

Effects of long-term exposure to solvents in the paint industry

A cross-sectional epidemiologic study with clinical and laboratory methods

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ØRBÆK P, RISBERG J, ROSÉN I, HÆGER-ARONSEN B, HAGSTADIUS S, HJORTSBERG U, REGNELL G, REHNSTRÖM S, SVENSSON K, WELINDER H. Effects of long-term exposure to solvents in the paint industry: A cross-sectional epidemiologic study with clinical and laboratory methods. *Scand J Work Environ Health* 11 (1985): suppl 2, 00 p. The effects of organic solvents on 50 male workers exposed 5—46 (mean 18) years were studied with a cross-sectional design. Referents were matched pairwise according to age and education. An analysis of confounders confirmed good comparability between the two groups. As indicators of organic brain dysfunction regional cerebral blood flow was measured and the power spectrum of the subjects' electroencephalograms was analyzed, the former being reduced 4 % and the latter showing increased power in the delta and beta bands in the exposed group. Symptoms of brain dysfunction were significantly more frequent among the exposed subjects and showed an exposure-effect relationship. Neuropsychological tests revealed definite indication of brain dysfunction in 14 % of the exposed subjects in comparison to none in the reference group. The exposed subjects performed significantly worse than the referents in tests measuring focused attention abilities. A neurophysiological examination of the peripheral nervous system showed no difference between the groups. Clinical chemistry demonstrated no differences that could be explained by solvent exposure.

Key terms: brain dysfunction, clinical chemistry, exposure-effect relationship, neurasthenic rating scale, neurography, neuropsychological testing, organic psychosyndrome, power spectrum analysis of electroencephalography, regional cerebral blood flow.

Introduction

The central nervous system has been recognized as a target organ for the toxic effects of organic solvents because of the acute narcotic effects that follow high exposures. Even the possibility of chronic mental disorders induced by long-term exposure to solvents has been pointed out (49). Case reports have continued to discuss this possibility (2, 6, 13). Epidemiologic studies using case-referent, historic cohorts and cross-sectional methods have given further evidence of mental disorders induced by long-term exposure to solvents (8, 26, 62, 66). The symptoms of the patients are, eg, fatigue, poor concentration, emotional instability, recent memory problems, and headache (44, 45, 56). This symptomatology is usually referred to as the neurasthenic or chronic organic psychosyndrome (65, 86, 89).

The neuropsychological test performance of exposed subjects has been studied extensively with diverse results, but the overall tendency has been towards poorer performance by exposed subjects than by non-exposed referents (4, 26, 33, 38, 42, 50, 55, 57).

To confirm the suggested organic brain dysfunction, electroencephalography (EEG) with visual reading has been applied in several studies, but no consistent effects have been shown. On the basis of subjective judgement of the EEG recordings according to principles generally used in clinical neurophysiology, the same proportion of EEG abnormalities has been found in a group of car painters as in the reference group of the same study, although workers with symptoms indicating an effect on the central nervous system showed a higher frequency of abnormalities (48, 76, 78). Among a group of patients with a diagnosis of chronic solvent poisoning, the percentage of EEG abnormalities was much higher, 64–67 % (79). The abnormality was, in most cases, reported as “a slight increase of slow waves in the waking record” (77, 79). An increase in fast activity (β) has also been reported for subjects with long-term exposure to mixtures of solvents and to styrene

(74). This observation has later been reproduced by Seppäläinen et al (79). To avoid the subjective component in EEG classification, automatized EEG frequency analysis was used in an investigation of car and industrial painters, and no significant differences between the solvent-exposed and their referents were found (26). In the present study we chose to use power spectrum analysis of EEG recordings from four separate areas of the brain.

A more recently developed method for studying brain function is regional cerebral blood flow (rCBF). It has proved very valuable in differential diagnoses of organic brain disease causing dementia (69, 71). The development of rCBF measurement with the ¹³³xenon inhalation method has provided the possibility to examine even healthy subjects in epidemiologic research. Pilot studies on solvent-exposed subjects have demonstrated a slightly reduced flow (61) and a substantial reduction in nine patients with solvent-induced organic psychosyndrome (7).

Toxic damage to peripheral neurons by certain well-defined solvents has been well established (17, 85). Early changes in the function of distal cutaneous nerves due to solvent toxicity have been demonstrated neurophysiologically by decreased sensory action potentials (15, 53, 54). Similar changes have been noted by us among workers with long-time exposure to styrene or mixtures of solvents (74). Peripheral neurography can demonstrate abnormalities of nerve conduction velocities and nerve action potentials before clinical signs of polyneuropathy appear.

