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Exposure to organic solvents

A cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system

by Stig-Arne Elofsson, PhD,¹ Francesco Gamberale PhD,² Tomas Hindmarsh, MD,³ Anders Iregren, MSc,² Anders Isaksson, DSc,⁴ Inger Johnsson, MSc,⁵ Bengt Knave, MD,² Eva Lydahl, MD,⁵ Per Mindus, MD,⁵ Hans E Persson, MD,⁵ Bo Philipson, MD,⁵ Maria Steby, MSc,² Göran Struwe, MD,⁵ Erik Söderman, MSc,² Arne Wennberg, MD,² Lennart Widén, MD⁵

ELOFSSON S-A, GAMBERALE F, HINDMARSH T, IREGREN A, ISAKSSON A, JOHNSSON I, KNAVE B, LYDAHL E, MINDUS P, PERSSON HE, PHILIPSON B, STEBY M, STRUWE G, SÖDERMAN E, WENNBERG A, WIDÉN L. Exposure to organic solvents: A cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. *Scand j work environ health* 6 (1980) 239—273. In the present epidemiologic study 80 car or industrial spray painters with long-term low level exposure to organic solvents were examined and compared with two matched reference groups of nonexposed industrial workers (80 persons in each group). The aim of the study was to investigate the possible effects of the solvent exposure on health. The investigation included psychiatric interviews, psychometric tests, neurological, neurophysiological and ophthalmologic examinations, and computed tomography of the brain. The painters' previous and present exposure was carefully assessed by interviews and on-the-job measurements both at modern places of work and in a reconstructed model of a workshop from 1955. On the basis of the psychiatric interviews the psychiatric symptoms were rated according to a specially designed scale of 46 different items, graded in seven steps of increasing severity. The psychological performance was assessed by a battery of 18 tests. The neurological and neurophysiological examinations comprised visual evoked responses (VER), electroencephalography (EEG), and computerized EEG analysis (SPA) for the central nervous system and electroneurography (ENeG), the estimation of vibration sense thresholds, and a quantified neurological examination for the peripheral nervous system. The ophthalmologic examination concentrated on the condition of the lens. Statistically significant differences between the exposed individuals and referents were found for psychiatric items indicative of a slight cerebral lesion (ie, a neurasthenic syndrome). The psychometric tests revealed statistically significant differences between the groups with respect to reaction time, manual dexterity, perceptual speed, and short-term memory. No differences were found with respect to performance on verbal, spatial, and reasoning tests. Significant differences between the groups were also found for the majority of the neurophysiological parameters measuring peripheral nerve functions, the most pronounced occurring in the long, sensory fibers. Moreover EEG and VER showed some differences between the groups, as did the results of the ophthalmologic examination and the computed tomography. Finally, it should be emphasized that the exposure levels, as measured at modern places of work and in the reconstructed workshop from 1955, were found to be considerably lower than the valid threshold limit values in Sweden.

Key terms: computed brain tomography, epidemiology, lens opacities, neurasthenia, neurotoxicology, polyneuropathy.

¹ Department of Statistics, University of Stockholm, Sweden.

² National Board of Occupational Safety and Health, Solna, Sweden.

³ Danderyd Hospital, Danderyd, Sweden.

⁴ The Swedish County Council, Stockholm,

Sweden.

⁵ Karolinska Hospital, Stockholm, Sweden.

Reprint requests to: Dr Bengt Knave, National Board of Occupational Safety and Health, S-171 84 Solna, Sweden.

The acute, narcotic effect of occupational exposure to organic solvents has long been known (14); it has also recently been the subject of systematic and experimental studies (2, 26). In the early literature, there are many case reports of exposed workers with chronic symptoms that indicate a more or less persistent injurious effect on the nervous system (59). A neurasthenic syndrome including abnormal fatigue, concentration difficulties, memory impairment, general irritability, and alcohol intolerance was described already at the end of the 19th century for workers exposed to carbon disulfide and during the first decades of the 20th century for workers exposed to other solvents, ie, trichloroethylene, xylene, terpentine. During 1930–1960 several investigations were published on groups of exposed workers.

The proportion of persons with neurasthenic symptoms was often about 50 %. The values of these results are however limited by the lack of reference material.

It is a fair assumption that the level of exposure was considerably higher during the 19th and the beginning of the 20th century than it is today, when the awareness of the work environment and its health hazards has gradually increased. Too, immediately after the Second World War, the levels of exposure were probably higher than they are today. This assumption is strengthened by the exposure determinations made in connection with a health examination of 50 trichloroethylene-exposed industrial workers (34). In this study in which 34 % of those examined showed signs of a chronic psychoorganic syndrome, the average exposure level was

Table 1. Levels of solvent exposure during different work phases of car and industrial painting. (Number of samples in parenthesis)

Solvents	Exposure, expressed as the hygienic effect ^a of the workphase						Thresh- old limit value (mg/m ³)
	Spray painting		Grinding, filling, masking, assembling		Color mixing, degreasing, cleaning		
	Car painting	Industrial painting	Car painting	Industrial painting	Car painting	Industrial painting	
Total	0.30 (106)	0.24 (243)	0.15 (218)	0.12 (61)	0.28 (137)	0.24 (136)	
Aromates							
Toluene	0.13 (106)	0.05 (243)	0.05 (218)	0.04 (61)	0.13 (137)	0.04 (136)	300
Xylene	0.04 (106)	0.03 (243)	0.01 (218)	0.01 (61)	0.02 (127)	0.02 (136)	350
Styrene	0.04 (28)	0.01 (45)	0.02 (97)	0.08 (18)	0.08 (28)	0.01 (22)	170
Alcohols							
Ethanol	0.01 (51)	0.01 (136)	0.01 (96)	<0.01 (35)	0.01 (60)	<0.01 (51)	1,900
Butanol	0.04 (47)	0.01 (218)	0.01 (103)	— (0)	0.03 (59)	0.02 (22)	150
Propanol	— (0)	<0.01 (58)	— (0)	<0.01 (21)	— (0)	— (0)	500
Ketones							
Acetone	— (0)	<0.01 (45)	— (0)	<0.01 (18)	— (0)	<0.01 (58)	1,200
Methyl ethyl ketone	0.06 (15)	<0.01 (150)	<0.01 (22)	<0.01 (32)	<0.05 (18)	0.01 (58)	440
Methyl-n-butyl ketone	0.25 (6)	0.02 (92)	— (0)	0.05 (18)	— (0)	0.02 (58)	20
Methyl-iso-butyl ketone	0.01 (34)	0.03 (200)	<0.04 (105)	0.01 (53)	<0.01 (52)	0.01 (114)	210
Ethyl amyl ketone	— (0)	0.03 (43)	0.02 (32)	— (0)	— (0)	0.02 (11)	130 ^b
Acetates							
Methyl acetate	— (0)	0.02 (82)	<0.01 (32)	— (0)	— (0)	0.03 (22)	610 ^b
Butyl acetate	0.01 (49)	0.01 (59)	<0.01 (163)	<0.01 (26)	0.01 (82)	0.01 (5)	710
Ethyl acetate	0.01 (106)	<0.01 (198)	0.01 (218)	<0.01 (43)	0.01 (137)	<0.01 (78)	1,100
Iso-amyl acetate	<0.01 (27)	0.01 (54)	<0.01 (32)	— (0)	0.01 (11)	<0.01 (22)	525
Chlorinated hydrocarbons							
Methylene chloride	0.11 (8)	0.03 (45)	0.09 (22)	0.02 (18)	0.07 (30)	0.04 (58)	250
Trichloroethane	— (0)	— (0)	— (0)	— (0)	— (0)	0.57 (11)	380
Trichloroethylene	0.05 (15)	0.13 (161)	— (0)	0.06 (18)	0.04 (11)	0.16 (69)	105
Others							
White spirit ^c	0.17 (28)	— (0)	0.22 (42)	— (0)	0.16 (51)	— (0)	500
Percentage of the total work time	15	60	60	20	25	20	

