factors.) The tests were given to all the subjects in the same order, with a scheduled break each hour. The tests were scheduled so that those in the same functional area were spread throughout the test period, in order to minimize the undesirable effects of fatigue.

Analysis

The results of each test were analyzed and reported separately, and the test variables were treated as continuous variables. Indices were also constructed by combining several test scores. Since each test was graded on a different scale, such as according to the number of mistakes or number of seconds elapsed, and these were not comparable, scale transformations to Z points were performed before the results were combined for the index. For each test, the results for the group of carpenters were given an average value of 0 and a standard deviation of 1. After the scale transformations, an index was created by summations of the Z points on each test. Indices were made for each functional area, and a total measure was made for all the tests.

Initial analyses were made which showed that there was no systematic difference in the test results obtained by the two examining psychologists. Therefore we did not account for the examining psychologist in the further analyses.

Psychiatric diagnoses

All the subjects who participated in stage II of the examination were interviewed for about 2 h by a trained psychologist, who made a personality assessment as described by Bellak et al (52). The results of the personality assessments will be published elsewhere.

The information obtained by the interviewer on the subject's present and previous psychiatric symptomatology was such that, with a few more questions, it was possible to test the criteria for psychiatric diagnoses given

in the Swedish translation of DSM III (Diagnostic and Statistical Manual of Mental Disorders, third edition) (53, 54). Before the examinations the interviewer was given basic training in DSM III diagnosis by an experienced psychiatrist (JH).

Neurophysiological examinations

Neurophysiological examinations were given to all the subjects who participated in stage II of the examination.

Electroencephalography

Electroencephalography (EEG) was performed according to usual practice. The subjects lay or reclined with their eyes closed. The electrodes were placed according to the international 10/20 system. If the EEG showed signs of drowsiness, a wake-up noise was made (knocking on the table). The EEG was recorded on paper for 15 min with a 16-channel EEG machine (Siemens-Elema). The subjects opened their eyes on four occasions.

Auditory cerebral evoked potential and the event-related evoked potential

A test of reaction potential is a test of an entire sensory system, such as hearing or vision. The stimulus can be a noise or a light signal, and the response of the brain to this stimulus is registered. The response is dependent on the functional condition of the sensory organ, the signal transmission from the organ to the brain (nerves and neural pathways in the spinal cord and brain stem), and finally the information processing that occurs in the various areas of the cerebral cortex. The response is thus an extremely complex function, and a disturbance in any one of its subfunctions can affect the registered reaction potential.

The latter portions of the potential are based on the associative processing of the information (the signal) from the sensory organ. It has been found that a particular positive component of auditory cerebral evoked potential (AEP), which appears about 300 ms after the stimulus, is dependent on how important the stimulus is. It is therefore called P-300 or the event-related evoked potential (55—57).

The test was given in a quiet room with the subject reclined in a comfortable examination chair. The stimulus consisted of sound pulses with a duration of 50 ms and a frequency of 1000 Hz (not interesting) or 2000 Hz (interesting). The interval between pulses was 2 s. There were 512 pulses; 25% of them were interesting and occurred at random. The pulses were generated with a Medelec ST 10 Sensor (Surrey, England), and the summations were made with a Medelec MS 92. The subjects were instructed to count the number of interesting pulses and to keep the total in mind during the course of the test.

Vibrometry

Vibrometry, or the determination of vibration thresholds, was performed at three points bilaterally: the back of the hand (metacarpal II), the upper part of the lower leg (ventromedial surface of the tibia), and the top of the foot (metatarsal I) using an electromagnetic biothesiometer (Somedic, Stockholm, Sweden) which produced a sinusoid vibration with a frequency of 100 Hz and an amplitude of 0 to 25 μ , and provided continuous digital amplitude readings. The vibration threshold was measured three times at each test point, with both increasing and decreasing stimulus strength.

Magnetic resonance tomography

MRT was done on a 1.0-tesla system (Siemens Magnetom) with a spin-echo sequence of the standard type, with repetition time of 2.3 s and readings at 25 and 90 ms. The entire brain was scanned in the transverse plane, using a 256×256 matrix (for both data collection and picture display) and taking 5-mm sections separated by 3-mm intervals. This sequence generates two sets of pictures, one of which, with 25-ms readings, provides a good anatomical image of the brain and the other, with 90-ms readings, shows the same section with lower spatial resolution but greater sensitivity for tissue changes.

A further five consecutive scans, with repetition times of 0.125, 0.5, 1.0, 1.5 and 2 s, were made to allow an accurate calculation of relaxation time T1. These scans yielded five sections, of which the central one was placed at the height of the foramen of Monro. This procedure provided material for the T1 calculation of the central nuclei and the central areas of all the lobes of the cerebrum. A special calculation program (58) was used to derive parametric pictures on which the intensity scale is represented by the calculated T1 value in each picture element. Using the region-of-interest program integrated into the magnetic camera system, the average T1 value was then measured in selected areas directly on the T1 maps. The measurements were made bilaterally in representative central areas of the white matter of all lobes and in the central thalamus. Contamination by tissue that was not representative for these structures, such as cerebral cortex, visible and well defined focal changes in white matter, or visible blood vessels, were not included in the measured areas. Since head fixation was not used, checks were made to be sure that the tissue content of the scanned areas did not change between the five scans due to head movements. Because of small movements, the material from most of the subjects did not provide areas within the putamen, the pallidum, the head of the nucleus caudatus, or within the cortex of the various lobes that were sufficiently consistent and uncontaminated by adjoining tissue to be acceptable as comparison parameters.

Expansion spaces filled with cerebrospinal fluid, as a possible sign of atrophy, was estimated on a three-point scale (no signs, probable signs, and definite signs of expansion of filled spaces).

The MRT pictures were further assessed for morphological deviations from normal and for the number of focal signal changes in white matter. Ventricle size was calculated with two simple measures: the maximum transverse diameter of the third ventricle and the anterior horn index, defined as the maximum width of the two anterior horns divided by the maximum inner skull diameter (59).

Statistical methods

In the statistical analyses, the results of the exposed group (painters), as a whole or divided into different subgroups, were compared with the results of the unexposed group (carpenters). The SAS (statistical analysis system) computer package was used for the analyses.

The individual estimates of exposure were obtained as continuous variables and divided into categories for the statistical analyses. (See table 3.) The potential confounding factors were similarly divided into categories (table 7). The categories thus created were then treated as dummy variables in the analyses.

All the estimates of exposure were cross-tabulated with all the potential confounding factors. (Table 7 shows the cross-tabulation between cumulative solvent exposure and the potential confounding factors.) The other measures of exposure were also cross-tabulated with the cumulative solvent exposure (table 8) to exclude collinearity. With one exception, there was an acceptable representation in all the cells of these tables. The exception was the covariation between cumulative solvent exposure and MEY; only one person with a high cumulative solvent exposure had a low MEY and only two persons with a high MEY had a low cumulative solvent exposure.

Age and alcohol consumption were included in all the analyses, using the alcohol measure that showed the strongest association to the outcome under study. The effects of other potential confounding factors were studied separately in relation to every relevant result, and the factors that affected the result were included in the final analyses. The association between exposure and outcome was then adjusted for differences in age, alcohol consumption, and the remaining potential confounding factors.

If the studied outcome was a continuous variable or a discrete variable with many values, the exposure-outcome relationship was analyzed by multiple linear regression accounting for potential confounding factors.

Table 7. Cross-tabulation of the exposure groups (cumulative solvent exposure) and all the potential confounding factors.

Potential confounder	Occupation				Painters' exposure group					
	Carpenters		Painters		Low		Intermediate		High	
	N	%	N	%	N	%	N	%	N	%
Age										
< 50 years	40	56	63	47	27	79	27	40	9	26
≥ 50 years	31	44	72	53	7	21	40	60	25	74
Alcohol (long-term consumption)										
Low	35	49	66	49	15	44	32	48	19	56
Intermediate	19	27	36	27	10	29	17	25	9	26
High	17	24	33	24	9	26	18	27	6	18
Alcohol (recent consumption)										
Low	40	56	72	53	18	53	34	51	20	59
Intermediate	19	27	35	26	8	24	18	27	9	26
High	12	17	28	21	8	24	15	22	5	15
Neurological disorder	3	4	9	7	2	6	5	7	2	6
Concussion	19	27	26	19	5	15	15	22	6	18
Medicines affecting the central nervous system	4	6	9	7	3	9	3	4	3	9
Vocational training										
Vocational school	25	35	62	46	13	38	31	46	18	53
Apprentice	46	65	71	53	20	59	35	52	16	47
Reading and writing difficulties	19	27	28	21	10	29	12	18	6	18
Not exclusively right-handed	14	20	42	31	13	38	23	34	6	18
Schooling ≥ 9 years	10	14	16	12	5	15	7	10	4	12
Primary intellectual capacity										
Result in conscription test A ≥ 25	33	46	77	57	20	59	41	61	16	47
Result in conscription test C ≥ 20	40	56	68	50	22	65	27	40	19	56
Smoking										
Current smoker	22	31	49	36	12	35	25	37	12	35
Previous smoker	22	31	38	28	13	38	16	24	9	26
Never smoker	27	38	48	36	9	26	26	39	13	38

Table 8. Cross-tabulation of the exposure estimate (cumulative solvent exposure) against all the other exposure estimates.

Exposure estimate	Carpenters		Painters		Painters' exposure group					
	N	%	N	%	Low		Intermediate		High	
					N	%	N	%	N	%
Lightheadedness at work										
Never	70	99	21	16	2	6	12	18	7	21
1—30 times	—	0	78	58	23	68	39	58	16	47
≥ 30 times	1	1	36	27	9	26	16	24	11	32
Solvent exposure during the last year	1	1	69	51	11	32	38	57	20	59
Solvent exposure during the most exposed year										
Very low	71	100	—	0	—	0	—	0	—	0
Low	—	0	33	24	18	53	14	21	1	3
Intermediate	—	0	69	51	14	41	39	58	16	47
High	—	0	33	24	2	6	14	21	17	50

On a qualitative level consideration was given to the P-value of the regression coefficient for the exposure under study.

All the continuous outcome variables that were not normally distributed were positively skewed. In these cases the outcome variables were logarithmized before the regression analysis.

Some of the outcomes were originally dichotomized; discrete outcome variables with few possible values were

dichotomized. Multiple logistic regression analysis was initially used to determine which confounding factors should be included in the final stage. The choice of potential confounders was made according to the aforementioned principles. In the final stage, the association between an exposure measure and the outcome measure was analyzed, with relevant confounders included, as described by Mantel and Haentzel. The final result was a prevalence ratio (PR) with a 95% confidence interval.

The 15 most highly exposed painters who participated in stage II were examined with MRT, as were 15 carpenters who were individually age-matched to the painters. The results were analyzed with paired t-tests.

The Mann-Whitney U-test was used to study the difference in organic solvent exposure between the painters with and without psychiatric diagnoses.

All the presented P-values are two-tailed.

Results

Cumulative solvent exposure (CSE) was used as the primary measure of exposure. The results for the other measures of exposure are presented only if they gave indications of exposure-response relationships.

Neuropsychiatric symptoms

Neuropsychiatric symptoms reported in the interview

Increasing cumulative exposure was associated with increasing risk of being assessed by the physician as having symptoms compatible with organic damage to the brain (table 9).

With increasing cumulative exposure, an increasing number of painters also reported individual subjective symptoms such as memory difficulties, increased irritability, depression, abnormal fatigue, anxiety and nervousness, sleeping problems, and vegetative symptoms (table 10). A higher proportion of painters than carpenters reported a decline in initiative and energy, but these symptoms were not related to increasing cumulative exposure. Emotional instability or sexual problems were no more common among the painters than among the carpenters, and there was no clear relationship to exposure.