Well-known toxic effects of benzene on bone marrow and of carbon tetrachloride and ethanol on the liver have placed clinical chemistry in a central position in the health control of solvent-exposed workers (12, 16, 29). Some reported results from carefully selected subgroups have, albeit the use of doubtful methodology, claimed that low exposure to solvent mixtures could be toxic to the liver (22, 52, 84).

Objectives and hypotheses

The main objective of the study was to search for solvent-specific changes in rCBF values according to the hypothesis that the organic involvement of the

brain should reduce the flow. Second, we wished to confirm the earlier-reported EEG observations by use of the objective power spectrum analysis of EEG

recordings. Increased power in slow and fast wave bands was expected. Present knowledge of solvent-induced mental effects gave expectations of more neuroathenic complaints in the exposed group, which was also expected to perform more poorly on some tests measuring intellectual and cognitive function and psychomotor performance. The aims of the study on the peripheral nervous system were to look for reduced nerve potential amplitude and late components in sensory nerve potentials as signs of solvent toxicity.

Reduction of conduction velocities and raised thresholds for temperature and vibration sensation would also demonstrate solvent impairment of peripheral nerves. Finally, we were interested in evaluating the covariation of any pathological findings and in determining whether an exposure-effect relationship could be established. With the use of blood chemistry we wished to determine whether any observed difference between the groups could be explained by solvent exposure.

Subjects

It was decided to examine 50 exposed subjects and 50 unexposed subjects (referents) matched according to age and educational level in three degrees. Inclusion criteria for the exposed group were a minimum of 10 years' employment in a solvent-handling occupation and Swedish as the subject's principal language. Exclusion criteria were any known disorders that could affect the nervous system, such as birth trauma, epilepsy, severe skull trauma, cerebral ischemic episodes, diabetes mellitus, alcohol or drug abuse, and earlier mental illness. Hobbies with the use of great amounts of solvents were not allowed. The referents were to fulfill the same criteria and were never to have been occupationally exposed to solvents.

During the planning phase of the study we were contacted by a large paint producing corporation because

of its concern about the increasing attention being given to solvents as a possible cause of toxic encephalopathy. After discussions with the security organization at the plant we selected 54 subjects who worked in the paint production section. Only 15 of this group fulfilled all the criteria. Too short an exposure time or Swedish as a secondary language among immigrant workers excluded 32 persons. Five workers were excluded for medical reasons, and two did not want to be examined. A second round included 41 subjects, who had worked in the production section earlier but had been promoted or transferred to another work-site in the plant. Medical reasons excluded three persons, and an additional three abstained from examination. The final study group consisted of 50 exposed workers aged 27–64 (mean 42) years, who fulfilled all the criteria. They were matched pairwise by 50 referents, who were employed by a nearby sugar refinery and who had never been exposed to neurotoxic agents. The age-matching succeeded with only one year as the mean difference and four years as the maximal difference between the matched pairs. Eighteen of the pairs had a primary school education (seven years) only, 24 pairs had completed 10 years of formal education, and eight pairs had a university degree. All 100 men adhered to their ordinary work schedule and gave their written consent to participate in the study.

Analysis of possible confounding showed that the most likely potential confounders concerning life-style and medical, mental, and sociological factors were well under control. The pairwise matching established a good basic comparability between the two groups. Further control revealed no anthropometric or life-style differences (table 1). A family history of mental or neurological disorders was reported by 16 % of the exposed and 20 % of the reference subjects. Alcoholism in families was reported by 12 % of the exposed and 26 % of the reference subjects. Very few in each group had ever sought professional help for mental problems, but 40 % of the exposed and 38 % of the referents

Table 1. Anthropometric and some life-style characteristics of the exposed and reference groups.

	Exposed group (N = 50)	Reference group (N = 50)
Weight (kg)		
Mean	80	76
SD	13	9
Range	55–131	60–120
Height (cm)		
Mean	179	178
SD	6	6
Range	158–189	167–193
Number reporting use of alcohol		
<200 g/week	43	44
200–400 g/week	6	6
>400 g/week	1	—
Number reporting use of CNS-active drugs ^a		
Never	45	48
Occasionally	4	2
Regularly	1	—
Cigarettes smoked/d		
Quartile 1	—	—
Median	—	2
Quartile 3	15	15
Range	0–20	0–40

^a CNS = central nervous system.

had experienced brief mental disturbance during life crises. They had all performed at ordinary levels in school and during military service. All 100 subjects had

had steady employment since they left school, and during the study period the psychosocial situation of all the subjects was stable.