^a The hygienic effect of a compound is defined as the ratio between the actual amount of the compound and its threshold limit value. For an estimation of the total or additive hygienic effect caused by several compounds with similar effects, when specific information about synergism does not exist, the calculation $C_1/G_1 + C_2/G_2 + C_3/G_3 + \dots + C_n/G_n$ is carried out, where C = the concentration of the compound and G = the threshold limit value of the compound. To avoid the exceeding of the total hygienic threshold limit value, the sum of the ratios are not allowed to exceed the value 1 (61).

^b Swedish threshold limit value does not exist. The value used here is taken from the American Conference of Governmental Industrial Hygienists (5).

^c 17–22 % by weight.

40 ppm, ie, twice as high as the present Swedish threshold limit value (TLV).

Around 1975 the first results from epidemiologic studies on solvent-exposed workers were published in Finland and Sweden. In investigations on industrial workers (52), house painters (9, 39), car painters (38, 75), and jet fuel-exposed workers (44, 45), the results indicated effects on the central and peripheral nervous systems as a result of long-term but relatively low exposure to different organic solvents. When the present study was initiated, the preliminary results of the epidemiologic studies had attracted great attention from both the general public and scientists, and uncertainty reigned as to whether or not the permitted limits could be regarded as adequate.

Against this background, it was considered pertinent to carry out an extensive epidemiologic investigation of a homogeneous group of workers with long-term occupational exposure to organic solvents. In consensus with representatives of employers and trade unions, we decided that car and industrial painters were an appropriate group. After a thorough occupational hygienic exposure determination, 80 spray painters, evenly distributed as to age, were selected as the exposed group and two groups of 80 age- and education-matched workers from the electronics industry were selected as reference groups. A total of 240 workers were then examined with psychiatric, psychological, neurological, neurophysiological, neuroradiological and ophthalmological methods.

EXPOSURE

At the workshops covered in this investigation the painting of repaired cars and new industrial products took place. The surface treatment also included degreasing, grinding, filling, assembling/reassembling of the treated objects, masking of untreated surfaces, and color mixing; the workers also had to clean tools and soiled skin. Analyses of 20 workshops showed that the relative time distribution of different work phases was somewhat different for the two groups of painters (table 1). The industrial painters primarily spray

painted, while grinding, filling and masking occupied most of the work time of the car painters.

The chemical hazards of painters consist of solvents, dust, and metals. Exposure to solvents is the most frequent during color mixing, degreasing, cleaning, and the evaporation from painted surfaces and open cans containing solvents. There is less exposure during the spray painting itself because this work phase is mostly carried out in ventilated spraying boxes and with the use of protective respiratory equipment. However, as shown in table 1, a much larger proportion of the work time of industrial painters is spent on operations involving direct contact with solvents (spray painting, color mixing, degreasing, cleaning) than that of car painters. The workshop studies have shown that industrial painters are exposed to a higher degree than car painters during evaporation from painted objects which are air-dried on the work premises.

Painters are always exposed to several solvents. A total of about 20 different solvents has been found during personal sampling measurements (fig 1), and often the painters are exposed simultaneously to eight to ten substances (49, 81). Table 1 gives a quantitative description of this mixture of solvents in relation to the Swedish TLV. (The description is given as the so-called hygienic effect, see note a of table 1). Toluene is the solvent most frequently occurring in the highest concentration, but high concentrations of xylene, trichloroethylene, and white spirit are also common. The summarized (additive) hygienic effect varies for the different work phases between 0.12 and 0.30. If the time used for each work phase is taken into consideration, a time-weighted average of 0.21 is obtained for the hygienic effect of both car and industrial painting.

The exposure to dust, lead, and chromium is shown in fig 1. Lead is of special interest because of its well-documented neurotoxic effects. The table gives the range of hygienic effects, as well as the mean and the median exposure values, for spray painting and grinding. As a negligible exposure to dust occurs during color mixing, degreasing, and cleaning, no measurements of dust exposure were carried out during these work phases. The range of the exposure values show that the hygienic-

Fig 1. Exposure to dust, lead and chromium during spray painting and grinding. For each occasion of sampling the limits of detection were determined by the amount of sampled dust. For cases in which an exact measurement could not be obtained, a limit was determined which was not exceeded by the real value. In the figure this limit is represented by an unfilled circle. Exact measurements are represented by filled circles.

ic effects are sometimes exceeded during the spray painting of cars and, sporadically, also during the spray painting of industrial components. Generally, during grinding, the exposure level is lower. Calculations of the mean values give higher exposure values than the corresponding median value for all work phases.

The work conditions described are currently valid, ie, the exposure measurements performed in 1975—1977 can be considered to represent the work conditions of the 1960s and 1970s. As many of the painters included in this investigation have been occupationally exposed prior to this period and as the development of chronic effects in the nervous system due to long-term exposure can be suspected, a car-painting workshop was constructed to simulate the work conditions of 1955, and exposure measurements of solvents and lead were carried out. The results from this study have been presented separately (82). The main results are presented in table 2. It appears from the table that the exposure levels of solvents were higher for the simulated model than for the occasions of measurement in 1975—1977, especially with respect to the presence of benzene (additive effect 0.80). It should be observed that the TLV of ben-

zene is low (15 mg/m³) in comparison to that of the other solvents referred to in this report, primarily because of its known effects on bone marrow and the blood and because of the fact that the absolute concentration in the air is therefore relatively low. However, the exposure levels in 1955 fell below the TLV for the solvents used today.

The values measured for lead showed a large variation depending upon the color used during the spray painting. Low concentrations of lead were measured during the use of all the colors except red. The exposure level with red exceeded the lead TLV 70-fold. It should be mentioned that the actual exposure to lead during the spray painting was reduced by the use of individual protective equipment.

EXAMINED GROUPS

Exposed group

The selection of the exposed group (N = 80) was based on information collected during semistructured individual interviews with 156 male Swedish spray painters (95 car painters and 61 industrial painters). During the interview they were questioned about occupational history,

special attention being given to the intensity and duration of the exposure, the use of personal protective equipment, and the work conditions in each workshop. Furthermore, information was collected concerning environmental background and education. So that age would not become a confounding factor, the exposed group was stratified into five age groups, ≥ 25 , 26—35, 36—45, 46—55 and 56—65 a. Each group consisted of eight car painters and eight industrial painters.