Previous neuropsychiatric symptoms

There were no clear differences between the painters and the carpenters with regard to reported former psychiatric

illness or reported previous prolonged consumption of psychoactive drugs. Only the painters had previously been examined for suspected chemical damage to the brain (table 11).

Mood

There were no differences between the painters and the carpenters for any factor on the POMS (table 12). Nor were there any differences between the carpenters and any single exposure category of painters, except that the painters with low exposure reported symptoms in the factor "confusion" less frequently than the carpenters. Among the painters, the symptoms in all the factors appeared more frequently with increasing exposure.

Insomnia

The painters clearly suffered more often than the carpenters from feeling tired when they woke up in the morning (table 13). The painters also reported more problems than the carpenters regarding all other factors and individual symptoms described on the questionnaire.

Among the painters, increasing cumulative solvent exposure was associated with lowered sleep quality, as well as more difficulty getting to sleep or getting back to sleep, restless sleep, waking up too early, and feeling tired on waking.

Table 9. Physician's summary index of symptoms compatible with organic brain damage. Prevalence ratios (PR) are given with 95% confidence intervals for the painters and for the three exposure groups of painters as defined by cumulative solvent exposure.

Symptom index ^a	Carpenters (N)	Painters (N)	Painters' exposure group		
			Low (N)	Intermediate (N)	High (N)
0	56	86	30	43	13
1	5	27	2	14	11
2	—	5	—	2	3
3	10	17	2	8	7
PR (1 + 2/0 + 3) ^b	1.0	3.0	1.2	2.5	4.5
95% confidence interval	Reference	1.3–6.7	0.3–5.5	1.0–6.4	1.8–12

^a Index 0 = no symptoms, 1 = slight symptoms of possible organic origin, 2 = marked symptoms of possible organic origin, 3 = symptoms likely to be functional.

^b Adjusted for age, alcohol consumption, results on conscription test A, and neurological disorder.

Table 10. Occurrence and prevalence ratios (PR) for the neuropsychiatric symptoms reported by the subjects during the interview. A symptom was considered to be present if reported regardless of whether it was slight or more pronounced. The exposure groups for the painters are by cumulative solvent exposure. (95% CI = 95% confidence interval)

Symptom	Occupation				Painters' exposure group								
	Carpenters		Painters		Low			Intermediate			High		
	N		N	PR 95% CI	N	PR 95% CI		N	PR 95% CI		N	PR 95% CI	
Impaired memory ^a	22		60	1.5 1.0—2.2	11	1.2 0.6—2.3		29	1.5 1.0—2.4		20	2.1 1.2—3.6	
Impaired concentration	7		25	1.9 0.9—3.9	5	1.4 0.5—4.5		12	1.7 0.7—4.0		8	2.0 0.8—5.2	
Impaired intellect	—		6		—			3			3		
Emotional lability	11		25	1.1 0.6—2.2	4	0.8 0.3—2.2		15	1.4 0.7—2.8		6	1.0 0.4—2.6	
Irritability	11		37	1.9 1.1—3.4	8	1.5 0.7—3.5		18	1.7 0.9—3.5		11	2.2 1.0—4.9	
Mood change	5		17	1.6 0.7—3.9	1	0.4 0.1—4.2		8	1.4 0.5—3.7		8	2.6 1.0—6.7	
Decreased speed ^a	12		44	2.7 1.5—5.1	10	2.9 1.1—8.0		19	2.4 1.1—5.3		15	3.9 1.7—9.2	
Loss of initiative	4		26	3.0 1.2—7.1	6	5.5 1.2—26		10	1.8 0.7—4.9		10	3.0 1.2—7.4	
Easily tired	33		67	1.1 0.8—1.4	12	0.9 0.5—1.6		30	0.9 0.7—1.4		25	1.4 1.0—2.0	
Anxiety, nervousness	10		24	1.2 0.6—2.4	3	0.6 0.2—2.6		11	1.2 0.5—2.8		10	2.0 0.9—4.4	
Sleeping problems ^b	6		23	1.9 0.8—4.4	4	1.1 0.3—3.8		11	1.7 0.6—4.7		8	3.8 1.2—12	
Vegetative symptoms	10		29	1.6 0.8—3.0	3	0.4 0.1—1.3		14	1.7 0.8—3.6		12	3.5 1.6—7.7	
Sexual problems	13		27	1.0 0.6—1.9	6	1.3 0.5—3.1		11	0.8 0.4—1.7		10	1.3 0.6—2.7	
Unsteadiness, vertigo	8		23	1.4 0.7—2.9	3	0.8 0.2—3.0		11	1.4 0.6—3.3		9	1.8 0.7—4.5	
Frequent headache	10		30	1.5 0.8—2.8	3	0.7 0.2—2.3		16	1.6 0.8—3.3		11	2.0 0.9—4.4	

^a Adjusted for age, alcohol consumption, and concussion.^b Adjusted for age, alcohol consumption, and medicines with effects on the central nervous system.**Table 11.** Indications of previous psychiatric problems in the study group.

Indication	Occupation				Painters' exposure group					
	Carpenters		Painters		Low		Intermediate		High	
	N	%	N	%	N	%	N	%	N	%
Previous long-term consumption of psychoactive drugs	3	4	8	6	3	9	3	4	2	6
Previous psychiatric illness	2	3	6	4	1	3	3	4	2	6
With hospitalization	—	0	2	1	1	3	1	1	0	0
Previously examined for suspected brain damage due to chemical exposure	—	0	4	3	—	0	2	3	2	6

Table 12. Occurrence and prevalence ratios (PR) for the factors identified in the questionnaire from the Profile of Mood State (POMS). The exposure groups for the painters are by cumulative solvent exposure. (95% CI = 95% confidence interval)

Factor	Occupation				Painters' exposure group								
	Carpenters		Painters		Low			Intermediate			High		
	N		N	PR 95% CI	N	PR 95% CI		N	PR 95% CI		N	PR 95% CI	
Tension	19		28	0.8 0.5—1.3	4	0.5 0.2—1.2		15	0.8 0.5—1.5		9	0.9 0.5—1.9	
Depression-dejection	17		26	0.8 0.5—1.4	4	0.4 0.2—1.1		12	0.8 0.4—1.5		10	1.3 0.6—2.6	
Anger, hostility	17		18	0.6 0.3—1.0	3	0.4 0.1—1.2		8	0.5 0.2—1.0		7	0.8 0.4—1.8	
Fatigue ^a	17		24	0.7 0.4—1.2	4	0.4 0.1—1.2		11	0.6 0.3—1.3		9	0.8 0.4—1.7	
Confusion ^a	20		31	0.8 0.4—1.3	3	0.2 0.0—0.7		18	1.0 0.5—1.8		10	1.1 0.5—2.2	
Reduced vigor ^b	17		32	1.1 0.6—1.9	7	0.9 0.4—1.9		14	1.1 0.6—2.2		11	1.6 0.7—3.3	

^a Adjusted for age, alcohol consumption, and smoking.^b Adjusted for age, alcohol consumption, and result on conscription test A

The painters reported a longer time in bed during the workweek than the carpenters did, and their time in bed during the workweek increased with increasing cumulative solvent exposure (table 14). Sleeping time on week-ends was the same, however, for both groups.

Difficulty waking up and feeling tired on waking also appeared to increase with the number of reported inci-

dents of intoxication from exposure to solvents at work (table 15).

Other symptoms

Stomach problems and a deterioration in the sense of taste were less common among the carpenters

Table 13. Occurrence and prevalence ratios (PR) for sleeping problems reported on the insomnia questionnaire. The painters are grouped according to cumulative solvent exposure. (95% CI = 95% confidence interval)

Factor or symptom	Occupation				Painters' exposure group								
	Carpenters		Painters		Low			Intermediate			High		
	N		N	PR 95% CI	N	PR	95% CI	N	PR	95% CI	N	PR	95% CI
Sleep quality	16		41	1.4 0.8—3.1	6	0.6	0.3—1.4	19	1.2	0.7—2.2	16	3.0	1.6—5.7
Recovery ^a	19		43	1.2 0.7—2.1	11	0.9	0.4—2.0	22	1.7	0.9—3.3	10	1.0	0.4—2.5
Sleep apnea	19		36	1.1 0.7—1.7	9	1.1	0.6—2.2	17	1.0	0.6—1.8	10	1.1	0.6—2.3
Trouble falling asleep ^b	18		38	1.2 0.7—2.1	7	0.7	0.3—1.8	21	1.7	0.9—3.3	10	1.4	0.6—3.2
Trouble waking up ^c	19		50	1.4 0.9—2.2	17	1.6	0.9—2.9	23	1.3	0.8—2.2	10	1.0	0.5—2.0
Wakes up often, trouble falling asleep again	37		84	1.2 0.9—1.5	16	0.8	0.6—1.3	44	1.3	1.0—1.7	24	1.5	1.1—2.2
Heavy snoring ^c	19		34	1.1 0.6—1.8	6	0.7	0.3—1.6	19	1.3	0.7—2.4	9	1.1	0.5—2.5
Feeling tired when waking up ^c	21		65	1.7 1.1—2.5	15	1.3	0.7—2.3	29	1.4	0.9—2.3	21	2.4	1.5—4.1
Waking up too early ^d	19		42	1.3 0.8—2.0	7	0.6	0.2—1.6	20	1.1	0.6—1.9	15	2.5	1.3—4.9
Disturbed, uneasy sleep	37		82	1.2 0.9—1.5	17	0.9	0.6—1.4	42	1.2	0.9—1.6	23	1.4	1.0—2.1
Tired, sleepy during work or leisure time ^b	25		53	1.3 0.8—1.9	11	0.9	0.5—1.8	27	1.7	0.9—3.2	15	1.2	0.7—2.1
Involuntary dozing during work	13		31	1.2 0.7—2.2	5	0.9	0.3—2.5	15	1.2	0.6—2.2	11	1.6	0.8—3.4
Involuntary dozing during leisure time	16		43	1.3 0.8—2.2	6	0.9	0.4—2.2	22	1.4	0.8—2.4	15	1.6	0.9—2.7
Awake long before falling asleep on weeknights	22		39	1.0 0.7—1.6	11	1.1	0.5—2.2	20	1.0	0.6—1.8	8	0.8	0.4—1.6
Awake long before falling asleep on weekends	20		46	1.3 0.8—1.9	12	1.2	0.6—2.3	24	1.2	0.7—2.0	10	1.3	0.7—2.4

^a Adjusted for age, alcohol consumption, prescription test C, and smoking.^b Adjusted for age, alcohol consumption, prescription test A, and prescription test C.^c Adjusted for age, alcohol consumption, and smoking.^d Adjusted for age, alcohol consumption, and concussion.**Table 14.** Means and standard deviations (SD) for stated times between going to bed and getting up during the week and on weekends. The painters are grouped according to cumulative solvent exposure.

Time in bed (min/night)	Occupation				Painters' exposure group					
	Carpenters		Painters		Low		Intermediate		High	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Week nights ^a	432	43.3	442	41.7	433	32.2	447	42.8	443	47.6
Weekends	506	47.2	518	65.3	519	40.8	521	70.5	509	76.3

^a P-values adjusted for age and alcohol consumption.**Table 15.** Numbers of painters with sleeping problems reported on the insomnia questionnaire, grouped according to the number of occasions of lightheadedness from inhaling solvents during work. Prevalence ratios (PR) are given with 95% confidence intervals (95% CI).

Symptom	No occasions			1—29 occasions			≥ 30 occasions		
	N	PR	95% CI	N	PR	95% CI	N	PR	95% CI
Trouble waking up ^a	4	0.8	0.3—2.1	29	1.2	0.7—1.9	17	2.2	1.2—4.2
Involuntary dozing during leisure time	5	1.3	0.5—3.2	22	1.4	0.7—2.6	16	1.6	1.0—2.7

^a Adjusted for age, alcohol consumption, and smoking.

than among the painters, for whom they appeared to be related to cumulative solvent exposure (table 16). Inability to tolerate the smell of solvents was also common among the painters. Dizziness and unsteadiness

were no more common among the painters than among the carpenters, although among the painters feelings of unsteadiness increased with increasing exposure.