Exposure

Sporadic measurements of the concentration of solvents in the air have been performed in the factory since 1970. These measurements are not representative for the environment of the whole group. More substantial measurements were first done in 1978. Twenty-six of the exposed group mainly worked in laboratories with control analyses, product development, service or sale and were not subjected to solvent monitoring. In the alkyd paint section, where four exposed subjects worked, there had only been exposure to white spirit. At the other work localities [industrial paint section involving mixing, grinding, tinting, finishing, and tapping (17 exposed subjects); miscellaneous (3 exposed subjects)], the exposure had been to mixtures of solvents. In the past there had been a tendency towards the use of more slowly evaporating solvents, and recently the production of water-based paints had increased.

The production of industrial paints was transferred to a new department in 1969. Until then the work environment in the old factory had been, by and large, unchanged. From 1970, and especially from 1976, on efforts were made to reduce the solvent exposure. We found no data to support precise calculations of exposure levels for individual workers over the years. However, we came to the conclusion that a qualified estimate of the exposures was feasible.

Methods

All participating workers were interviewed regarding exposure history. A compilation of the measurements in the factory was supplemented with measurement data from other similar paint factories (3, 27). Färgindustrins arbetsmiljö (27) has reported measurements from 10 factories and Andersson & Rosén (3) reported later measurements from eight of these same factories. We have assumed that the solvent exposure in the factory studied had been close to the average of the other 8–10 factories. These measurement data have been supplemented by interviews with persons who had long experience in the corporation.

We report the solvent exposure levels related to the Swedish occupational standard (OS) for mixtures of solvents, here called hygienic effect (HE) (5). The

hygienic effect from a mixture of solvents is defined as:

$$HE = C_1/OS_1 + C_2/OS_2 + \dots + C_n/OS_n,$$

where C_1 is the observed atmospheric concentration of solvent 1 and OS_1 the occupational standard for the same solvent. As the unit for our calculations we have used HE 1.0 according to the Swedish occupational standards from 1982 (5).

The results of measurements have often been presented only in terms of hygienic effect. To make it possible to compare results from years with different hygienic standards, we have calculated the average change in the hygienic standard for the eight solvents most frequently used in the factory. These solvents were as follows (occupational standards for 1982 in parentheses): acetone (250 ppm), butanol (50 ppm), butyl acetate (150 ppm), ethanol (1 000 ppm), ethyl acetate (200 ppm), white spirit (85 ppm), methyl isobutyl ketone (50 ppm), toluene (80 ppm), and xylene (80 ppm). The following relative values expressed in our unit HE 1.0 (1982) were determined: 1969: 1.75, 1974: 1.25, 1978: 1.15, 1982: 1.0.

Average exposure levels for different work tasks or sections of the factory were calculated for three different time periods (up through 1969, 1970–1975, 1976 on) (table 2). For each individual the accumulated solvent dose was calculated as the sum of the exposure time (in years) multiplied by the average exposure level for exposure during the three time periods.

Results

The distribution of the subjects' exposure indices expressed in the unit $HE \times \text{years}$ is given in figure 1. The arithmetic mean of the exposure indices is 16 $HE \times \text{years}$ (range 1–68). Fifty percent of the group had been exposed to less than 10 $HE \times \text{years}$. For the exposure-effect calculations, three subgroups were defined (table 3). All the subjects were active workers at the time of the medical examinations. The investigations were performed on Mondays with the intention of reducing effects from actual exposure. However we are aware of the fact that solvents are not completely eliminated from the body in 3 d. Using the

Table 2. Estimated exposure levels determined as the hygienic effect (HE) discussed in the text and based on reference 5.