During the selection of the examined group, the exposed workers in each age group were ranked according to two indices of exposure. The indices were based on the period of employment during which exposure to solvents occurred (t), estimation of the intensity of the exposure on a three-grade scale (i), the use of personal protective equipment (p), and the work conditions in each workshop (c). The two exposure indices were calculated as $t(i \times p \times c)$ and $t(i + p + c)$.

Individuals ranking highly on both exposure indices were selected to be included in the exposed group. When the exposure indices did not give the same ranking or when the indices did not sufficiently differentiate the examined persons, the selection was made after careful comparisons between the data on occupational history. Thirteen persons, four belonging to the age group of car painters < 25 a and nine being randomly distributed among the other groups, refused to participate in the

medical examinations and were replaced by the next person on the ranking list.

Reference groups

This investigation was planned as a cross-sectional epidemiologic study. The aim was to compare the spray painters to biologically and socially similar persons without exposure to organic solvents. The intention was therefore to select a group of nonexposed male Swedish industrial workers of the same age, type of work, and level of education as the spray painters. The selections were made in cooperation with representatives of the unions, managements, and health departments of the plants.

Reference group 1

Methods of selection. The first reference group was taken from an electronics plant in Stockholm. The selections were made from departments with (i) high- and (ii) low-qualified work. There was no individual classification of the education and description of occupation of the employees. Because the enterprise wished to avoid possible production disturbances, the reference group could not be chosen freely from all the employees, as some departments essential from the production point of view were not accessible to the investigators.

Table 2. Exposure to solvents and dust during car painting in 1975 and during simulated work conditions of car painting in 1955. — Distribution of time between different work phases.

Year	Exposure (hygienic effect)/percentage of the total time spent in different work phases		
	Spray painting	Grinding, filling, masking, assembling	Color mixing, degreasing, cleaning
1975			
Solvents	0.30/15	0.15/60	0.27/25
Lead	0.40/15	0.10/60	—/25
1955			
Solvents	0.40 (0.80 a) /20	—/65	0.25/15
Lead	0.0/20 (black)	—/65	—/15
	0.2/20 (green)		
	0.2/20 (white)		
	70/20 (red)		

a Hygienic effect when benzene was used as a solvent.

Four hundred possible referents remained after the age-matching. Among these, 40 persons with highly qualified work operations and 40 persons with less qualified work operations were randomly selected as referents.

Comments. In the choice of the first reference group a minimum of criteria of selection was used to attain a satisfactory variation of the background factors. However, an unintentional selection did occur in the first phase of work. The enterprise did not allow some groups of workers to be included in the reference group. The significance of this deficiency has not been investigated. Furthermore, it was later shown that many of the referents from departments with highly qualified types of work did not actually have very exacting work phases (storage work, cleaning work, etc). Obviously the collective assessment concerning education and occupation did not turn out satisfactorily because these departments had a more heterogeneous personnel than was expected. Therefore, the selected reference group was probably more heterogeneous than the exposed group with respect to different background factors.

During the project, assessments of the psychiatric health status and psychological performance level were carried out and showed alarmingly high frequencies of disorders that caused even more apprehension about unintentional mechanisms of selection. This suspicion was strengthened when a dropout of 39 % occurred in the primary selection of the reference group.

It was decided to obtain a description of the dropouts through an interview with the 51 persons who had refused to participate after being primarily selected. The interviews, of 15—20 min, took place at the workplace, 21 of the persons were not available for interview for different reasons — however only one actually refused to participate. Therefore, only 30 interviews were carried out. A comparison was made between the 30 interviewed dropouts and the reference group included in the study (reference group 1). Some differences ($p < 0.05$) were found that were important with respect to the suitability of reference group 1 as a reference group. Concerning medical history, a greater part of this group had had head injuries (15 %

to 0 %), other prolonged illness (15 % to 0 %), and illness which required surgical operation (46 % to 3 %). In addition a greater part of reference group 1 had been employed by the enterprise for less than 5 a (32 % to 7 %). The results revealed that this group had shorter employment periods in the enterprise than the dropouts and that more persons in reference group 1 had had short employment in different enterprises. Also, a greater part of reference group 1 (62 %) than the dropouts (23 %) had admitted using alcohol daily or once a week. Finally, a much larger proportion of reference group 1 (50 %) than the dropouts (26 %) was unmarried.

The summary assessment of the magnitude and structure of the dropout confirmed the suspicion of negative selection. Since the original aim of the selection did not seem to be fulfilled, a new reference group was chosen and examined.

Reference group 2

Methods of selection. At two other electronics plants in Stockholm, all the personnel ($N = 800$) was placed at the disposal of the project. The first step was to select the subjects with the same methods used for the first reference group. The second step was to make individual assessments concerning occupational classification, education, and employment stability based upon staff lists and inquiries.

So that the type of problems connected with the first reference group would be avoided, an individual matching with the exposed group was carried out. The criteria of this individual matching were (i) age (± 1 a), (ii) same educational level, (iii) position (foreman, not foreman), and (iv) employment stability (time of employment at the actual or previous workplace).

For each exposed person, lists of all the possible persons to be included in a reference group were drawn up. Among these potential referents, one person was randomly selected to be included in reference group 2 and one was chosen as a reserve in case the person first selected should refuse to participate for some reason in the investigation. Fifteen reserves were called to the examination. The reasons for the dropout of 15 of the primarily chosen persons are shown in table 3.

Comments. The introduction of individual matching limited the selection to the reference group. Thus there was a risk that the variation in the potential background factors tended to be too small. However, the risk was compensated for by the big pool from which reference group 2 was taken. The total dropout from reference group 2 was of the same order of magnitude as from the exposed group. In light of the fact that motivation to participate in an investigation is normally much lower in a reference group than in an exposed one, the results can be considered good. On the basis of the magnitude of and reasons for the dropout, it was considered that reference group 2 could be used for comparison with the exposed group. However, for the sake of completeness in the presentation of the results — despite the deficiencies — reference group 1 has also been included.

SCHEDULE OF THE MEDICAL EXAMINATION AND PRESENTATION OF THE RESULTS

Each of the selected subjects was examined at the Karolinska Hospital during two consecutive days following the schedule shown in table 4. Two subjects belonging to the same age stratum were examined on the same day, one from the exposed group and one from reference group 1. Through a period of two weeks 12 subjects were examined: 3 car painters, 3 industrial painters, 3 referents with highly qualified work and 3 referents with low qualified work. The examination was performed on weekdays (Tuesday—Friday).

For the reasons already presented, reference group 2 was examined separately, after the examination of the other two groups had been completed; however the same schedule was followed for this group also.

In the following text the results have been presented in the form of Z diagrams, which are the results of a statistical analysis of the differences between the exposed group and each of the reference groups. The Z values have been calculated as follows:

$$Z = \pm (\bar{X}_e - \bar{X}_r) / S_p,$$

where $\bar{X}_e$ is the mean value of the variable

in the exposed group, $\bar{X}_r$ is the mean value of the same variable in a reference group, and S_p is the standard deviation pooled within groups and age strata. For those variables in which the results were available as number of "yes" responses to a question on the questionnaires, the Z value was calculated as follows:

$$Z = (P_e - P_r) / \sqrt{P(1-P)(1/N_e + 1/N_r)},$$

where P_e is the percentage of "yes" responses in the exposed group, P_r is the percentage of "yes" responses in a reference group, P is the total percentage of "yes" responses in both these groups, and N_e and N_r are the corresponding sample sizes.