Table 16. Occurrence and prevalence ratios (PR) for certain symptoms involving the nervous system and the gastrointestinal tract. The painters are grouped according to cumulative solvent exposure. (95% CI = 95% confidence interval)

Symptom	Occupation				Painters' exposure group								
	Carpenters		Painters		Low			Intermediate			High		
	N		N	PR 95% CI	N	PR 95% CI		N	PR 95% CI		N	PR 95% CI	
Rotational vertigo	11		16	0.7 0.3—1.4	1	0.2 0.0—1.1		8	0.7 0.3—1.6		7	1.1 0.4—2.8	
Impaired balance in daylight	7		20	1.4 0.6—3.2	2	0.6 0.1—2.7		12	1.7 0.7—4.1		6	1.6 0.5—4.7	
Impaired balance in darkness ^a	4		11	1.0 0.4—3.0	2	2.3 0.2—27		8	1.4 0.5—4.1		1	0	
Lower alcohol tolerance ^b	19		37	1.0 0.8—1.2	7	0.8 0.4—1.8		17	1.0 0.5—1.7		13	1.4 0.8—2.5	
Cat not stand smell of solvents	15		72	2.6 1.7—4.0	18	2.3 1.3—4.0		35	2.6 1.6—4.2		19	2.8 1.5—5.1	
Impaired sense of smell ^c	16		46	1.4 0.9—2.4	10	1.3 0.6—2.7		20	1.3 0.7—2.4		16	1.7 0.9—3.0	
Impaired sense of taste ^c	5		30	2.7 1.2—5.8	4	1.6 0.6—4.8		12	2.2 0.9—5.7		14	3.8 1.6—9.3	
Abdominal pain ^c	5		21	2.0 0.8—5.3	3	1.0 0.2—5.4		9	1.6 0.5—4.8		9	3.6 1.3—10	
Acid eructation	6		31	2.8 1.3—6.0	7	2.6 0.9—7.3		14	2.4 1.0—6.0		10	3.7 1.4—10	

^a Adjusted for age, alcohol consumption, and neurological disorder.^b Not adjusted for alcohol consumption.^c Adjusted for age, alcohol consumption, and smoking.

Coordination and clinical status

Clinical status

There were no clear differences between the painters and the carpenters on any of the clinical tests of coordination, although painters with high exposure had a tendency to do worse on the line-walking test (table 17). For nearly all the tests, however, the painters with low exposure had a tendency towards better results than the carpenters.

None of the other examinations of clinical status showed any differences between the painters and the carpenters or between the carpenters and any exposure group of painters. In comparison with the carpenters, however, painters with intermediate or high exposure tended to have lower vibration sensitivity in their big toes (table 17).

Computerized coordination test

There were no differences between the painters and the carpenters for any variable in the CATSYS (table 18). In the finger-tapping test, however, painters with intermediate or high cumulative solvent exposure had a lower maximum frequency than the carpenters. For several of the subtests, there was a tendency for the painters with low exposure to do better than the carpenters and for the painters with high exposure to do worse, but the differences were never statistically significant.

Psychometric tests

Twelve different psychometric tests, with 29 outcome variables, were analyzed (table 19). Only one test, block design, showed a definite difference between the paint-

ers and the carpenters, the painters doing worse ($P = 0.05$ with adjustment for potential confounding factors).

The painters in the low-exposure group had numerically better results than the carpenters for 23 of the 29 outcome variables, and the painters in the high-exposure group had numerically worse results than the carpenters for 20 of the outcome variables. There was thus a tendency among the painters for scores on several tests to get worse as exposure increased.

There was a clear tendency for the painters with intermediate or high exposure to do worse than the carpenters on the block design test and on two memory tests, the Benton and the Corsi block reversed. When the scores of these two exposure groups were combined and compared with those of the carpenters, there was a clear difference for block design ($P = 0.02$). Painters in the low-exposure group had clearly better performances than the carpenters on the verbal test synonyms and in the digit symbol memory test.

In the analysis of the other exposure estimates, it was found that exposure during the previous year was associated with numerically poorer test results on three tests and numerically better results on one test, synonyms. After control for confounding factors, the effect remained for synonyms and block design (table 20). However, in the synonyms test there was no tendency towards a difference between painters with and without exposure during the last year.

To differentiate between the effects of previous year and cumulative solvent exposure both exposure estimates were studied in the same regression model. Only painters were included in these analyses, and the low-exposure categories of both estimates were used as the reference categories. Both were found to have independent effects on the results of the synonyms test. The previous year was associated with better results on the synonyms

Table 17. Subjects with abnormal results on the clinical coordination or vibration sensitivity test. The painters are grouped according to cumulative solvent exposure. Prevalence ratios (PR) are given with 95% confidence intervals (95% CI).

Test	Occupation				Painters' exposure group								
	Carpenters		Painters		Low			Intermediate			High		
	N	N	PR	95% CI	N	PR	95% CI	N	PR	95% CI	N	PR	95% CI
Knee-heel	40	64	0.8	0.6—1.1	11	0.6	0.3—0.9	31	0.8	0.6—1.1	22	1.1	0.8—1.6
Tremor	5	10	0.9	0.3—2.4	1	0.5	0.0—5.6	4	0.7	0.2—2.1	5	1.5	0.5—4.2
Finger-nose	25	59	1.2	0.9—1.7	13	1.1	0.6—1.9	32	1.3	0.8—1.9	14	1.2	0.7—2.0
Romberg	36	52	0.8	0.6—1.1	10	0.6	0.3—1.0	28	0.8	0.6—1.2	14	0.8	0.5—1.3
Line walking	29	58	1.0	0.7—1.4	10	0.7	0.4—1.1	28	0.9	0.6—1.4	20	1.3	0.9—2.0
≥ 3 tests abnormal	22	35	0.8	0.5—1.2	4	0.4	0.1—0.9	19	0.9	0.5—1.4	12	1.0	0.5—1.9
Vibration sensitivity (toe)													
Right	2	11	2.4	0.6—10	—	.	.	7	2.7	0.6—13	4	2.8	0.6—15
Left	1	8	3.7	0.5—26	—	.	.	4	3.4	0.4—27	4	5.7	0.8—41

Table 18. Means and standard deviations (SD) for the results of the computerized coordination tests (CATSYS). The painters are grouped according to cumulative solvent exposure. A minus sign before a mean indicates that, when following a rhythm, the subjects, on the average reacted before the sound stimulus.

Test	Occupation				Painters' exposure group					
	Carpenters		Painters		Low		Intermediate		High	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Screen-nose pointing test										
Mean (cm)	2.97	1.61	2.86	1.63	2.53	1.19	2.74	1.58	3.44	1.98
Standard deviation	1.53	0.53	1.52	0.53	1.55	0.55	1.44	0.47	1.64	0.62
Hand supination-pronation test										
Slow test										
Mean (s)	-0.056	0.088	-0.047	0.088	-0.046	0.069	-0.040	0.088	-0.063	0.10
Standard deviation	0.061	0.070	0.062	0.067	0.053	0.064	0.063	0.062	0.069	0.078
Fast test										
Mean (s)	-0.021	0.025	-0.022	0.026	-0.019	0.024	-0.022	0.026	-0.024	0.027
Standard deviation	0.032	0.023	0.032	0.027	0.029	0.024	0.033	0.026	0.035	0.033
Maximum frequency (number · s ⁻¹)	4.85	1.36	4.95	1.35	5.28	1.21	4.94	1.18	4.63	1.72
Finger tap test										
Slow test										
Mean (s)	-0.030	0.036	-0.026	0.042	-0.028	0.028	-0.020	0.045	-0.037	0.048
Standard deviation	0.030	0.023	0.032	0.024	0.027	0.012	0.037	0.031	0.027	0.012
Fast test										
Mean (s) ^a	-0.015	0.025	-0.011	0.019	-0.0074	0.016	-0.011	0.021	-0.012	0.020
					P = 0.04					
Standard deviation	0.032	0.024	0.031	0.023	0.028	0.021	0.031	0.023	0.033	0.026
Maximum frequency (number · s ⁻¹) ^a	5.22	0.99	4.93	1.35	5.31	0.84	4.84	1.57	4.74	1.25
							P = 0.04		P = 0.04	

^a P-values adjusted for age and alcohol consumption.

test ($P = 0.03$, when compared with the results of painters unexposed during the previous year, with adjustment for cumulative solvent exposure and the confounders listed in table 19). Increasing cumulative solvent exposure was associated with declining results on the synonyms test ($P = 0.08$ for intermediate exposure and $P = 0.05$ for high exposure, compared with low exposure, with adjustment for previous year and the confounders listed in table 19) (table 21). For the block design test, both previous year and cumulative solvent exposure were found to be associated with somewhat worse results (table 22). The effects of previous year seemed somewhat stronger than the effects of cumulative solvent expo-

sure, but for both exposure estimates the results were far from statistically significant. For the Benton test (table 23) exposure during the last year was associated with a significant effect ($P = 0.02$ with adjustment for cumulative solvent exposure and the confounders listed in table 19), while cumulative solvent exposure also seemed to show some effect ($P = 0.09$ for high exposure with adjustment for previous year and the confounders listed in table 19). For the Corsi block test reversed, both previous year and increasing cumulative solvent exposure were associated with somewhat worse results, but for both exposure estimates the results were far from significant.

Table 19. Means and standard deviations (SD) for the results of the psychometric tests. The painters are grouped according to cumulative solvent exposure. (WCST = Wisconsin card sorting test)

Test	Occupation				Painters' exposure group					
	Carpenters		Painters		Low		Intermediate		High	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Synonyms ^{a,b}	19.6	5.7	20.8	4.6	21.6	4.7	20.5	4.5	20.5	4.7
Block design ^{a,c}	31.4	6.4	29.6	7.5	31.0	7.0	29.1	7.9	29.2	7.3
			P = 0.05		P = 0.04		P = 0.03		P = 0.08	
WCST										
Mismatches ^d	35.2	20.1	34.4	21.6	29.8	21.5	36.8	20.4	34.3	23.8
Perseverative errors ^{d,e}	20.9	13.3	20.1	14.9	18.5	15.3	22.5	14.9	17.3	14.3
									P = 0.08	
Categories ^a	4.39	1.73	4.19	1.83	4.47	1.80	4.05	1.77	4.18	1.99
Benton ^{d,e}	4.37	2.09	4.50	2.33	3.65	2.25	4.57	2.29	5.24	2.28
									P = 0.07	
Claeson-Dahl										
Weighted score ^d	108.8	64.6	114.1	68.2	94.4	57.6	120.2	74.0	122.1	63.9
Recognition ^a	7.58	1.54	7.76	1.53	7.94	1.50	7.70	1.62	7.70	1.38
Words memorized ^a	6.64	2.00	6.56	1.91	7.06	1.77	6.36	2.02	6.47	1.76
Corsi block										
Sum ^a	12.8	2.1	12.4	2.4	12.8	2.4	12.4	2.5	12.1	2.2
Forward ^a	5.70	1.47	5.68	1.36	5.71	1.34	5.72	1.41	5.59	1.33
Backward ^{a,f}	7.09	1.42	6.75	1.59	7.06	1.54	6.72	1.66	6.50	1.48
									P = 0.05	
Digit span										
Sum ^a	12.1	3.0	11.9	2.6	12.9	2.7	11.6	2.4	11.4	2.4
Forward ^a	6.26	1.81	6.37	1.50	6.91	1.64	6.18	1.46	6.21	1.34
Backward ^a	5.80	1.66	5.53	1.61	6.03	1.62	5.42	1.55	5.24	1.63
Complex figure										
Copy ^a	35.3	1.02	35.4	1.17	35.4	1.04	35.3	1.27	35.4	1.12
Reproduction ^a	22.1	5.72	21.4	5.97	23.0	6.32	21.2	6.12	20.2	5.04
Digit symbol										
Conventional ^{a,g}	42.3	8.5	42.1	9.2	46.2	9.0	41.2	8.8	39.7	9.2
Memory ^b	5.43	2.22	5.64	2.38	6.88	2.10	5.46	2.30	4.79	2.36
					P = 0.01					
Trail making										
A ^d	36.8	11.0	36.5	12.4	32.8	8.0	38.2	14.2	36.9	11.6
B ^d	92.0	27.3	94.1	35.1	80.9	22.6	97.8	40.2	100.1	32.2
Simple reaction time										
Mean (s)	0.27	0.035	0.27	0.039	0.27	0.022	0.27	0.048	0.27	0.030
SD	0.041	0.016	0.045	0.026	0.041	0.012	0.047	0.032	0.046	0.021
Shortest	0.21	0.022	0.20	0.025	0.20	0.017	0.20	0.029	0.20	0.023
Longest	0.42	0.093	0.45	0.15	0.43	0.11	0.46	0.19	0.44	0.12
Purdue pegboard										
Dominant hand ^a	13.3	2.01	13.4	1.94	13.6	1.97	13.2	1.94	13.5	1.94
Non dominant hand ^a	13.0	1.99	13.1	1.85	13.5	1.89	12.8	1.84	13.1	1.79
Both hands ^a	10.5	1.62	10.3	1.73	10.7	1.74	10.2	1.76	10.1	1.66
Combination ^{a,g}	30.8	5.98	29.4	6.59	31.5	5.76	28.7	6.48	28.7	7.29

^a A higher value denotes a better performance.