Work area	Period		
	1969 and earlier	1970—1975	1976 and later
Industrial paint section			
Mixing	2.00	1.30	0.70
Grinding	3.00	1.80	0.90
Tinting-finishing	2.20	1.50	0.60
Tapping	2.20	1.20	0.60
Cleaning of vessels	4.50	3.00	1.50
Alkyd paint section			
Mixing	..	..	0.10
Tinting-finishing	..	..	0.20
Tapping	..	..	0.20
Small batch manufacturing	..	1.40	0.70
Filler manufacturing	0.20	0.15	0.10
Storage	0.20	0.15	0.10
Cellulose paint section	2.50	..	..
Laboratory			
Product development	0.70	0.40	0.15
Control laboratory	1.00	0.75	0.40
Process engineering	2.00	1.00	0.40

Table 3. Exposure subgroups according to the exposure index.

Subgroup	N	Mean	Range
Low exposure	17	2.6	1—5
Medium exposure	18	9.9	6—15
High exposure	15	38.8	18—68

Table 4. Relation between the exposed subjects' actual exposure according to the hygienic effect (HE) determinations and their subgrouping according to the accumulated exposure index. (See table 3.)

Exposure index	Actual exposure (HE)		
	<0.1	0.1—<0.4	0.4—<0.6
Low	8	6	3
Medium	8	7	3
High	—	5	10
Total number	16	18	16
Exposure index mean	6.6	14.6	27

Statistical methods

The statistical method most frequently used in the analysis of the recorded variables was Student's paired t-test, in which each exposed person was compared with his matched referent, variable by variable. When analyses of certain sets of variables were carried out simultaneously, Hotelling's T-test was used for mul-

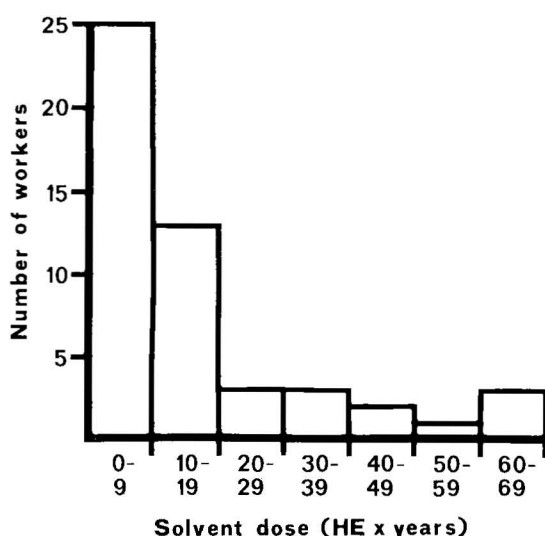


Figure 1. Distribution of the accumulated exposure index. (HE = hygienic effect)

actual exposure levels, we again divided the exposed group into three subgroups (table 4).

Commentary

Many objections can be raised against calculations that, to a substantial extent, are based on general estimates. However, we think that the exposure was described for the group as a whole in a realistic way and that we were able to distinguish well enough between the high- and low-exposed subgroups. Admittedly, the errors in individual calculations must be considerable. The differences in the individual's subgrouping according to the exposure index and actual exposure are too small to allow statistical control for the acute effects of solvents remaining in the body after an exposure-free interval of 72 h.

tivariate comparisons. In cases in which dichotomous variables were considered, methods based on the binomial distribution were used.

Missing values in the material were generally caused by temporary malfunctioning in technical devices, and they were few. They were not considered to be sys-

tematic in appearance and should not have introduced any bias into the analysis. Consequently no special analysis was carried out for missing values.

The statistical analysis of the data was performed at the Department of Statistics, Lund University. The well-known statistical system BMDP was the main tool (21).

It should be pointed out that a well-known statistical problem, the mass-significance problem, occurs in an analysis of a variable set of this size (almost 500 variables). Even when no real difference exists, it is

likely that certain variables show a statistically significant result by pure chance. It is therefore of utmost importance that all differences found in the investigation between the two groups be scrutinized and considered in relation to the other results. Differences caused by mere randomness are mostly single-handed and difficult to explain.

Though in certain areas a hypothesis could have been established prior to the investigation, we have performed all statistical tests in the same way and consequently used two-sided tests in all parts of the investigation.