The Z values can easily be transformed into a measure of significance of a more familiar type, as p-values ($p < 0.05$, < 0.01 and < 0.001).

The Z diagrams are presented in the form of bars showing the Z values for the different variables presented in the diagram and thus giving the difference (or more precisely the reliability of the dif-

Table 3. Reason for dropout from reference group 2.

Reason	Number
Prolonged illness	2
Previous exposure	1
Refusal	12
(among whom an expressed fear for hospitals and physicians)	(5)
Total	15

Table 4. Schedule for the different examinations.

Examination	Time required (h)
<i>First day (0800—1730)</i>	
Blood sample	0.5
Medical inquiry	1.5
Neurophysiological examination	2
Neurological examination	2
Psychological examination	2
Neuroradiological examination	0.5
<i>Second day (0830—1630)</i>	
Sociopsychological interview	1.5
Psychological examination	3
Psychiatric examination	1.5
Ophthalmologic examination	0.5
Total	15

ference) between the groups. A Z bar directed to the right in a figure means that the difference was regarded as indicative of a poorer state of health or level of function in the exposed group than among the referents, while a bar directed to the left means a better state in the exposed group.

GENERAL MEDICAL EXAMINATION

The general medical examination included a questionnaire concerning present and previous state of health (table 5) and a

Table 5. Content of the medical questionnaire.

Contents	Number of questions
Previous state of health	40
Present state of health	
General symptoms	23
Neurological symptoms	38
Psychiatric symptoms	52
Symptom present only at or immediately after work	11

number of blood sample analyses. As shown in table 5, the inquiry comprised questions on neurological and psychiatric symptoms. It must be stressed that the completed questionnaire was used as a basis for the interview at the following medical examination, during which the subject could clarify the answers given in the questionnaire.

Previous state of health

The Z diagrams in fig 2 illustrate the difference between the exposed and reference groups with respect to previous illness. It appears that the morbidity, in general, was somewhat higher in the exposed group as compared to the referents. Statistically significant differences were found for psychiatric symptoms ($p < 0.01$), as well as for infections of the urinary tract, gastritis and backache ($p < 0.05$), when the exposed group and reference group 2 were compared. The differences versus reference group 1 were somewhat smaller and sta-

Fig 2. Differences, between the frequencies of "yes" responses in the exposed group and the two reference groups, concerning questions in the medical questionnaire regarding previous state of health. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

tistically significant only for gastritis ($p < 0.05$).

Present state of health

General symptoms

One group of 23 questions on the part of the questionnaire dealing with present state of health covered symptoms concerning the respiratory, circulatory, and digestive systems and the skin. The average number of "yes" responses was larger among the exposed than the reference groups. This difference was statistically significant with respect to skin trouble when the exposed group and reference group 1 were compared. When the frequency of "yes" responses in the groups were compared for separate questions, 7 of the 23 questions separated the exposed group from one or both of the reference groups. These particular questions and the differences are displayed in fig 3.

Another group of 11 questions concerned symptoms only present at or immediately after work. The following five acute symptoms were found more often among the exposed: vertigo, headache, difficulty in breathing, slurred speech, and feeling of intoxication (fig 4).

Psychiatric symptoms

In the analyses of the answers in the psychiatric part of the self-administered questionnaire, a statistically significant higher frequency of "yes" responses was found for the exposed group in comparison to the

referents for 8 of the 52 questions. They concerned increased fatigability, memory disturbances, absentmindedness, dysphoria, and nightmares (fig 5).

Neurological symptoms

The 38 questions in the neurological part of the inquiry dealt with symptoms from the central nervous system (11 questions), the cranial nerves (8 questions), and the peripheral nerves (19 questions). For this part of the questionnaire also, the average frequency of symptoms was higher for the

Fig 3. Differences, between the frequencies of "yes" responses in the exposed group and the two reference groups, concerning questions in the medical questionnaire regarding present state of health of the respiratory, circulatory, and digestive systems and the skin. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

Fig 4. Differences, between the frequencies of "yes" responses in the exposed group and the two reference groups, concerning questions in the medical questionnaire regarding symptoms only present at or immediately after work. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

Fig 5. Differences, between the frequencies of "yes" responses in the exposed group and the two reference groups, concerning questions in the medical questionnaire regarding psychiatric symptoms related to present state of health. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

Fig 6. Differences, between the frequencies of "yes" responses in the exposed group and the two reference groups, concerning questions in the medical questionnaire regarding neurological symptoms related to present state of health. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2. (CNS = central nervous system).

exposed group than for the two reference groups. For 21 of the questions the difference was statistically significant with the exposed group versus one or both of the reference groups. These 21 questions are presented in fig 6, where it is demonstrated that the differences were the most pronounced for the questions concerning symptoms indicative of peripheral neuropathy (paresthesia and muscle pain).

Blood analyses

The blood analyses comprised sedimentation rate, hemoglobin, hematocrit, erythro-

cytes, leucocytes, and liver function tests [alkaline phosphatases, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and bilirubin in serum]. The group mean values were all within current normal limits. However, some statistically significant differences were found between the exposed group and reference group 2; higher values were found in the exposed group for alkaline phosphatases (3.14 versus 2.72 $\mu\text{kat/l}$, $p < 0.01$) and for hemoglobin, hematocrit, and erythrocytes ($p < 0.05$).

Comments

It appears from the results that the solvent-exposed workers had a higher frequency of neurological and psychiatric symptoms than their referents. Also skin symptoms occurred more frequently among the exposed, a finding not surprising since it is well known that occupational exposure to solvents may cause irritative changes of the skin (14). Other differences in the previous and present state of health between the groups were spurious, and some of them (eg, some gastrointestinal symptoms) may merely have been a reflection of disturbances of neuropsychiatric health. The increase, although not statistically significant, in chronic bronchitis and some respiratory symptoms among the exposed may on the other hand be a manifestation of a solvent effect on the lungs, as recently demonstrated in epidemiologic (21, 58) and experimental studies (72).

PSYCHIATRIC INVESTIGATION

Acute psychoorganic syndromes are characterized by disturbed consciousness and hallucinations, whereas the chronic syndromes are distinguished by reduced mental performance, personality changes, and subjective symptoms. They may be individual reactions to reduced physical and mental ability and can be prominent in cases of a slight to moderate cerebral lesion or in the early phases of the psychoorganic syndrome. Moreover, subjective symptoms can occur much earlier than objective signs (54). The clinical picture is

characterized by, eg, fatigue, worrying, and memory and concentration difficulties, and it is often described as a neurasthenic syndrome. Similarly, subjective symptoms with a concurrent and varying reduction in mental capacity following long-term exposure to organic solvents have been reported in a great number of case reports and in epidemiologic studies (59). Therefore, the present study included a psychiatric assessment of a number of neurasthenic symptoms. However, the neurasthenic syndrome has been attributed to psychological and social factors. Furthermore, such factors can be influenced by organically induced personality changes (83). Hence, the present study included investigations of certain personality traits and of the adjustment of the individual to social life.