^b P-value adjusted for age, alcohol consumption, reading and writing difficulties, conscription test A, and conscription test C.

^c P-value adjusted for age, alcohol consumption, conscription test A, vocational training, and handedness.

^d A higher value denotes a worse performance.

^e P-value adjusted for age, alcohol consumption, and conscription test A.

^f P-value adjusted for age, alcohol consumption, conscription test A, and handedness.

^g P-value adjusted for age, alcohol consumption, and handedness.

More frequent episodes of lightheadedness were associated with a greater standard deviation in the reaction times and higher average values for the longest reaction times (table 24).

None of the indices created from tests within the same functional area showed a clear difference between the painters and carpenters, nor was there any tendency towards the expected exposure-response relationships

observed when the exposure groups of painters were compared with those of the carpenters.

Psychiatric diagnoses

Four of the 52 examined painters and three of the 45 examined carpenters satisfied the criteria for a psychiat-

Table 20. Means and standard deviations (SD) for the results of some of the psychometric tests. The painters are grouped according to solvent exposure during the year prior to the examination.

Test	Carpenters		Painters unexposed last year		Painters exposed last year	
	Mean	SD	Mean	SD	Mean	SD
Synonyms ^{a, b}	19.6	5.66	20.6	4.89	20.9	4.34
Block design ^{a, c}	31.4	6.40	30.6	7.47	28.6	7.48
Benton ^{d, e}	4.37	2.09	3.92	2.05	5.06	2.47
Corsi block reversed ^{a, f}	7.09	1.42	6.94	1.48	6.57	1.68
					P = 0.11	

^a A higher value indicates a better performance.

^b P-value adjusted for age, alcohol consumption, conscription test A, conscription test C, and reading and writing difficulties.

^c P-value adjusted for age, alcohol consumption, conscription test A, vocational training, and handedness.

^d A higher value indicates a worse performance.

^e P-value adjusted for age, alcohol consumption, conscription test A, and conscription test C.

^f P-value adjusted for age, alcohol consumption, conscription test A, conscription test C, and handedness.

Table 21. Means and standard deviations (SD) for the results of the synonyms test for the painters grouped according to cumulative solvent exposure and solvent exposure during the year prior to the examination. The results of the statistical analysis are given in the results section.

	Cumulative solvent exposure					
	Low ^a		Intermediate ^b		High ^c	
	Mean	SD	Mean	SD	Mean	SD
Painters not exposed last year	21.3	4.95	20.4	4.66	19.9	5.46
Painters exposed last year	22.2	4.38	20.6	4.42	20.9	4.27

^a Painters not exposed last year = 23, painters exposed last year = 11.

^b Painters not exposed last year = 29, painters exposed last year = 38.

^c Painters not exposed last year = 14, painters exposed last year = 20.

Table 22. Means and standard deviations (SD) for the results of the block design test for the painters grouped according to cumulative solvent exposure and solvent exposure during the year prior to the examination. The results of the statistical analysis are given in the results section.

	Cumulative solvent exposure					
	Low ^a		Intermediate ^b		High ^c	
	Mean	SD	Mean	SD	Mean	SD
Painters not exposed last year	31.9	7.03	29.8	7.75	30.0	7.80
Painters exposed last year	29.0	6.80	28.6	8.02	28.6	7.10

^a Painters not exposed last year = 23, painters exposed last year = 11.

^b Painters not exposed last year = 29, painters exposed last year = 38.

^c Painters not exposed last year = 14, painters exposed last year = 20.

Table 23. Means and standard deviations (SD) for the results of the Benton test for the painters grouped according to cumulative solvent exposure and solvent exposure during the year prior to the examination. The results of the statistical analysis are given in the results section.

	Cumulative solvent exposure					
	Low ^a		Intermediate ^b		High ^c	
	Mean	SD	Mean	SD	Mean	SD
Painters not exposed last year	3.22	1.57	4.38	2.38	4.14	1.79
Painters exposed last year	4.55	3.17	4.71	2.24	6.00	2.32

^a Painters not exposed last year = 23, painters exposed last year = 11.

^b Painters not exposed last year = 29, painters exposed last year = 38.

^c Painters not exposed last year = 14, painters exposed last year = 20.

Table 24. Means and standard deviations (SD) for the results of the simple reaction time test for the painters grouped according to the number of reported occasions of lightheadedness from inhaling solvents during work. (All the groups were compared with the carpenters.)

Simple reaction time test	No occasions		1—29 occasions		≥ 30 occasions	
	Mean	SD	Mean	SD	Mean	SD
Mean (s)	0.26	0.025	0.27	0.029	0.28	0.056
Standard deviation	0.037	0.0090	0.043	0.020	0.054	0.038
					P = 0.01	
Shortest ^a	0.20	0.030	0.20	0.022	0.21	0.025
	P = 0.02					
Longest ^b	0.39	0.074	0.44	0.16	0.49	0.17
					P = 0.01	

^a P-value adjusted for age, alcohol consumption, and neurological disease.

^b P-value adjusted for age, alcohol consumption, and medicines with effects on the central nervous system.

Table 25. Psychiatric diagnoses of the painters and carpenters examined in stage II. The diagnoses were made according to the guidelines in DSM III. The painters participating in stage II were ranked from the highest (1) to lowest cumulative solvent exposure (CSE rank).

Occupation	Birth year	CSE rank	Diagnosis (DSM III)
Painter	1929	3	Phobic personality traits but does not meet criteria for phobic personality disorder, 301.82
Painter	1934	4	Unspecified neurotic disorder 300.90
Painter	1930	14	Dysthymic disorder, 300.40
Painter	1934	16	Dysthymic disorder, 300.40
Painter	1934	19	Atypical personality disorder with depressive features, 301.89
Painter	1939	21	Compulsive personality traits but does not meet criteria for compulsive personality disorder, 301.40
Carpenter	1929		Dysthymic disorder, 300.40
Carpenter	1934		Atypical anxiety disorder, 300.00
Carpenter	1939		Bordeline personality disorder, 301.83

ric diagnosis according to the DSM III (table 25). A dysthymic disorder, moderate chronic depression, was diagnosed for two painters and one carpenter. Four other diagnoses occurred for one person each. In addition, two painters showed pathological personality traits, one phobic and one compulsive, without meeting the criteria for phobic or compulsive personality disorder.

According to the guidelines of DSM III, the dysthymic disorders, the unspecified neurotic disorder and the atypical anxiety disorder, if considered to be of organic origin, can be transferred to the category organic mental disorders, for which the dysthymic disorders would be classified as organic affective syndrome, and the unspecified neurotic disorder and the atypical anxiety disorder would be classified as atypical organic brain syndromes. The personality disorders were not compatible with a solvent origin, however, since the symptoms would have become apparent during youth or adolescence.

There were thus three psychiatric diagnoses among the painters and two among the carpenters that were, in principle, compatible with the diagnosis of chronic toxic encephalopathy due to organic solvent exposure. The six painters with the DSM III diagnoses or pathological personality traits had higher solvent exposure than average for the painters examined in stage II (Mann-Whitney U-test, $P = 0.01$). There was no agreement between the psychiatric diagnoses and the physician's assessments of neuropsychiatric symptoms with a suspected organic basis. Of the four painters with psychiatric diagnoses, three had been assessed by the physician as lacking organically based neuropsychiatric symptoms and one (with the diagnosis dysthymia) had been assessed as having marked symptoms. None of the three carpenters with psychiatric diagnoses had been judged to have organically based neuropsychiatric symptoms.

Neurophysiological examinations

Electroencephalography

In the visual assessment, the EEG values were judged to be normal or not definitely pathological for 46 (90%) of the painters and 40 (89%) of the carpenters. Four EEG values in each group were considered slightly pathological, while one of the painters had a light-to-moderate, focal, episodic but not epileptogenic abnormality laterally on the left side and one of the carpenters had a slight episodic but not epileptogenic frontotemporal abnormality with left-side dominance. These results did not differ from those of most normal populations, for which EEG deviations from normal are reported to range from 10 to 30%. Nor did the visual assessments of the EEG values, when placed on a five-point scale (normal, within normal limits, not definitely pathological, slightly or moderately pathological, other abnormal EEG values), show any differences in distribution between the painters and the carpenters.

The visual assessment also included a calculation of the average frequency of alpha activity during recording

Table 26. Means and standard deviations (SD) for the vibration thresholds of the painters and carpenters who participated in stage II.

Localization	Painters				Carpenters			
	Left		Right		Left		Right	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Back of the hand	0.45	0.32	0.41	0.33	0.43	0.28	0.38	0.24
Lower leg	0.95	0.92	0.91	0.74	1.07	1.00	1.03	1.05
Top of the foot	4.29	4.76	3.65	3.44	4.24	4.80	4.26	5.81

while the subject was awake but relaxed with the eyes closed. The average values for the painters and the carpenters were similar: 9.7 (SD 0.7) Hz and 9.6 Hz (SD 0.9) Hz, respectively. Persons with particularly high or low alpha activity were about equally common in both groups.

Auditory cerebral evoked potential and event-related evoked potential

The average latency time to P-300 was 306 (SD 29) ms for the painters and 316 (SD 30) ms for the carpenters. The differences were not statistically significant, and all of the individual values were within clinically normal limits. Persons with a particularly long latency time to P-300 were not overrepresented in either group.

Vibrometry

The average values for vibration thresholds were also similar in the two groups. There were no statistically significant differences (table 26). Particularly high thresholds were not overrepresented among the painters at any location.

Magnetic resonance tomography of the brain

Table 27 gives a summary of the comparison between the painters and the carpenters with regard to the continuous outcome variables. It can be seen from the table that no significant differences were found between the groups either for the T1 relaxation in white matter or in ventricle width. The obtained values showed no systematic tendency indicating a difference between the groups, with the possible exception of the width of the third ventricle, which was a bit larger among the painters.

Table 28 presents the qualitative measures occurrence of nodular signal changes in white matter, expansion of areas filled with cerebrospinal fluid, and other morphological deviations. There was no significant difference between the groups in this respect either, even though there were definite indications of expansion of

Table 27. Results of the paired t-test for several continuous outcome variables from the magnetic resonance tomography of 15 painters and 15 age-matched carpenters participating in stage III.