Clinical examination and clinical chemistry

Methods

Before their visit to the Department of Occupational Medicine all subjects answered a questionnaire with 60 questions about general health, symptoms of the nervous system, and life-style. Later, a specialist in occupational medicine took a complete medical, social, and occupational history. The answers given by the subjects on the questionnaire were reviewed with special attention to drinking habits and drug use. Finally the subjects were given a complete neurological and physical examination. Blood samples were taken with the subjects fasting. The analyses were carried out at the Department of Clinical Chemistry at the Malmö General Hospital. Blood cells were counted by a Linson counter 431. Serum enzymes were analyzed by an auto-analyzer using recommended Scandinavian methods (18, 19, 20). Serum cholesterol and high-density lipoprotein cholesterol were also included in the auto-analyzer package (14, 72). Serum amylase isoenzymes and plasma proteins were determined by agarose gel electrophoresis (47, 82). Serum bilirubin was initially not included in the autoanalyzer package but was included during the study together with a new method of analysis.

Results

None of the 100 subjects had signs of any major disease that could affect the nervous system or daily life activity. Two subjects in each group had clinical signs of slight neuropathy. Only 78 % of the exposed group considered themselves to be in good health compared to 94 % of the referents ($p < 0.05$). Of the exposed group 52 %, and of the referents 28 %, experienced mental exhaustion during the workday ($p < 0.05$).

Physical exhaustion was rare in both groups (16 % of the exposed, 10 % of the referents). The exposed subjects complained more of symptoms from the central and peripheral nervous system; they had also more psychosomatic symptoms (table 5). There was a trend towards an increased number of symptoms in the subgroup with the highest exposure index.

Multivariate analysis of the results of the blood analyses revealed an overall statistically significant difference between the groups (Hotelling's T-test, $p = 0.0025$). Blood cell counts were generally lower in the exposed group (table 6). The leukocyte differential count showed a different distribution of leukocytes in the two groups (table 6). The exposure-effect relationship was considered in a regression analysis with exposure index as the independent variable. No variation of the observed blood cell counts could be explained by the subjects' exposure index.

The serum enzyme activities varied mostly within the reference ranges, but, as expected, some extreme values were found in both groups (table 7). No consistency was found in the group differences. Differences between the three subgroups defined by exposure index were considered in an analysis of variance. No statistically significant differences were found, and consequently an exposure-effect relationship could not be demonstrated. Serum bilirubin has been reported semi-quantitatively because the laboratory changed the method of analysis during the sampling period (table 8). The subjects with levels exceeding $20 \mu\text{mol/l}$ had normal values in a later control. The two subjects who had values above $30 \mu\text{mol/l}$ were diagnosed to have constitutional hyperbilirubinemia. Plasma protein electrophoreses were done only on plasma from the exposed subjects. The results had the same dis-

Table 5. Symptoms of the central and peripheral nervous systems and psychosomatic symptoms reported by the exposed and reference groups.

Symptom	Exposed group (%)	Reference group (%)	p-Value ^a
<i>Neurasthenic and emotional</i>			
Fatigue	62	2	<0.01
Recent memory failure	56	10	<0.01
Concentration difficulties	20	6	NS
Mood lability	12	2	NS
Depressive feelings	8	0	NS
Irritability	26	4	<0.01
Vertigo	4	0	NS
Alcohol intolerance	16	8	NS
Sleep disturbances	14	6	NS
Tremor	12	6	NS
<i>Peripheral</i>			
Tingling paresthesia	30	4	<0.01
Creeping paresthesia	20	2	<0.01
Numbness	24	0	<0.01
Restless legs	10	0	NS
<i>Psychosomatic</i>			
Headache	32	8	<0.05
Excessive sweating	16	4	<0.05
Chest oppression	26	4	<0.01
Cardiac palpitations	16	4	NS
Dyspepsia	38	26	NS
Sexual dysfunction	6	0	NS

^a NS = not significant.

Table 6. Blood cell counts and differential counts of the leukocytes of the exposed and reference groups.

	Mean	SD	Range	p-Value ^b
<i>Blood cell counts^a</i>				
<i>Hemoglobin (g/l)</i>				
Exposed group	152	11	122—173	
Reference group	152	9	135—172	NS
<i>Erythrocytes (10¹²/l)</i>				
Exposed group	4.6	0.8	4.0—5.6	
Reference group	4.8	0.4	4.0—6.0	NS
<i>Leukocytes (10⁹/l)</i>				
Exposed group	6.1	1.9	3.1—12.2	
Reference group	6.6	1.8	3.6—11.3	NS
<i>Thrombocytes (10⁹/l)</i>				
Exposed group	205	52	125—340	
Reference group	218	67	110—370	<0.05
<i>Differential count of the leukocytes</i>				
<i>Neutrophils (%)</i>				
Exposed group	57	10	35—76	
Reference group	51	11	30—77	<0.01
<i>Eosinophils (%)</i>				
Exposed group	2.6	1.9	0—8	
Reference group	2.4	1.8	0—6	NS
<i>Basophils (%)</i>				
Exposed group	0.7	0.7	0—2	
Reference group	0.8	0.8	0—3	NS
<i>Lymphocytes (%)</i>				
Exposed group	33	9.6	17—59	
Reference group	39	11	11—60	<0.01
<i>Monocytes (%)</i>				
Exposed group	5.5	2.6	0—13	
Reference group	6.3	2.9	1—13	NS