Methods

Questionnaires

The self-administered psychiatric questionnaires contained the 52 questions described in the section on the general medical examination and 29 questions about the social situation of the individual according to Gardell (30) and Westlander (85). In addition, five questions concerned the use of alcohol. The information so obtained was used as the basis for the psychosocial and psychiatric interviews. Certain questionnaires about the individual's habitual behavior (inventories) were also presented so that some personality traits could be studied which had been postulated by factor analyses [Eysneck's Personality Inventory (EPI)] or were based on theoretical considerations (Marke-Nyman's Temperament Scale (MNT)).

Psychosocial interview

The structured interview contained 20 items which, together with the aforementioned questions, have been used in previous studies (30, 85). Questions and items of similar content were brought together in 18 indices. These 18 indices were assembled into three general indices giving an overall assessment of the conditions at home, those at work, and any signs of social maladjustment (eg, abuse, criminality).

Psychiatric interview

The prevalence of various symptoms experienced during the last six months was rated according to the examinee's reports given during a semistructured interview (with a duration of approximately 45 min). Thirty-three reported items were rated on a seven-step scale. Twenty-one of the items were drawn from the CPRS (Comprehensive Psychopathological Rating Scale) (8). The 12 remaining items were constructed according to the same principle. Also, the interviewer rated his own observations of 12 symptoms and signs observed during the interview. He assessed the "assumed reliability" or "credibility" of the reports given during the interview and, finally, the overall mental health of the subject (two items). The psychiatric interviews were recorded on tape to permit assessment of observer bias and inter-rater reliability. Individuals in the exposed group and the first reference group were interviewed in random order by two senior psychiatrists. Individuals in the second reference group were also interviewed by a resident in psychiatry. Each one of the three interviewers of the second reference group rated approximately one-third of all the individuals in every age stratum. As regards the exposed group and reference group 1, the interviewers endeavored to remain blind as to the nature of the examinee's work. However, the second reference group was examined separately and the individual work was known by the interviewers. In all cases, any information about type of work was erased from the tapes and could therefore not influence later reratings. Thirty-five tapes were selected at random and rerated (five per age stratum and rater). This rerating took place 1 to 2 a after the original interview. The product-moment correlation (r) between the raters was computed from the sum score of all the reported items. It varied between 0.82 and 0.88. The correlation (r) between the original ratings and reratings performed by the same interviewer varied between 0.92 and 0.95. The average score of the rerating was very close to that obtained at the original rating. The two senior psychiatrists arrived at almost exactly the same score when rerating the same tape. The resident, however, gave higher scores. The inter-

view technique used may be considered to be "conspective" (ie, it gives the same result regardless of the rater, at least between senior psychiatrists). In the statistical procedures the original ratings were used, with some exceptions. Multivariate statistics were applied to 13 selected items drawn from the ratings made by the senior psychiatrists. This material consisted of

ratings from 77 exposed and 127 reference workers.

Results

Questionnaires

The frequencies of certain mental complaints as expressed in the medical questionnaire have already been given. As for the personality inventories (EPI & MNT), the results agreed with those of previous normalization studies (11, 55). Neuroticism in the EPI and validity in the MNT were of particular interest, since they can be regarded as reflecting a constitutional disposition for the development of neurotic reactions. However, neither the exposed nor the two reference groups seemed to be handicapped by any such disposition. The results of the inventories speak against selective factors (eg, choice of work) influencing the psychological comparativeness of the groups. If such factors had been operating, they would have induced difficulties in the assessment of the psychiatric and the psychosocial interviews. (We have made an exception, however, of the factors operating in the composition of the first reference group).

Psychosocial interview

A considerably higher work stress was reported by the exposed group in comparison with both reference groups (fig 7). When car painters and industrial painters are compared only with their subgroup among reference individuals, this difference persists. The exposed individuals reported a greater subjective work stress than did the reference groups; this finding was attributed to experienced risks at work (not only those connected with organic solvents). The exposed workers clearly reported a lower general ease in their work conditions. They also experienced more difficulties than reference group 2 in their relationships with fellow workers. The remaining indices revealed no differences. As expected, the exposed group reported more complaints about their work situation than the referents when general indices were compared (fig 8). In a comparison of the exposed and the first reference group a trend was observed which became a statistically significant difference when

Fig 7. Differences between the mean values of the psychosocial indices of the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

Fig 8. Differences between the mean values of the general psychosocial indices of the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

the same comparison was made with the second reference group. However, the exposed individuals reported more favorable conditions at home than both reference groups. This finding was particularly marked for the married painters when they were compared to married individuals in reference group 2. The general index for disturbed adjustment to social life, which contained criminality, alcohol and drug abuse, did not differ between the groups.

Psychiatric interviews

Reported items. Fig 9 shows the results of the ratings of the 33 reported items. In comparison with both reference groups, the exposed group had a clearly higher symptom score for 11 items (inner tension, irritability, fatigability, aches and pains, learning problems, short- and long-term memory problems, nausea, epigastric pain, headache and, finally, precision movement). Statistically significant differences between the exposed group and one of the reference groups were found for five additional items (worrying over tri-

fls, concentration difficulties, vertigo and dizziness, dyspnea, and mood lability). The most pronounced differences were observed for memory problems, headache, and fatigability. The figure shows, too, that there were trends towards differences for several other items between the exposed and reference groups.

For further statistical analysis, a reduction of the amount of data was desired. Those 13 items were selected that were clearly correlated to items that best differentiated between the groups ($r > 0.3$, $p < 0.001$). These 13 items correlated clearly with group residence "exposed" (multiple $r \sim 0.54$, $p < 0.001$).

The correlation was mainly derived from symptoms such as short-term memory problems, headache, mood lability, and precision movement difficulties (table 6). Furthermore, the items were subjected to factor analysis. In the search for symptom clusters with a common variance related to exposure to organic solvents, the analysis was confined to ratings obtained in interviews with the painters. According to the factor structure, 13 items were grouped into three general indices (fig 10). The first index showed the most prominent dif-

Fig 9. Differences between the mean values of the ratings of symptoms reported by the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

Fig 10. Differences between the mean values of the three psychiatric general indices. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2. Symptom group 1 comprises fatigue, concentration difficulties, memory problems, vertigo, gastritis, and headache. Symptom group 2 comprises hostile feelings, worrying over trifles, indecision, inertia, thoracic oppression, and inner tension. Symptom group 3 consists only of precision movement difficulties.

Table 6. Multiple regression analysis of selected psychiatric items.

Step	Item	Multiple r	p
1	Short-term memory problems	0.454	0.000
2	Headache	0.493	0.002
3	Mood lability	0.512	0.028
4	Precision movement difficulties	0.522	0.105

ference between the groups and contained the largest factor, corresponding to 25 % of the total variance.

Observed items. Generally, the observed items displayed less difference than the reported items between the examined groups. The following differences were obtained: The word fluency of the painters was significantly higher, and they displayed problems with their short-term memory significantly more often than the reference groups. In comparison with either reference group, there were also signs of long-term memory problems, increased motor restlessness, and increased muscle tension in the exposed group. The general credibility of the ratings was scored as high for all groups.