Variable	Mean	SD	P-value
Ventricle index	0.010	0.0062	0.13
Third ventricle width	0.87	0.45	0.07
T1 frontally, right	24.9	19.0	0.21
T1 frontally, left	14.5	17.7	0.43
T1 parietally, right	5.87	26.9	0.83
T1 parietally, left	2.13	35.7	0.95
T1 cerebrospinal fluid	44.8	26.4	0.11
T1 temporally, right	27.5	22.4	0.24
T1 temporally, left	7.73	21.9	0.73
T1 occipitally, right	8.67	29.7	0.78
T1 occipitally, left	-6.20	25.5	0.81
T1 thalamus, right	-50.2	38.3	0.22
T1 thalamus, left	-28.1	31.7	0.39

Table 28. Results of the discrete or dichotomous variables from the magnetic resonance tomography of 15 painters and 15 age-matched carpenters participating in stage III.

Variable	Painters (N)	Carpenters (N)
Expansion of areas filled with cerebrospinal fluid		
None or very slight	9	5
Slight	2	5
Definite	4	1
Nodular high signal changes in white matter		
≤ 5	13	14
6—10	1	1
≥ 11	1	0
Focal morphological changes	2	1

areas filled with cerebrospinal fluid in four painters and one carpenter.

Gross morphological changes were noted in three subjects, two painters and one carpenter. These were an old infarct, a postoperative defect in the mastoid bone, and an old temporal hygroma.

There was no clear correlation between indications of an expansion of areas filled with cerebrospinal fluid and the physician's assessments of organically based neuropsychiatric symptoms. Of the four painters who had definite signs of expanded areas filled with cerebrospinal fluid, two had been assessed by the physician as having organically based slight neuropsychiatric symptoms and two as not having such symptoms. The only

carpenter who had definite signs of expanded areas filled with cerebrospinal fluid had also been assessed as lacking symptoms. The two painters and four of the five carpenters with probable expansion of areas filled with

cerebrospinal fluid had been assessed by the physician as lacking organically based neuropsychiatric symptoms, while the other carpenter had been judged to have slight symptoms of this nature.

Discussion

Evaluation of the results and agreement between different results

Neuropsychiatric symptoms and psychiatric diagnoses

In the judgment of the examining physician, more painters than carpenters had neuropsychiatric problems with a possible organic basis. Many of the individual symptoms on which her judgment was based appeared more frequently with increasing cumulative exposure. The risk for the group of painters with low exposure appeared to be no higher than that for the carpenters, however, either according to the physician's overall assessment or for the majority of the individual symptoms.

Other symptoms involving the nervous system, such as deterioration in the sense of taste or smell, were also more common among the painters than among the carpenters, and they increased in frequency with increasing solvent exposure. The results of the insomnia questionnaire confirmed the information obtained by the physician during the interviews. Sleep quality appeared to decline with increasing solvent exposure.

In the POMS questionnaire, the subjects were asked the extent to which they had felt various moods during the previous week. In themselves these moods had no pathological relevance although many of the POMS questions were similar to questions asked in the medical interview. The responses were grouped into several different factors so that a higher point total in one factor expressed, for example, higher tension and anxiety. High values were no more common among the painters than among the carpenters for any of the factors. The painters appeared to have felt less anger and hostility than the carpenters during the previous week. For several factors, the proportion with high scores was clearly smaller for the painters with low exposure than for the carpenters, and for all factors the proportion with high scores was no greater for the painters with high exposure than for the carpenters.

Thus there seems to be a discrepancy between the results of the POMS questionnaire and the medical interview. One factor contributing to the difference may have been that the physician asked the subjects

whether they had noticed any changes in irritability, memory and the like, whereas on the POMS questionnaire they were asked to report how they had been feeling recently. We believe that the symptoms noted in the medical interview should be given more weight, since the interview questions on symptoms were based on descriptions given by people with long-term solvent exposure (60).

The psychiatric diagnoses among the subjects examined in stage II were no different in either number or kind from those expected for workers in general. Our hypothesis was that organic mental disorders would be overrepresented among the painters. We found three cases among the painters and two among the carpenters that were compatible with such a diagnosis; in other words, there was no overrepresentation among the painters. It is worth noting, however, that the six painters with psychiatric diagnoses or phobic or compulsive personality traits had clearly higher exposure to solvents than the other painters examined in stage II.

Coordination, other clinical status, vibrometry

In the results of the clinical examinations, the differences between the painters and the carpenters were small. Among the painters, however, there was a tendency towards increased unsteadiness with increased exposure; this phenomenon was seen for the line-walking test (both forward and backward) and agreed with the corresponding subjective symptoms. The painters with low exposure, as defined by the cumulative solvent exposure, had more favorable scores than the carpenters on nearly all the clinical tests. The results of the finger-to-nose test were consistent with results from the computerized screen-nose-point test. In both tests, the painters showed increasing uncertainty with increasing cumulative solvent exposure.

The computerized coordination tests confirmed the results of the clinical examinations, with small differences between the studied groups. The vibrometry tests showed no differences between the painters and the carpenters examined in stage II.

Psychometric tests

In general, the psychometric tests showed little difference between the painters and the carpenters. On most of the tests, the painters with low exposure did somewhat better than the carpenters, and the painters with high exposure did somewhat worse. For the block design test, the performance of the painters was significantly worse than that of the carpenters, and it declined with increasing cumulative exposure. For the Corsi block reversed test there was also a tendency towards poorer scores among the painters; these scores also declined with increasing exposure. For the Benton test the painters with high exposure tended to do a bit worse than the carpenters. The latter two results provide support for a slight decline in learning ability among the exposed subjects.

Both the longest reaction time and the standard deviation of the average value for reaction time clearly increased with an increase in the number of reported occasions of lightheadedness.

No clear differences between the painters and carpenters were noted in the perception tests.

Other neurophysiological tests and magnetic resonance tomography of the brain

The EEG and AEP-300 revealed no differences between the painters and the carpenters. The MRT revealed that the expansion of areas filled with cerebrospinal fluid at the expense of the brain might have been more common among the 15 highly exposed painters than among the 15 age-matched carpenters.

Potential sources of bias

Carpenters were chosen as a reference group because they were assumed to resemble painters with regard to primary intellectual capacity, education, and socioeconomic factors. This assumption was confirmed by the results of the psychometric military conscription tests and by questions on education and socioeconomic status.

Selection

The population from which our study material was drawn consisted of painters and carpenters who had been union members for at least 10 years before 1970. Those who had left their jobs after 1970 were included in the study. Nine percent of the invited painters and 16% of the invited carpenters did not come to the first examination. Our data from registers indicate that, especially for the painters, neuropsychiatric problems may have been somewhat more common among those who did not come to the examination than among those who came. Con-

sidering that the attrition was so small, however, this difference should hardly have influenced the results. Similarly, those who did not come for stage II of the examination (both painters and carpenters) had done somewhat more poorly on the psychometric tests than those who came. There may thus have been some positive selection for the groups examined in stage II, but the selection problem seems to have been the same for both the painters and the carpenters.

Consequently, selection should not have led to an underestimation of the prevalence ratio of solvent-induced CNS effects among persons with at least 10 years of membership in the Swedish Painters' Union.

Our study did not include painters who may have developed serious symptoms and therefore changed jobs before they had belonged to the union for 10 years. In the Nordic countries, however, a diagnosis of chronic toxic encephalopathy from solvent exposure generally requires at least 10 years in a high-exposure job (61). This criterion is based on wide clinical experience which argues against the possibility that a large number of people had developed chronic psychiatric problems and had been forced to quit working as a painter after less than 10 years in the profession.

Misclassification of exposure

Painters were chosen as the exposed group because most of them were heavily exposed to solvents from the 1950s, when solvent-based paints were introduced on a wide scale, until the mid-1970s, when water-based paints began to replace the solvent-based paints for many uses (62). Carpenters had been occupationally exposed to solvents to some extent, but this exposure was assumed to be too low to have much effect on the studied outcomes. Both the earlier high exposures of the painters and the generally low exposures of the carpenters were confirmed in the exposure interviews.

Misclassification of the degree of exposure is unavoidable when earlier exposure is assessed from interviews, since the subjects doubtlessly find it difficult to remember exposure conditions a long time ago. The occupational hygienist's exposure assessments were probably also subject to this type of misclassification. Solvent exposure from the work of other painters (secondary exposure) was not included in the exposure measures since it was difficult to assess from uncertain information on solitary work and group work. Therefore, for example, exposure for a painter who occasionally hung wallpaper only, while someone else was painting in a neighboring room, was given too low an estimation. It is likely that for some carpenters the major source of solvent exposure was work around painters. It seems unlikely, however, that secondary exposure contributed to extensive misclassification in our exposure categories.

All the exposed subjects had painted surfaces of various sizes. Painting apartments was by far the most common job, and prolonged periods of painting in confined spaces or large rooms seldom occurred. The painters who had worked on special objects for prolonged periods had usually used paints containing xylene or toluene. Exposures to white spirit, toluene, and xylene were weighted against each other with their respective exposure limits, since the limits are generally set on the basis of acute CNS effects.

Only exceptionally did the painters have access to any exhaust ventilation to reduce exposure, usually with work done in rooms without windows, such as large warehouses or subterranean storage areas. The painters usually worked with the windows open when the weather allowed. Most of the painters said that when they were working with apartment renovation they could not open windows as much as they would have liked, out of consideration for the tenants. Differences in ventilation conditions are therefore not considered to have contributed to much misclassification.

All of the circumstances mentioned would, to various extents, have contributed to exposure misclassification independent of the studied outcomes and thus reduced the observed, as compared with the true, prevalence ratios.

There is a risk that some exposure-response associations may have been overestimated among highly exposed painters if painters with CNS problems reported higher exposure than those without symptoms, although exposures were the same. Such overreporting of exposure is not unlikely, since more sensitive persons may have had more acute problems from exposure than less sensitive ones and therefore experienced the exposure as higher (63). The detailed exposure interview, which covered all types of jobs done by the subject, should have reduced any such overestimate. The limited validation of the exposure data that we were able to perform may also support this interpretation. Persons affected by the illness under study do not generally seem to over-report exposure in occupational studies (64).

We cannot see any convincing reason why painters with problems would deliberately exaggerate their exposure. Painters in Sweden have long had the option of being referred to an occupational medicine clinic if they themselves associated their symptoms with occupational exposure.

If the occupational hygienist who conducted the interviews knew about the problems of the individual painters, there may likewise have been a tendency to classify individuals with problems as more highly exposed. We could not assess this possibility, but the occupational hygienist's interview was detailed and provided little leeway for conversations on anything but exposure conditions.

Misclassification of outcomes

Most of the outcome measures used in our study are dependent on the cooperation of the subject. It can therefore be assumed that there was some misclassification of results that was independent of the studied exposure, with a consequent underestimate of the true prevalence ratios.

A misclassification of the outcomes that is dependent on the studied exposure is also conceivable. It can be assumed that the symptoms commonly associated with solvent exposure were fairly well known to the examined painters. They may therefore have paid more attention to such symptoms than the carpenters did and would thus have reported them to a greater extent, which would lead to false high prevalence ratios among the painters. Arguing against this, however, is the fact that several of the symptoms commonly associated with solvent exposure, such as emotional instability and abnormal fatigue, were not overrepresented among the examined painters.