^a Reference values of the laboratory: hemoglobin 131—163 g/l; erythrocytes 4.1—5.4 · 10¹²/l; leukocytes 4—10 · 10⁹/l; thrombocytes 125—340 · 10⁹/l.

^b NS = not significant.

Table 7. Serum enzyme values determined for the exposed and reference groups.

Enzyme ^a	Mean	SD	Range	p-Value ^b
<i>Aspartate aminotransferase (μkat/l)</i>				
Exposed group	0.38	0.09	0.22—0.72	
Reference group	0.43	0.16	0.23—1.16	<0.05
<i>Alanine aminotransferase (μkat/l)</i>				
Exposed group	0.36	0.17	0.16—1.17	
Reference group	0.42	0.35	0.07—1.99	NS
<i>Lactate dehydrogenase (μkat/l)</i>				
Exposed group	5.4	0.8	3.1—7.8	
Reference group	5.0	0.9	2.3—6.2	<0.05
<i>Glutamyl transferase (μkat/l)</i>				
Exposed group	0.62	0.64	0.23—3.67	
Reference group	0.57	0.42	0.22—1.83	NS
<i>Alkaline phosphatase (μkat/l)</i>				
Exposed group	2.9	0.8	1.1—5.7	
Reference group	2.9	0.7	1.6—4.6	NS
<i>Amylase (μkat/l)</i>				
Exposed group	3.3	1.1	0—6.1	
Reference group	3.2	1.0	0—5.8	NS
<i>Amylase isoenzyme (μkat/l), salivary gland</i>				
Exposed group	1.5	0.8	0—3.5	
Reference group	1.3	0.7	0.1—2.8	NS
<i>Amylase isoenzyme (μkat/l), pancreas</i>				
Exposed group	1.8	0.8	0—4.1	
Reference group	2.0	0.7	0.1—4.0	NS

^a Reference values of the laboratory: aspartate aminotransferase <0.7 μkat/l; alanine aminotransferase <0.7 μkat/l; lactate dehydrogenase <8.0 μkat/l; glutamyl transferase <1.0 μkat/l; alkaline phosphatase <4.6 μkat/l; amylase 1.2—5.0 μkat/l; amylase isoenzyme (salivary gland) 0—2.8 μkat/l; amylase isoenzyme (pancreas) 0.75—2.9 μkat/l.

^b NS = not significant.

Table 8. Serum bilirubin values determined for the exposed and reference groups.

	Bilirubin (μmol/l) ^a		
	< 20	> 20	> 30
Exposed group	45	5	1
Reference group	46	3	1

^a Reference value of the laboratory: 3—20 μmol/l.

Table 9. Results of the plasma protein electrophoresis, performed only for the exposed group (N = 50).

Protein	Reference value ^a	Mean	SD	Range
Albumin (g/l)	40—52	47	4	37—55
α ₁ -Antitrypsin (g/l)	0.90—1.70	1.20	0.22	0.68—1.60
Orosomukoid (g/l)	0.55—1.05	0.81	0.22	0.36—1.40
Haptoglobin (g/l)	0.45—2.75	1.43	0.72	0.45—4.44
Fibrinogen (g/l)	2.0—4.4	3.2	0.8	1.8—5.4
Ceruloplasmin (g/l)	0.22—0.48	0.31	0.07	0.18—0.48
Immunoglobulin G (g/l)	7—15	11	2	6—16
Immunoglobulin A (g/l)	0.5—3.0	1.9	0.7	0.7—3.1
Immunoglobulin M (g/l)	0.4—2.0	0.9	0.6	0.3—3.6

^a Of the laboratory.

tribution as the laboratory's reference material (table 9). Erythrocyte sedimentation rates were equal in both groups and normal in all 100 subjects. Plasma lipid levels were slightly higher in the exposed group, but no statistical significance or exposure-effect relationship was found (table 10).