Relationship with psychosocial findings. Some differences between the exposed and the reference groups were observed for

certain psychosocial items, as well as certain mental complaints. A relationship between psychosocial and psychiatric findings is essential for the interpretation of the origin of the psychiatric symptoms.

The existence of neurotoxic agents such as organic solvents in an individual work environment can give rise to mental symptoms. Such symptoms can lead to increased subjective work stress and social adaptation problems. On the other hand, high work stress and unfavorable conditions at work can also provoke mental symptoms such as fatigability. However, the relationships are probably very complicated, and only a rough assessment can be attempted in this report.

An examination of the relationship between the general psychosocial and psychiatric indices of the two reference groups can provide an estimate of the extent to which the psychiatric ratings were influenced by the examinee's experience of his environment at work and at home. No such correlations were noted. However, the general index for work situation contained one index for work strain (fig 7), which showed a weak correlation with the first symptom group ($r = 0.21$ $p < 0.006$). No correlations between the psychiatric rating and the remaining separate psychosocial indices were found. Therefore it appears that the ratings of the psychiatric symptoms were influenced only to a small extent by the examinee's experience of, eg, work conditions.

As for the exposed group, only a slightly higher correlation between work stress and psychiatric symptoms was found ($r = 0.35$ $p < 0.36$). The index for subjective work stress contains items relevant to experienced risks at work. Of course the painters may be more concerned over work risks, and this concern can explain the difference between the two groups.

Discussion

The psychiatric investigation showed that psychiatric complaints were considerably more common among painters than among the individuals in both reference groups. This result could be due to a tendency to give exposed subjects higher scores. This contention, however, is contradicted by the

findings of high rating-rerating reliabilities and of the observation that the interviewing psychiatrists arrived at approximately the same average scores. Some individuals in reference group 2 were interviewed by a psychiatric resident, who gave higher average scores than the two specialists. This occurrence induced a systematic error which, however, would suppress observed differences. Reference group 2 has thus been given ratings that are somewhat too high.

At the interviews, the painters did not give impressions of overstating their complaints. The presence of such a tendency would have influenced the general credibility of the interviews. However, in this respect, painters and reference workers were equal. The possibility remains, however, that the selection of the groups can have induced considerable differences between the painters and reference workers with respect to certain background factors that could affect their mental state. The inventories used in the study did not reveal personality traits likely to cause mental symptoms. The psychosocial investigation showed that the painters viewed their work situation more negatively and experienced their work situation as more negative than did the referents. However, since the correlations were weak, they cannot explain the higher incidence of mental complaints among the exposed workers. Therefore, a relationship between mental symptoms and exposure to organic solvents seems to be a more plausible presumption. This view is supported by the observations that those symptoms that best differentiated between the groups are also common in persons with slight cerebral damage (24). The symptomatology also agrees with previous case reports or epidemiologic studies (59). A closer analysis of the ratings indicates that memory difficulties, the single item that best differentiated between the groups, was connected with a number of cerebrolesional symptoms (83).

The CPRS (1) formed the basis for the used psychiatric rating scale. The scale should be of the interval type (79) to permit the proper use of parametric statistics, but any imperfection in this respect would have little bearing on the results (6, 19). Similarly, certain theoretical ob-

jections can be raised against the use of factor analysis of ratings, particularly if the object is to give the factor structure a mathematical interpretation. However, the actual use of the method for data reduction is generally accepted (16, Schalling: personal communication).

The stability of the factor structure must be regarded with caution. The comprehensive psychiatric indices were based on factors of first order, and it may be difficult to reproduce them exactly with other materials.

Furthermore, the validity of the rating scale has not been tested. It is of interest to note that preliminary data show significant relationships between the first psychiatric index and results of psychometric tests indicative of cerebral damage. The third psychiatric index also showed a statistically significant correlation with a psychometric test demanding manual dexterity. These correlations will be the subject of further analysis.

PSYCHOLOGICAL EXAMINATION

A fairly large number of studies has shown that experimental exposure to solvent vapors can cause changes in central nervous functions as measured by behavioral performance tests. Thus, for several solvents, performance decrement on tests of, eg, sensory, perceptual and psychomotor functions was found to be related to the concentration of solvent in inspiratory air and to the total uptake of solvent in the organism (2, 27, 28). The results of these and other experimental investigations have provided a basis for the evaluation of the risks for acute effects due to the presence of solvents in the work environment.

The risk for decrement in performance capability due to long-term exposure has not yet been satisfactorily evaluated. Epidemiologic investigations of occupationally exposed workers do, however, clearly indicate that long-term exposure to solvent vapors can cause a decrement in behavioral performance capability (29, 33, 37, 38, 39, 44, 52, 53).

Methods

A total of 18 different behavioral performance tests were used in this investigation (table 7). Fourteen of these tests were from a recently standardized test battery for investigations in behavioral toxicology (80), and four were tests on electronic apparatus which were developed in the work psychology division of the Swedish National Board of Occupational Safety and Health (44).

Except for the tests on the electronic apparatus, the factor structure of the test battery was already known from previous investigations (80). A number of factor analyses was however performed also on the results from the present investigation (25). These analyses showed that the factor structure for the exposed and reference groups was the same as for the population of an earlier investigation (80). In these latter analyses, all of the tests from the present investigation had been included, and thus an analysis of the relations between the tests of the battery and

the tests on the electronic apparatus was possible.

Statistical analysis

From the first inspection of the data, it was obvious that the results of all the tests except the two verbal ones were highly correlated with age. This fact, and the heterogeneity of the groups with respect to age, would make the t-testing of the mean differences between groups inadequate. A t-test would result in a highly underestimated significance level. The statistical analyses were therefore made with two-way analyses of variance with exposure and age as the two sources of variation. This method was preferred to alternative models of analysis, such as the t-test for matched pairs or an analysis of covariance. The analysis of variance was chosen because of the fact that it gives information about a possible effect of interaction between exposure and age. Furthermore, this model does not require

Table 7. Means and standard deviations from different tests for the reference and exposed groups and for the car and industrial spray painters.

Test	Exposed group (N = 80)		Reference group (N = 80)		Car painters (N = 40)		Industrial painters (N = 40)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Synonyms	19.8	6.1	20.5	5.8	19.7	6.4	20.0	5.9
Distinction	16.1	6.3	16.2	6.3	15.9	6.5	16.3	6.2
Spatial transposition	26.0	7.9	26.5	7.4	25.9	7.2	26.1	8.6
Block design	22.5	7.3	24.7	6.4	22.2	7.3	22.9	7.3
Figure classification	20.7	4.6	21.2	4.2	19.8	4.2	21.6	4.8
Visual gestalt ability	134	21	137	17	137	19	131	23
Digit symbol	39.5	13.2	44.9	11.9	39.5	12.7	39.5	13.7
Identical numbers	79.0	17.5	85.9	17.0	79.3	15.3	78.8	19.6
Dots	654	145	712	141	656	132	652	159
Mental arithmetic	2.6	1.3	2.3	1.0	2.5	1.2	2.7	1.3
Benton (reproduction)	6.9	1.5	7.3	1.5	6.7	1.4	7.0	1.7
Memory test (recognition)	28.1	4.1	28.9	4.1	28.7	3.7	27.6	4.3
Memory test (reproduction)	52.7	9.6	56.5	6.2	53.9	8.4	51.5	10.6
Hand dexterity test	76.8	8.0	80.7	8.8	77.8	7.0	75.7	8.8
Finger dexterity test 1	26.0	6.0	29.4	6.4	27.2	4.9	24.8	5.0
Finger dexterity test 2	26.4	5.0	29.0	5.8	27.2	4.9	25.7	5.0
Simple reaction time, speed	264	28	243	30	258	29	270	29
Simple reaction time, decrement	24	27	14	23	23	24	24	30
Finger tapping	203	26	202	28	209	30	197	21

any assumption about a linear relationship between performance and age.