To avoid prejudice in the evaluations, the persons who conducted the various examinations were not told whether the subject was a painter or a carpenter. To assess the effects of this blinding, the physician and the psychologists who conducted the psychometric tests were asked to note whether they considered the person they had examined to be a painter or a carpenter, and whether they knew or were guessing. It turned out that 30% of the examined painters, compared with 15% of the examined carpenters, had revealed their profession to the physician. In the psychometric examination as well, more painters (44%) than carpenters (27%) had revealed their work to the examiner. In the psychometric examinations there was also a tendency for more of the painters in the high-exposure group to reveal their identity (56%) than in the intermediate-exposure group (43%) or the low-exposure group (35%). We therefore also calculated the prevalence ratios for the three exposure groups of painters', compared with the carpenters', possibility of being judged by the physician as having signs of organic brain damage and the prevalence ratios of having results on the psychometric tests that were worse than the 90th percentile among the carpenters, separately for those whom the examiner knew were painters, those the examiner correctly guessed were painters, and those the examiner incorrectly guessed were carpenters. The results in the various exposure groups were similar regardless of whether or not the profession of the subject was known.

We therefore consider that the blinding, in spite of considerable effort to maintain it, did not work satisfactorily. However, the comparisons of the prevalence ratios among the individuals when the examiner knew, guessed, or did not know the profession indicate that knowledge about the profession played little role in the assessments.

Confounding factors

Alcohol consumption and primary intellectual capacity are factors suspected of being able to contribute to neuropsychiatric morbidity. We made considerable effort to control these potential confounding factors and consider that control in the present study was better than that in most previous studies.

Several studies support the assumption that painters, who in most studies of neuropsychiatric effects from solvent exposure make up most of the exposed group, have more alcohol damage than workers in similar professions (21, 28, 65, 66).

Indicators of alcohol consumption in our study were interview questions on current consumption, a reliable and widely used questionnaire on alcohol problems (MAST), serum activity of the enzyme gamma glutamyl transferase, and register data on alcohol problems. We found no indication in this study that alcohol consumption was higher among the painters than among the carpenters or that alcohol consumption increased with increasing exposure; there was instead a tendency for the reported consumption to be lower for painters with high cumulative exposure than for the other groups.

Some cross-sectional studies have also reported that subjects exposed to solvents showed a lower primary intellectual capacity than referents, as measured with verbal psychometric tests, and that differences in test results pertaining to functions assumed to be sensitive, such as memory and perception, disappeared after control for primary intellectual capacity (5, 17). In our study, primary intellectual capacity was controlled by the results from military conscription tests, which were available for all the subjects. These test scores did not indicate that the painters had lower primary intellectual capacity than the carpenters. The painters in our low-exposure group had achieved somewhat better numerical results than those in our intermediate- and high-exposure groups when they took their conscription tests for military service, but the differences were far from statistically significant (Mikkelsen & Lundberg, unpublished manuscript).

Illnesses, accidents, and the consumption of medicines with conceivable effects on the studied results were covered in detail in the physician's interview. In the occupational hygienist's interview, note was also made of exposure to other substances known to have CNS effects.

Most of the potential confounding factors that we included in the data analyses were in practice also associated with one or another of the studied outcomes. However, there was seldom a definitely skewed distribution of the potential confounders between the exposure groups, and their actual confounding properties were therefore limited. Age was strongly associated with the cumulative exposure measure, but it often had no effect

on the studied outcomes, probably because the age range in the study group was only 15 years.

In conclusion, confounding is not considered to have markedly influenced the results of this study.

Comparisons with earlier studies

Studies of the neuropsychiatric effects of solvent exposure have usually been either cross-sectional or longitudinal. However, one pseudolongitudinal study, that is, a study in which a group that was exposed at a particular time is studied a number of years later, regardless of current job or exposure (67), was published by Mikkelsen et al in 1988 (10). Thus our study is the second pseudo-longitudinal study, and we have compared our results to those of Mikkelsen et al whenever possible.

In cross-sectional studies, the general procedure has been to ask currently exposed workers about symptoms and do psychometric testing and some supplementary examinations. These studies were the most recently surveyed by Mikkelsen et al (10). The longitudinal studies made in the area were the most recently surveyed by Hogstedt & Lundberg (67).

According to Mikkelsen et al (10), the exposure-response relationships strongly supported a connection between solvent exposure and chronic CNS effects in those studies that quantified exposure over longer periods and that included a sufficiently large number of subjects with high exposure. Hogstedt & Lundberg (67) stated that "It seems quite safe to summarize that workers exposed to moderate or high concentrations of organic solvents will have decreased performance in psychological tests [p S9]" and that all published longitudinal studies show an "increased risk for workers with long-term exposure to organic solvents to have to retire early due to neuropsychiatric disorders before the normal pension age [p S10]." In the vast majority of cross-sectional studies, however, the exposed subjects have been examined after only one night or at most a few days without exposure, and residual acute effects may partially explain their poorer results. In our report we primarily discuss recent literature that has not been covered in the aforementioned surveys.

Exposure

There have been three earlier studies with cumulative exposure estimates that we have been able with reasonable confidence to convert to exposure-limit months, the measure used in our study.

Mikkelsen et al (10) used an exposure estimate based on both time spent painting and solvent use with different painting methods. The average value for cumula-

tive exposure among the housepainters in this study was 32 (range 2—283) $l \cdot d^{-1} \cdot year$. The average solvent use was $3.4 l \cdot d^{-1}$. This value corresponds to an average exposure of $31.8/3.4 = 9.3$ solvent-exposed years or 93 solvent-exposed (range 4—830) months, if we assume 10 work months per year. This figure can be compared with the average value for solvent-exposed months in our study, which was calculated to be 98 (range 29—206).

There thus appears to be good agreement between the calculated exposures in our study and those of Mikkelsen et al (10). Considering our requirement of at least 10 years of union membership, while there was no similar requirement in the study by Mikkelsen et al (10), it is reasonable that the lowest exposure in our study was higher than the lowest exposure in the Danish study. The average values in the two studies are very similar, and it is therefore likely that the extremely high highest exposure value in Mikkelsen's study represented the exposure of one or a few painters with extreme work conditions.

Mikkelsen et al (10) divided their material into three exposure groups approximately corresponding to <45, 45—89 and ≥ 90 solvent-exposed months, whereas our divisions corresponded to about <70, 70—120 and >120 solvent-exposed months. The class boundaries in our study were thus higher.

The decisive difference in construction between the exposure measure used by Mikkelsen et al (10) and that in the present study appears to lie in our weighting for the exposure limits. The monitoring data we managed to find support the assumption that the levels of solvent exposure present during actual painting tended to follow changes in the exposure limit for white spirit (Nise et al, unpublished manuscript), and we believe that this weighting increases the accuracy of the exposure estimates. If the exposure-limit weighting is exchanged for solvent-exposure months in our calculations, four of the subjects move from the low-exposure group to the intermediate-exposure group and vice versa, and three in the high-exposure group move to the intermediate group and vice versa. Thus, also with solvent-exposed months as the exposure estimate, the associations we found between exposure and outcomes would not change.

In a Finnish study of the solvent exposure of housepainters (29), in which the estimates were used in a cross-sectional study of neuropsychiatric effects (5), an average white spirit concentration of 132 ppm was measured around painting painters. The average cumulative amount of white spirit inhaled by the subjects during their worklife was calculated to be 11.9 (SD 8.5) kg, based on an inhalation volume of $1.2 m^3$ per hour (Riiala, personal communication). If we assume that the average exposure to white spirit during actual painting was at the exposure limit ($500 mg \cdot m^{-3}$), the level is equiva-

lent to about 120 exposure-limit months in our study (SD 85 exposure-limit months). The average value of our cumulative exposure measure was 197 (SD 80) exposure-limit months. The difference may be explained by the fact that the painters in our study had been working an average of 10 years longer than the painters in the Finnish study.

In their cross-sectional study of the neuropsychological function of paint factory workers, Ørbæk et al (9) used a cumulative exposure index calculated as the product of the number of years of employment and the exposure level expressed as a proportion of the exposure limit at the time of the study. Cumulative exposures in this study, expressed in our exposure-limit months, ranged from 10 to 680, compared with a range of 55 to 438 in our study. That the highest exposure in this study is higher than in ours is very probably due to the fact that there are jobs in the paint industry that involve extremely high exposure.

An American study of housepainters used exposure estimates that can be translated to our measurement units in the same way as for the three studies already discussed. The calculated average solvent use per painter was, however, about 15 to 20 l per day, which seems unreasonably high, and the results of the study are difficult to assess with regard to exposure-response relationships (30, 68).

The estimates reported in other studies could not be translated to the exposure measures we used. In the studies that are reviewed in the following discussion and give some form of exposure estimate, the average exposures were, however, probably lower than that of our group of painters.

Neuropsychiatric symptoms, psychometric tests, psychiatric diagnoses

Neuropsychiatric symptoms

The physician's overall judgments of whether there were indications of organic brain damage showed a clear relation to the cumulative exposure level. In the study by Mikkelsen et al (10) there was no such assessment based only on reported symptoms. However, the examining psychologist made an assessment based on both symptoms and the results of psychometric tests and found prevalence ratios for the exposure groups which agree well with our findings.

Ørbæk et al (9) found that several neuropsychiatric symptoms were more common among exposed paint-factory workers than among referents. The exposure-response relationships were poorly described, and it was impossible to determine the cumulative exposure at which symptoms began to increase. Lindström & Wickström (5) found increases in a few neuropsychiatric

symptoms among their exposed subjects, but they provided no information on exposure-response relationships.

In most of the cross-sectional studies made in the past few years, it was often found that symptoms generally considered to appear after prolonged and intense exposure to solvents were not overrepresented in the exposed groups (19, 20, 68—74). In some of these studies, some symptom or symptoms considered to be characteristic of the chronic neurotoxic effects of solvent exposure, such as emotional lability or depression (20, 70, 72), "loss of interest and concentration" (72), fatigue (68, 74), and irritability (74), were overrepresented among the exposed subjects, but the overall picture in these studies was that exposure had little or no effect on the occurrence of characteristic symptoms.

In two studies, most of the symptoms of this nature appeared to be more common in the exposed group than in the unexposed group (75, 76). In both of these studies most of the subjects were housepainters. In one of them (75) there was also a clear exposure-response relationship in that increasing cumulative lifetime exposure was associated with increasing frequencies of forgetfulness, disorientation, depression, fatigue, insomnia, and headache. In the other study (76), all the characteristic symptoms occurred more frequently in the exposed group, but the difference was significant only for fatigue and emotional lability. An attempt was made to quantify exposure, but the quantitative exposure measure was not related to an overall index of neurasthenic symptoms.

Thus our results concerning symptoms taken to be characteristic of long-term heavy solvent exposure seem to agree well with those of most earlier studies and also more recent studies of housepainters. Although they may seem to disagree with some recent studies, the solvent exposures in most of these studies have probably been low (19, 20, 71—73) or difficult to assess in terms of cumulative exposure (68, 70).

Mood

In several cross-sectional studies mood scale results, from POMS or based on POMS, have been related to solvent exposure indices (68, 75, 77). However, other studies did not find exposure-related effects in the POMS (73, 74). We saw no effect from exposure on any POMS factor, and this result may be explained by reversibility of previous effects. In addition the Swedish translation of the questionnaire, although painstakingly made, may also have caught the essence of the feelings described less well than the original.

Insomnia

Sleeping problems appear to be a common effect of exposure to solvents. Difficulty getting to sleep has been

found to be increasingly common with increasing exposure among currently exposed painters (75). Waking up tired in the morning was more frequent among lacquerers and printshop workers exposed to solvents than among referents, but waking early and still tired was more frequent only among the lacquerers, who also had nightmares more often than their referents (78). Increased frequency of sleep apnea compared with that of referents was demonstrated in a small group of workers with high exposure to trichloroethane (79). There are several studies in which solvent-exposed patients with suspected or confirmed chronic toxic encephalopathy have been found to have higher frequencies of sleep apnea than referents (79—82).