Commentary

The exposed group had more registered symptoms that could be classified as neurasthenic due to brain dysfunction. This observation gives support to earlier reports on solvent effects (9, 35, 44, 45, 50). The trend towards more symptoms in the subgroup with the highest exposure index indicates that long-term exposure to solvents plays a substantial role in the development of complaints.

Our results of the blood and serum analyses indicate that it is impossible to demonstrate effects of solvents by routine clinical chemistry. These findings agree with those of other authors, who have reported some statistically significant results, but all within the reference ranges of their laboratories (26, 42, 51). As expected, we found some subjects with values above the traditional reference ranges, eg, those for the aminotransferases. The subjects with such high values belonged in equal proportions to the exposed and unexposed groups, and the findings should not be taken as an indication of liver damage, but more reasonably as normal, expected results due to group size and a skewed normal distribution (32, 80). Our results from this and other solvent-exposed groups are consistent

Table 10. Plasma lipid values determined for the exposed and reference groups.

Lipid ^a	Mean	SD	Range	p-Value ^b
Cholesterol (mmol/l)				
Exposed group	5.9	0.9	4.0–8.2	NS
Reference group	5.6	1.1	3.2–8.2	
Triglycerides (mmol/l)				
Exposed group	1.6	1.0	0.6–5.0	NS
Reference group	1.4	0.8	0.7–4.9	
High-density lipoprotein cholesterol (mmol/l)				
Exposed group	1.2	0.3	0–1.9	NS
Reference group	1.1	0.3	0–1.9	

^a Reference value of the laboratory: cholesterol 3.8–8.3 mmol/l; triglycerides 0.4–2.2 mmol/l; high-density lipoprotein cholesterol 0.8–1.7 mmol/l.

^b NS = not significant.

with those of other reports (39, 59, 67, Ørbæk unpublished), and we can only agree with a recent discussion on this matter (52). The evaluation of liver function with advanced methods does not in itself however give evidence of solvent toxicity to the liver under good hygienic control if the subjects have preselected serum enzyme activities above reference values (22, 84). Use of liver tests for routine controls of solvent-exposed workers will lead to a large number of false “pathological” findings. This possibility might induce anxiety and lead to traumatic and expensive diagnostic procedures. These considerations do not exclude possible effects of accidental intoxication due to high exposure levels or interactions with drugs (23, 25).

Psychiatric examination

Methods

A rating scale consisting of 60 items was used in the psychiatric examination. Forty-one of these items referred to symptoms experienced by the person examined (reported variables), and 19 were ratings of symptoms observed by the psychiatrist during the interview (observed variables). The scale had four steps (0–1–2–3). Absence of the symptom concerned was registered as 0 (zero), while 1, 2, and 3 stood for symptom present to a slight, moderate, and pronounced degree, respectively. Symptoms that were part of the neurasthenic syndrome were covered more extensively than other symptoms of mental illness. The basis of the rating scale was taken from the Comprehensive Psychopathological Rating Scale (CPRS) and the Comprehensive Neurasthenic Rating Scale (CNRS)

(1, 63). These rating scales are well established and have proved useful in evaluations of both patients and nonpatients. The possibility of using half scale steps that exists with both scales was not used in the present study, and we added 18 items concerning other symptoms of interest for the study of solvent effects.

The symptoms were rated during a semistructured interview lasting about 45 min. The examination also briefly probed the possible presence of current psychosocial problems that might influence the mental status of the person examined at the time of the interview. The subjects were also questioned about previous medical care due to nervous symptoms, presence of mental illness in the family, abuse (alcohol/drugs), injuries or diseases afflicting the central nervous system, gastric/duodenal ulcer, thyroid disease, diabetes, or migraine.