This first inspection revealed that reference group 1 was much more heterogeneous in performance than reference group 2 or the exposed group. Reference group 1 thus showed a greater standard deviation than the other two groups on almost all performance tests. Furthermore the distributions of the performance scores for reference group 1 showed a marked negative skewness in most of the tests. These observations accentuated the interpretation of reference group 1 as being negatively selected. Because of these facts, the results of reference group 1 were excluded from the analysis of variance.

In the analyses of variance, the material was grouped into five age classes according to the sampling criteria. Four groups were used, car painters, industry painters and one matched reference group for each of the exposed groups. The resulting design was 5×4 with eight individuals in each cell. This grouping made possible the simultaneous testing of the differences between the two exposed groups and between each of these and the reference groups. Combining the two exposed groups and the two reference groups, respectively, made it possible also to make a test for interaction between exposure and age.

The reaction-time test, Simple RT, could also be analyzed for performance changes during the test period. For this test, a two-way analysis of variance with repeated measurements was employed in which the trend of the performance changes over time was introduced as a further source of variation.

For more information concerning the correlation between groups (exposure/no exposure) and performance on different tests, a series of multiple regression analyses was performed. These analyses resulted in a multiple correlation coefficient for the relationship between groups (exposure/no exposure) and performance variables from the same factor (table 8).

Results

The means and standard deviations for the different groups and performance tests are shown in table 7. The relative magnitude and direction of the difference in

performance between the exposed group and the reference groups are illustrated in fig 11, where the mean differences for each test have been transformed into standardized scores.

The result of the analyses of variance showed that the main sources of variation,

Table 8. Multiple correlation coefficients for the relation between performance on tests belonging to the same factor and group membership (exposed group/reference group).

Factor	Multiple r	p
Verbal comprehension	0.070	0.700
Reasoning and spatial relations	0.187	0.158
Perceptual speed	0.230	0.047
Numerical ability	0.147 ^a	0.072
Memory	0.240	0.034
Manual dexterity	0.281	0.007
Simple reaction time	0.360	< 0.001
Motor speed	0.031 ^a	0.703
All the tests	0.529	< 0.001

^a Pearson correlation coefficients for factors represented by only one test.

Fig 11. Mean performance differences between the exposed group and reference group 2 on the different psychological tests. The differences are expressed in standardized scores. (REL = relations, RT = reaction time)

exposure and age, had a significant influence on performance on most tests. On the other hand, there were no signs of any interaction between exposure and age. The performance of the older subjects was worse on the tests irrespective of exposure.

With one single exception the mean performance on the tests was poorer for the exposed group than for the reference group (fig 10). From fig 10 it can be seen that the exposed group had a significantly

Fig 12. Change in mean reaction time (RT) over time (1-min time blocks) for the exposed group and reference group 2. Each point is a mean of the individual median values for the time block.

Fig 13. Mean values of the reaction time (RT) of the exposed group and reference group 2 at different percentiles in the individual distributions of reaction times.

poorer performance than the reference group on all three tests of perceptual speed ($p < 0.01$) and manual dexterity ($p < 0.01$). The test of Simple RT also showed a distinct difference between the two groups ($p < 0.001$).

The results of the memory tests also indicated poorer performance for the exposed group as compared to the reference group. The mean difference in performance was clearly significant ($p = 0.003$) for one of the tests (memory, reproduction) and very close to significance ($p = 0.057$) for another test (Benton, reproduction).

The group differences in cognitive functions such as reasoning, spatial relations, and numerical ability were more ambiguous. The four tests of reasoning and spatial relations showed only one significant difference (block design test, $p = 0.046$), while the differences for the others were small. A tendency towards a performance difference can be seen in the results of the test of numerical ability (mental arithmetic, $p = 0.070$). Tests of verbal comprehension and motor speed did not differentiate between the groups.

From table 7 it can be seen that both car painters and industrial painters generally performed less well than the reference group. However, there was a clear tendency for the industry painters to perform still worse than the car painters on the tests for manual dexterity and simple reaction time. Manual dexterity and reaction time are also the functions for which the greatest and most unambiguous differences between the exposed groups and the reference group were found. This fact is illustrated in table 8, where the correlation between exposure and performance is described with reference to the factor structure of the test battery. It can be seen that reaction time, manual dexterity, memory, and perceptual speed clearly correlated with exposure. In addition, the simple reaction time test obviously had nearly half of the discriminative power of the test battery (0.360^2 as compared to 0.529^2). Fig 12 and 13 give a more detailed description of the results for the reaction time test. Fig 12 illustrates the change in reaction time over the test time (10 min) for the exposed and reference groups. As already mentioned, the difference in reaction time between the two groups was sig-

nificant ($p < 0.001$). Furthermore, the analyses of variance and trend showed that the change in reaction time over time was approximately linear ($p < 0.001$), and the change was significantly greater ($p = 0.024$) for the exposed group. These analyses also pointed out that still another aspect of reaction-time performance correlated with exposure. This phenomenon is illustrated in fig 13, in which the mean values of each group have been presented for the different percentiles in the distribution of reaction times of every individual in the test. As can be seen in the figure, the mean differences between the groups increased over the percentiles ($p = 0.025$). Therefore the individual distributions of reaction time tended to be more positively skewed in the exposed group than in the reference group.

Discussion

Unambiguous differences in performance between the exposed and reference groups were found in the psychological examinations. The exposed group performed significantly less well on tests of functions such as simple reaction time, manual dexterity, perceptual speed, and memory, ie, in not very complex perceptual and psychomotor functions.

The results in general showed a clear relationship between exposure and performance on the tests. This correlation also appears to be more unambiguous in this investigation than in the earlier studies of house painters (39) and car painters (53). It is not probable that the groups differed initially with respect to intellectual ability because no differences between the groups were found in the more intellectual tests of the battery, eg, verbal comprehension. The results also seem to favor the hypothesis that verbal ability is relatively resistant to the effect of solvent exposure (39). In a previous study of car painters (53), differences between an exposed and reference group were found for all the functions tested but reaction time, while in this investigation the greatest difference between the exposed and reference groups was found on the reaction-time test. This is a very im-

portant difference because it is well known that performance on a reaction-time test is independent of intellectual capacity. This is not the case for the tests of other functions. Thus the result on the test of reaction time can be interpreted as due to solvent exposure, even if the comparability of the groups in intellectual ability is questioned.

As already mentioned, the exposed group performed less well also on the memory tasks. It should be stressed, however, that performance on these and other available memory tests is highly dependent on the attention and concentration of the subject. Furthermore, retention was measured after a very short time. The poorer performance on these tests is therefore not necessarily related to the subjective memory impairment reported by some exposed individuals.