In our study, we found a clear decline in our insomnia questionnaire factor "sleep quality" among the painters with high exposure when compared with the carpenters, but we saw no such tendency for the factors recovery and sleep apnea. As to the individual questions, it was primarily waking up often with difficulty getting back to sleep, not feeling rested in the morning, waking too early, and restless and disturbed sleep that were overrepresented among the highly exposed painters. The sleep apnea factor was constructed from questions on pronounced snoring, fatigue, and drowsiness during work or free time and involuntary dozing during work or free time. None of these symptoms were overrepresented among the painters when they were compared with the carpenters, but among the painters there was a clear exposure-response relationship for involuntary dozing. The question on pronounced snoring, which showed no association with exposure, may be difficult to answer correctly. This result would probably lead to a dilution of genuinely increased prevalence ratios.

Our results appear to confirm that sleeping problems and poor sleep quality are common symptoms of high, long-term solvent exposure and that these symptoms also seem to be irreversible. The reason for this is not clear, but sleep apnea is a conceivable explanation even though this factor showed no correlation to exposure.

Other symptoms

We found a strong exposure-response relationship between cumulative solvent exposure and reported deterioration in the sense of taste or smell. Deterioration of the sense of smell in subjects exposed to solvents has been found in earlier studies using more objective methods (83—85). The sense of taste was studied with objective methods in workers exposed to trichloroethylene, but no exposure-related effects were found, although effects on the sense of smell were noted (86). Since our findings are based only on questionnaire responses, they do not indicate anything specific concerning effects on taste and smell from organic solvent exposure. However, they suggest that future studies of nervous system effects from

solvent exposure on painters may preferably include more objective measurements of the senses of taste and smell.

Psychometric tests

Mikkelsen et al (10) found differences between their reference group (masons) and the combined intermediate- and high-exposure groups of painters on the block design test and the visual gestalt test. The painters in the low-exposure group did better than the referents on nearly all the tests used, the differences between this group and the other two exposure groups combined were thus also found for the symbol digit modalities and in the combined measure of performance on tests assumed to be sensitive. The large majority of the tests assumed to be sensitive revealed no differences between the masons and the three exposure groups of painters.

In a study by Ørbæk et al (9), it was only on a perceptual speed test (dots fluctuation) that the exposed subjects showed clearly worse results than referents. The individual test results were not reported separately for the different exposure categories, but on a combined index the test results clearly deteriorated with increased exposure.

In the study made by Lindström & Wickström (5), the performance of the painters was worse than that of the referents on only one memory test (visual retention) after control for primary intellectual capacity with the military conscription tests. Among the painters the results on some tests, including the block design test, appeared to be related to exposure level. The results were reported only as regression coefficients, however, and it is therefore impossible to make a direct comparison with the results of our study.

Neuropsychiatric symptoms have generally been considered to appear earlier than declines in performance on psychometric tests as indications of effects on the CNS from solvents and other neurotoxic agents (67). In several of the cross-sectional studies made since 1987, however, the effects on psychometric tests seem to be more apparent than the increases in symptoms (69, 74, 87, 88). Daniell et al (74) found clear exposure-related effects in some psychometric tests of visual perception and memory in the NES (neurobehavioral evaluation system) battery, but no effects on moods in the abbreviated version of POMS that is included in the NES. Bleeker et al (87) found clear exposure-related effects in the digit symbol substitution, serial digit learning, truncated reaction time, trails A, and trails B tests, but virtually no exposure-related increase in symptoms (20). Spurgeon et al (69) found clear exposure-related effects in the symbol digit substitution test, and probable exposure-related effects in the paired associate learning test. Moen et al (88) found that the results of an auditory memory test and a visual abstraction test (Ravens progressive matrices) declined

with increasing exposure. Triebig et al (19, 71) found no differences between referents and housepainters or spray painters in results on psychometric tests. Within the group of painters in the latter study there were strong correlations between the results of several psychometric tests and cumulative solvent exposure weighted by the occurrence of intoxication symptoms. The age of the subjects also increased with increasing exposure, however, and the extent to which the results of the psychometric tests can be explained by age is not clear.

Baker et al (75) used the NES test battery in their study of housepainters and found that only the results of the symbol digit substitution test showed clear deterioration with an increasing intensity of average exposure during the exposed years. Some of the results of the subtests of the continuous performance test also showed a tendency to decline with increasing exposure, as defined by this exposure measure. The majority of the tests in the study showed no relation between the results and exposure however. Hänninen et al (73), in a study of twins from the Finnish twin register, found that on the associative learning, digit span, and block design tests exposed subjects had poorer results than their unexposed twins.

Our findings of very small effects in psychometric tests seem to be in accordance with the results of previous studies of housepainters and paint industry workers with exposures comparable to ours (5, 9, 75).

The findings of some exposure-related effects in recent cross-sectional studies of workers with mixed solvent exposures, sometimes despite low exposure levels, seem to be in accordance with previous cross-sectional studies. It is possible that effects from ongoing exposure may have contributed to the results. However, it is also possible that the computerized test batteries may be somewhat more sensitive to solvent-related effects than the paper and pencil tests used by us.

In our study, like that of Mikkelsen et al (10), we found few differences between the studied painters and the reference group. In both our study and Mikkelsen et al's (10), however, the block design test appeared to be sensitive to the effects of solvents. This test has also been found to be sensitive to solvent exposure in several studies in which acute effects of solvents were probable (6, 73, 89). However, our data suggest that the comparatively small effects shown by the block design test were at least partly dependent on low current exposure and thus probably at least partly reversible. We also found small effects in the Benton and Corsi block memory tests. Effects on memory tests have been demonstrated in a large number of cross-sectional studies of workers with current solvent exposure and also in studies made after long exposure-free periods (10, 88).

In many studies of painters currently exposed to solvents, tests of simple reaction time have shown differ-

ences between painters and referents (61). We found no differences between the carpenters and the painters when grouped according to cumulative exposure. This finding may be explained by the fact that the painters in our study had little or no current exposure to solvents and that in many cases the effects on reaction time are reversible. However, there were clear exposure-related differences regarding the standard deviation for reaction times and the longest measured reaction time, when the painters were grouped according to the number of reported occasions of lightheadedness at work. This finding may indicate that frequent peak exposures can have a slight chronic effect on reaction time.

We constructed several combined measures of test performance corresponding to the measures used by Mikkelsen et al (10), but these combined measures showed no stronger relationships with exposure than the individual tests, and a weaker relationship than the block design test.

The combined measure used by Mikkelsen et al ("test score index") showed no difference between the group of painters and the group of masons, however, and the painters in the low-exposure group performed considerably better than the masons, while the painters in the high-exposure group performed considerably worse (ie, the results on most tests agree well with ours). This agreement between the two studies suggests that the superior performances of the low-exposure group of painters may be an effect of factors that lead to low solvent exposure among painters, and it is not necessarily random. Such factors are further discussed in the concluding remarks of this report.

Psychiatric diagnoses

No previous study of workers exposed to solvents has attempted to make psychiatric diagnoses from clinical examinations. Our findings indicate that psychiatric diagnoses may be more common among highly exposed painters than among carpenters. Organic mental disorders did not appear, however, to be more common among painters than among carpenters. These results seem to be the most compatible with an effect of factors that lead to high solvent exposure among painters, but, considering the small size of the sample, they are also compatible with a chronic CNS effect of solvents.

Coordination tests

In their clinical neurological examination of coordination, which was very similar to ours, Mikkelsen et al (10) found that, in all the tests, deviations from normal became increasingly common with increasing exposure. In our study, we used a computerized version of some of the tests used by Mikkelsen et al (10). Neither the clinical examination methods nor the computerized tests re-

vealed any differences between the painters and the carpenters. For nearly all the tests, however, we found a tendency for the painters with low exposure to do better than the carpenters, and the painters with high exposure to do worse — the same pattern we found in many other sections of the study.

In our study, the painters in the intermediate- and high-exposure groups had clearly worse results than the carpenters only with regard to maximum frequency in the finger-tapping test. In the study by Mikkelsen et al (10), the finger-tapping test was one of the coordination tests that showed the least difference between the exposure groups.

Thus our study did not confirm the exposure-related impairment of performance on coordination tests found by Mikkelsen et al (10). The reasons for this difference are unclear. Contributing factors may have been that the examiner in Mikkelsen et al's study (10) was aware of the exposure status of the subject and that the outcome measurements always involved a substantial amount of personal interpretation. It is also likely that the average alcohol consumption among the subjects in the Mikkelsen et al study (10) was higher than in our study since 23% of the masons and 15% of the painters were defined as alcohol abusers (a daily alcohol consumption of more than 120 g for more than a year). It is possible that alcohol consumption might interact with solvent exposure to impair coordination.

Neurophysiological examinations

Electroencephalography and auditory potentials

There was no difference between the painters and the carpenters examined in stage II with regard to either visually assessed EEG variables or auditory evoked potentials. There are also some earlier studies in which the EEG values were assessed visually, and no differences were noted between the unexposed subjects and those exposed to solvents (7, 11, 19). In one of these studies a frequency analysis of the EEG values was also made, but it revealed no differences between the groups (7). In a study of paint-factory workers (9), both visual assessments and frequency analyses were made of EEG recordings from four parts of the brain, and both methods revealed a general increase of beta activity among the exposed. Frequency analyses revealed more changes in the EEG values of patients with the diagnosis of solvent-induced chronic toxic encephalopathy than in a healthy reference group (90). The differences between the groups became smaller after the termination of exposure, but they did not altogether disappear.

Our negative findings can thus conceivably be due to normalization of earlier EEG changes after exposure had dropped considerably or stopped. Since we did not make

frequency analyses, we cannot comment on the small differences that were not apparent between the exposed and unexposed subjects in the visual assessment.

It has previously been found that patients with CNS complaints, putatively due to organic solvent exposure, had significantly delayed P-300 latencies compared with unexposed referents. Furthermore the length of exposure was related to P-300 latency, but it is unclear to what extent this finding may have been explained by age. Whether these findings were caused by organic solvent exposure or not remains to be elucidated (91).

To our knowledge AEP-300 has not previously been studied in solvent-exposed workers regardless of whether they showed symptoms or not. The lack of effect in our study suggests that AEP-300 is not very sensitive to possible irreversible solvent-induced effects.

Vibration thresholds

One aim of the study was to investigate whether occupational exposure to organic solvents increases the risk of chronic damage to the CNS. According to the previous literature on the association between organic solvent exposure and effects on the peripheral nervous system we had little reason to suspect any more marked effects from common paint solvents on peripheral nerves. However, vibrometry was included since it was at hand at our laboratory and since some authors have reported increased vibration threshold among solvent-exposed workers. We did not attempt to make a full investigation of the peripheral nervous system.

We found no differences between the painters and carpenters examined in stage II with regard to vibration thresholds on the back of the hand, the lower leg, or the top of the foot. With a tuning fork, however, we found a clear tendency for reduced sensitivity to vibration in the big toe, on both the right and the left side, when the painters in the intermediate- and high-exposure groups were compared with the carpenters.

Bleeker et al (87) found that for paint-factory workers the vibration thresholds of the second toe on the dominant side clearly rose with increasing average exposure level during the exposed years. Clear effects on vibration thresholds at various locations on the foot have also been found in most other cross-sectional studies of workers exposed to mixtures of organic solvents (7, 92, 93).

Elevated vibration thresholds may be a result of disturbed function in both the central and peripheral nervous systems. Our findings are difficult to interpret, but the results of the more objective examination method used to determine vibration thresholds in the intermediate- and high-exposure groups chosen for stage II of our study suggest that any earlier differences between the painters and carpenters may have been reversible. It has

already been shown that, at least with regard to the peripheral nervous system, alcohol-induced neuropathy can be reversible (94).

Magnetic resonance tomography of the brain

The studied MRT measures showed no clear difference between the 15 painters and the 15 carpenters who were examined. The results suggested an elevated occurrence of expansion of spaces filled with cerebrospinal fluid in the group of painters, since definite signs of such expansion were observed in four of the painters but in only one of the carpenters and there was a clear tendency for the painters to have a wider third ventricle than the carpenters. These results are compatible with observations of signs of increased brain atrophy made in a few earlier computerized tomography studies of patients with the diagnosis of chronic toxic encephalopathy due to solvent exposure (95, 96), whereas in one study (97) no increased atrophy was found. Our observations are also compatible with the findings in another study of a group of patients with this diagnosis; in that study it was found that MRT could show atrophy better than computerized tomography (98).