Table 11. Psychiatric symptoms with scores statistically significantly different in the exposed (E) and reference (R) groups. Percentages relate to pairwise comparisons of the rating points. [Exposed subjects' scoring higher (E > R), lower (E < R), or equal (E = R) to the referents' or symptom absent (E = R = 0) in both]

Variable	E > R (%)	E < R (%)	E = R (%)	E = R = 0 (%)	p-Value
<i>Reported</i>					
Inner tension	32	2	18	48	<0.001
Worrying over trifles	36	8	8	58	<0.01
Hostile feelings	34	2	0	64	<0.001
Mood lability, aggressiveness	34	6	0	60	<0.01
Reduced sexual interest	16	0	0	84	<0.01
Constipation, diarrhea	18	2	0	80	<0.05
Epigastric pain	22	4	0	74	<0.01
Increased sleep	14	2	0	84	<0.05
Headache attacks	30	12	14	44	<0.05
Use of analgesics, headache	34	12	2	52	<0.05
Fatigability	48	2	0	50	<0.001
Concentration difficulties	30	8	0	62	<0.01
Learning problems	32	6	2	60	<0.01
Short-term memory problems	44	8	6	42	<0.001
<i>Observed</i>					
Muscular tension	20	2	0	78	<0.01

The ratings could not be done blind, since it was impossible for the interviewer to avoid knowledge about the workplace of the subjects. He was, however, unaware of the results from the other investigations.

Results

The symptom score for the exposed group was, throughout, higher (tables 11, 12). The most striking differences between the groups were found for symptoms concerning memory function, concentration difficulties, and fatigability, as well as inner tension, worrying over trifles, and hostile feelings. The group-dividing symptoms may roughly be classified as belonging to the neurasthenic/psychoorganic syndrome. The complete list of symptom scores shows that the scoring of zero was, for many symptoms, the dominant outcome in both groups, especially in the case of the observed variables (table 12).

With the aim of investigating a possible connection with exposure, we calculated the sum of the scores that each exposed subject received for the group-dividing symptoms listed in table 11. These sums of scores were tested for possible covariation with the exposure indices. A statistically significant correlation was found (Spearman rank correlation $r = 0.49$, $p < 0.001$). There was no significant correlation between the symptom scores and age.

Table 12. Psychiatric symptoms with scores that were not statistically significantly different in the exposed and reference groups. Percentages relate to pairwise comparisons of the rating scores. [Exposed subjects' scoring higher (E > R), lower (E < R), or equal (E = R) to the referents' or symptom absent (E = R = 0) in both]

Variable	E > R (%)	E < R (%)	E = R (%)	E = R = 0 (%)
<i>Reported</i>				
Sadness	8	8	0	86
Inability to feel	10	4	0	86
Pessimistic thoughts	12	4	0	84
Suicidal thoughts	4	0	0	96
Restlessness	18	6	2	74
Lassitude	8	2	0	90
Indecision	8	2	0	90
Difficulties in falling asleep	8	6	0	86
Early awakening	10	2	0	88
Use of sleeping pills	2	2	0	96
Reduced appetite	2	2	0	96
Sexual impotence	2	0	0	98
Hypochondriasis	8	0	0	92
Rituals	14	4	0	82
Phobias	14	6	2	78
Mood lability, soft-heartedness	22	12	0	66
Ideas of persecution	4	4	0	92
Headache, continuous	2	0	0	98
Aches and pains (not headache)	34	18	12	36
Dizziness	4	0	0	96
Breathing difficulties	10	4	2	86
Sweating, blushing	26	14	6	54
Palpitations	18	16	0	66
Feeling sick, indigestion	2	0	0	98
Increased carefulness	12	4	0	84
Stimulus hypersensitivity	10	6	0	84
Manual dexterity	4	2	0	94
<i>Observed</i>				
Apparent sadness	4	2	0	94
Reduced speech	10	4	2	84
Slowed movement	8	2	2	88
Increased movement	0	2	0	98
Increased speech	4	2	0	94
Agitation	8	2	0	90
Lack of appropriate emotion	8	6	0	86
Lack of appropriate emotional distance	0	2	0	98
Rigidity	6	4	0	90
Circumstantiality	4	2	0	94
Perseveration	4	2	0	94
Mood lability, aggressiveness	0	2	0	98
Fatigability	2	6	0	92
Short-term memory problems	6	4	2	88
Autonomic disturbances	10	12	8	70
Lack of insight	0	4	0	96
Tremor	8	8	0	84
Disturbed gait	4	0	0	96

Commentary

The results of the psychiatric examination show that the exposed subjects had significantly more symptoms of mental disturbance included in the neurasthenic syndrome than the unexposed subjects had. In the majority of cases low scores were obtained for the observed variables, a finding that seems reasonable when it is remembered that it was not patients who were ex-

amined. These findings are in accordance with the results of earlier investigations (26, 50). The correlation between the sum scores and the exposure index

suggests that the heavier the load of exposure to organic solvents, the more frequent and serious the mental disturbances experienced by workers.