Mikkelsen et al (10) have reported that increasing cumulative solvent exposure is associated with increasing atrophy observed in computerized tomography. However, the examined group had originally been chosen because of CNS symptoms, and the study was thus more like an examination of a group of patients.

The expansion of the spaces filled with cerebrospinal fluid at the expense of the brain may be due to brain atrophy, but it has also been found to vary with changes in functional conditions. In a Swedish study (7) of workers exposed to solvents, computerized tomography indicated some tendency towards increased brain volume at the expense of the spaces filled with cerebrospinal fluid. It is also well known that the relative sizes of these spaces and brain tissue varies noticeably with dehydration, with cortisone treatment (99), with various stages of alcoholism (100), and with several other metabolic conditions. These observations indicate that the hydration of the brain has some effect on brain volume and thus also on the width of the interstitial spaces, particularly fissures and sulci. Thus it is unclear to what extent an observed expansion of spaces filled with cerebrospinal fluid indicates true brain atrophy. The presence of such expansion seemed weakly or not at all related to the occurrence of neuropsychiatric symptoms, a finding which suggests that determinants other than atrophy may have been operating.

Relaxation time measures showed no differences between the groups. The relaxation times T1 (the longitudinal or spin-lattice relaxation) and T2 (the transverse or spin-spin relaxation) reflect primarily water content and

water bound in the tissues. T1 is considered to be primarily an expression of free water ("bulk water") or interstitial water, and for that reason it was chosen for careful assessment in this study. T1 values also depend on a large number of physical and chemical factors of tissues, such as temperature, oxygenation and pH, and they vary naturally within wide limits, with a standard deviation on the order of 10%.

Our examination showed no definite functional disturbance with effect on the hydration of the white matter as reflected by T1 measurements. The same seems to apply to central structures, where however only thalamic could be assessed in this study.

White matter changes of the small-nodule type, which are characterized by high signals on T2-weighted pictures, had the same frequency in the groups of painters as in the referents. There were no differences in character, size, or extent from those commonly seen in older individuals and those which are probably due mostly to demyelinating centers connected to arteriosclerotic penetrating arteries (101).

Interactions between solvents and alcohol

In our study of psychiatric diagnoses and diagnoses leading to early disability retirement among the painters and carpenters in the cohorts from which we obtained our subjects, we found that psychiatric diagnoses were over-represented among painters and that alcoholism was by far the most common psychiatric diagnosis, especially among the painters (28). The results of the study suggested an interaction between solvent exposure and high alcohol consumption, such that a combined exposure greatly increases the risk of a neuropsychiatric diagnosis. These conclusions are also supported by the results of another study (66). Among toluene-exposed workers alcohol consumption has been shown to increase with increasing toluene exposure (102).

In this study we did not find that alcohol consumption increased with increasing solvent exposure or that alcohol consumption and solvent exposure acted synergistically to increase the likelihood of any of the outcomes. We and others have previously shown that high alcohol consumption is probably necessary for the appearance of interactive effects (28, 66). In our present study only a few individuals had high alcohol consumption, and our present findings are incompatible with our earlier ones.

Are solvent exposure estimates other than cumulative exposure more closely related to risk of neuropsychiatric disorders?

Most studies of neuropsychiatric effects among solvent-exposed workers have used exposed-unexposed compar-

isons or number of years exposed as exposure estimates. In studies in which exposures have been estimated the estimation has generally concerned cumulative solvent exposure.

A few studies have used other exposure estimates, most commonly average exposure during the exposed period (ie, the cumulative solvent exposure divided by years exposed) (68, 75, 87, 103). The authors have generally reported some associations between this estimate and outcomes, but the overall impression is that their findings are no more impressive than in the cross-sectional studies that use cumulative exposure. The major rationale for using average exposures seems to be that this index is generally not confounded by age (75).

In our study average exposures were found to be somewhat confounded by age, due to the decreasing exposure levels in similar tasks over time and the requirement for all participants to have been at least 10 years in their trade. Calculations performed for the effects of average exposure on the summary assessment of neuropsychiatric symptoms and the block design test showed similar results when compared with the cumulative estimate. If average exposures were divided into groups according to the same principle used for cumulative exposure (25% in low exposure, 50% with intermediate exposure, 25% with high exposure) nine men classified as having low cumulative exposure moved to intermediate average exposure and eight men classified as having high cumulative exposure moved to intermediate average exposure and vice versa. Thus, in our study, average exposure could not be expected to yield very different exposure-response relationships than cumulative exposure.

In a study in which cumulative solvent exposure was calculated according to Mikkelsen et al (10) no relationship was found between this exposure estimate and psychometric test results, while limited effects were found for recent exposure and occasions of lightheadedness (104).

Apart from cumulative exposure, the exposure estimates used by us were exposure during the last year, in order to exclude subacute effects, number of peak exposures, reflected by occasions with lightheadedness, and comparatively long-term heavy exposure, reflected by the number of exposure-limit months accumulated during the most exposed year. The two latter estimates assume that exposures above a certain threshold will cause relatively more marked effects than exposures below the threshold. We did not find that any of these exposure estimates was consistently more strongly associated to the outcomes than cumulative exposure. This finding supports the conclusion that the generally weak effects of cumulative solvent exposure seen in our study were not due to an inappropriate choice of exposure estimate.

Concluding remarks

The fact that symptoms usually associated with solvent exposure became more common with increasing exposure may be regarded as confirmation that the symptoms were caused by the exposure. The interview questions pertained to just the sort of symptoms that in previous studies have repeatedly been shown to be connected with exposure, a result which also supports a real association.

That most of our outcomes showed no differences between the painters and the carpenters may be at least partially explained by the fact that the subjects' solvent exposure had dropped markedly in the decade prior to our study. If so, some of the effects documented in previous cross-sectional studies might also have been acute or subacute and reversible over time. Our data on previous psychiatric problems reported by the painters and carpenters indicate, however, that serious problems of this nature were not clearly more prevalent among the painters in the past either.

For the majority of the outcomes that did not show average differences between the painters and the carpenters, the painters in the low-exposure group had a tendency to do better than the carpenters and those in the high-exposure group tended to do worse. The differences between these two groups of painters were often fairly large.

Cumulative exposure was related to age, and age might therefore be an alternative explanation of the differences between the three exposure groups of painters, as well as between these and the carpenters. We included age in all of our analyses, however, and the results were the same as when only the effect of solvent exposure was analyzed. In addition, age was seldom related to the outcomes even when only the effect of age was studied, probably due to the fact that we studied individuals within a fairly small age range (15 years).

In a simultaneous study of changes in performance on conscription tests over time (Michélsen & Lundberg, unpublished manuscript), we found a definite improvement over time among the painters with low exposure, whereas the highly exposed painters did not improve. The carpenters and the painters in the intermediate-exposure group were in between. These results seem to agree with several of the findings of the present study. Mikkelsen et al (10) also found that the psychometric test results were frequently better than referent's results among painters with low exposure and worse among those with high exposure.

Some likely explanations for these observations are the following:

1. If solvent exposure is experienced as unpleasant, individuals with better qualifications may have chosen to minimize their exposure on the job or to change jobs, while individuals with less potential would more likely

have had to remain in the same job and exposure. In this case our findings would be an expression of a selection within the profession due to acute solvent effects, and they would not reflect chronic neuropsychiatric effects of solvents.

2. If a selection occurred within the profession because of the acute effects of solvents, it is also probable that painters who switched to other jobs often sought jobs with generally better work conditions and more intellectual challenge, which may be associated with a generally low frequency of symptoms (105) and better results on psychometric tests. The inferior performance of the highly exposed painters in most stages of this study could thus be an effect of exposure. If such a hypothesis is to be considered probable, the standard deviation of the results would have to be greater for the group of painters than for the group of carpenters, and for most of the results the standard deviation was somewhat greater for the painters than for the carpenters.

Several other explanations may be offered which we consider less likely:

1. An exposure equivalent to that of the low-exposure group in our study improves neuropsychological status, whereas exposure equivalent to that of our high-exposure group makes it worse. This explanation must be regarded as extremely unlikely, since the painters in our low-exposure group also had high exposure to solvents and such exposure has never previously been associated with a better-than-expected neuropsychological status, except with regard to certain psychometric tests in the study by Mikkelsen et al (10).

2. Some exposed subjects with neuropsychiatric symptoms may have overestimated their exposure in comparison with those without problems. The detailed exposure interview should have considerably reduced the risk of such misclassification. In order to eliminate this possibility, it would be necessary to have access to objective information on earlier work conditions that could be compared with the reported information, but data of this nature were not available.

3. If the job of painter offers greater opportunities for intellectual development to most painters than the job of carpenter to most carpenters, carpenters constitute an unsuitable reference group for painters and painters with low exposure should be expected to show symptom frequencies and psychometric test results that painters with intermediate and high exposure would have exhibited if they had not been exposed to solvents. However, there is no evidence that the carpenters were an unsuitable reference group. On the contrary they were very similar to painters regarding the conscription test results, socioeconomic circumstances, education, and the like.

Most of these hypotheses are difficult to test. A study of initial selection to the profession of painter in relation to personality and primary intellectual capacity and the

relevance of these factors to the subsequent selection of those leaving the profession would provide answers to some questions. It could be possible to use an interview study to discover why some painters get high exposure to solvents while others get low exposure. A study comparing the distribution of job requirements over time in the painting profession with that in similar professions would also be enlightening, but would be extremely difficult to carry out.

In forthcoming studies we intend to explore the suggested possible selection processes among painters and to describe the pattern of diagnoses leading to early retirement when the oldest members of the original cohort have passed the normal retirement age of 65 years.

Our study shows that cumulative exposure to solvents below about 130 exposure-limit months does not lead to lasting effects or functional disturbances of the nervous system, as measured by the methods we used.

An exposure of about 130 to 250 exposure-limit months was related in our study to an elevated risk of symptoms associated with chronic toxic encephalopathy and showed an indication of effects on one psychometric test, which, however, seemed to be entirely or partly due to confounding from recent exposure.

Exposure above about 250 exposure-limit months was related to a much higher risk of symptoms associated with chronic toxic encephalopathy, slightly worse results on a few psychometric tests, a probable increase in the risk of psychiatric diagnosis, and a probable increase in risk for the expansion of areas filled with cerebrospinal fluid at the expense of the brain, as measured with MRT. The last finding may have several determinants, brain atrophy being one.

A cause-effect relationship between the solvent exposure and the symptoms associated with toxic encephalopathy thus seems probable.

In the psychometric tests, the tendencies for the highly exposed painters to achieve worse results than the carpenters was balanced by the tendency for the painters with low exposure to do better. It could not be determined in our study whether the differences between the groups of painters were effects directly attributable to exposure or effects of the conceivable selection factors that were described. Since only persons with high exposure were interviewed for psychiatric diagnosis and examined with MRT, our study may not determine whether the tendencies towards increased morbidity among the highly exposed painters were a result of solvent exposure or a result of selection factors.

Thus, apart from neuropsychiatric symptoms, very slight effects clearly attributable to organic solvent exposure were found. This finding indicates that the pseudo-longitudinal design did not add a substantial number of painters to the study group which had left the job because of irreversible neuropsychiatric illness.

The results of the study are compatible with the aforementioned probable interaction between alcohol consumption and solvent exposure, a finding which postulates that the neuropsychiatric effects of solvent exposure are more apparent among those who also have high alcohol consumption. In our study there were few individuals with high alcohol consumption, and, provided that the hypothesis is correct, there were small possibilities of detecting clear differences between the exposed and unexposed individuals.

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