The effects of long-term exposure to solvents already described seems to be of the same kind as those found in laboratory investigations of acute exposure (27).

The analyses of variance illustrated a negative correlation between age and performance on the test. However, there was no effect of interaction between age and exposure. Thus the differences in performance between the exposed and reference groups were relatively stable with respect to age. The variation of age in the exposed group was almost identical with that of length of exposure (painter years). Therefore it was not possible to demonstrate any effect or correlation that indicated a dose-response relationship. Nor has such a relationship been found in the earlier investigations of house painters (39) and car painters (53).

The general results can, on the basis of a cursory analysis, seem somewhat contradictory. While on one hand unambiguous mean differences occur between exposed and reference groups, there are on the other no correlations between length of exposure and test performance. However, there is the possibility that the exposed population has been subject to a systematic dropout, a "healthy worker effect." It is obvious that it would be very difficult to prove a dose-response relationship in such a selected population. These results would also be explained if the effects are subchronic rather than chronic.

NEUROLOGICAL AND NEUROPHYSIOLOGICAL EXAMINATIONS

There are several reports in the literature on objectively demonstrable lesions in the central nervous system due to occupational exposure to organic solvents. Even recently, relatively serious functional disturbances of the central and peripheral nervous systems have been reported due to such exposure (3, 15, 18). The exposure conditions described in these studies seem to have been worse than in comparable Swedish industries. However, the results of recent Scandinavian epidemiologic studies (44, 45, 66, 75, 77) indicate that even a low degree of long-term exposure to industrial solvents can affect the nervous system to the point that changes can be detected in neurological and neurophysiological examinations. The changes

Fig 14. Visual evoked responses (VER) — At the top of the figure is the square checkerboard pattern screen with which the "pattern reversal" stimulation was performed. Below it is the skull of the examined subject (seen from above) with the two recording electrodes. Fz and Oz indicate the electrode positions according to international electroencephalographic standards. The recorded signals pass through an amplifier and a computer to give a response (VER) as shown at the bottom of the figure. Two variables were measured from this response, the amplitude (A) and the latency (L). P₁₀₀ is the dominating positive wave since its latency is around 100 ms in normal cases.

found with these methods have been slight, eg, an increased occurrence of slight, peripheral neuropathy — mainly sensory — and nonspecific electroencephalographic (EEG) changes.

Methods

Neurological examination

In the clinical neurological examination, the function of the central nervous system (aphasia, gait, coordination, tremor, Romberg's sign, muscle tone, Babinski's sign) and the cranial nerves (sense of smell, eye movements, nystagmus, facial movements and sensibility) was tested. The peripheral nervous system was assessed with an examination especially designed to detect early signs indicative of polyneuropathy (12, 44, 45).

Sensibility (pain, temperature, discriminative sensibility and kinesthetic sense), tendon reflexes, and muscle strength were evaluated. The findings were scored as 0 = normal, 1 = mild changes, and 2 or 3 = varying severity of manifest disease.

Electroencephalography

The EEG recording was performed according to international standards; it included hyperventilation for 3 min and photic stimulation. Drowsiness was prevented by sound stimulation. For the computer analysis, the EEG signals were stored on magnetic tape.

The EEGs were visually examined by two neurophysiologists independently and without knowledge of whether the EEG belonged to the exposed or the reference groups.

A representative 10-s section of each EEG was selected and ranked with regard to the amount of low-frequency activity. The stored EEG signals were computer-processed by means of spectral parameter analysis (SPA) (84). SPA describes the frequency content of the EEG signal in one to three components (the delta, alpha and beta components). Each component is characterized by three parameters (peak frequency, bandwidth and power).

Visual evoked responses

Pattern reversal in visual evoked responses (VER) was recorded. The stimulus was produced by a commercially available device (Digitimer D 110); it consisted of a back projection of a black and white checkerboard pattern with a reversal frequency of 2 Hz (fig 14). [For details of the stimulus parameters see Nilsson (63)]. A bipolar recording of VER was made with two scalp electrodes, one applied at the midline 5 cm above the inion and the other placed midfrontally. Responses to 200 or 400 reversals were averaged. The pattern reversal VER has a typical waveform and good intraindividual reproducibility. The interindividual variability of the latency is small. In the analysis of the responses, the latency and amplitude were measured as is shown in fig 14.

Electroneurography

Six peripheral nerves (median, peroneal and sural nerves on both sides) were examined electroneurographically. Conduction velocities of motor nerves, as well as conduction velocities and action potential amplitudes in sensory and mixed nerves, were measured with surface electrodes (table 10). The electrode positions are presented in fig 15.

Vibratory perception thresholds

The vibration thresholds were determined at three different locations of the extremities, ie, the bony parts of the dorsum of the foot (tarsal), the lower leg (tibial), and the wrist (carpal). An electromagnetic biotinesiometer with a plastic stimulator shaft, 6 mm in diameter, provided a 100-Hz sine wave stimulus movement, the amplitude of which could be varied between 0 and 25 μ . An accelerometer mounted on the stimulator shaft registered peak to peak amplitude of the stimulation, which was monitored digitally during the procedure.

Results

Neurological examination

Significant differences between the exposed group and reference group 2, with more positive findings in the exposed group, were found for the following: Rom-

berg's test, finger-to-nose test, finger-to-finger test, and finger tremor. In all cases the findings were minor, and, since the examinations were performed by two physicians, for whom the distribution of exposed and reference subjects was unequal, the results must be regarded with caution.

The quantified neurological status concerning the function of the peripheral nerves did not reveal any significant differences between the groups.

Electroencephalography

As shown in table 9, the visual evaluation of the EEGs did not reveal any significant differences between the exposed group and the referents. The proportion of abnormal

Fig 15. Electroneurography — The figure shows the position of the electrodes in the electroneurographic examinations. (M = muscle response recording electrode, D = digital stimulating electrode)

Table 9. Visual evaluation of the electroencephalograms (EEG).

EEG evaluation	Exposed group (N = 80)	Reference group 1 (N = 80)	Reference group 2 (N = 80)
Normal	44	47	47
Not definitely abnormal	33	23	28
Slightly abnormal	2	2	3
Fairly slightly abnormal	0	3	1
Moderately abnormal	1	5	1

Fig 16. Differences between the mean values of the visual evoked response variables of the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2. (bilat. = bilateral)

Fig 17. Differences between the mean values of the electroneurographic variables of the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2. The notations of the distances along the nerve refer to the electrode positions in fig 15. MCV = motor nerve conduction velocity, NAP = nerve action potential (in mixed nerves), SNAP = sensory nerve action potential, c.v. = conduction velocity).

Fig 18. Differences between the mean values of the vibration thresholds of the exposed group and the two reference groups. The differences are given as Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

EEGs was of a magnitude expected for a population of this kind. When the EEGs were ranked by one of us (AW), the distribution of exposed subjects and referents indicated that the former showed more alpha activity than the latter. This tendency was statistically significant ($p < 0.01$, Mann-Whitney rank correlation test). However, when a new ranking was made by two of us (HP and LW) jointly, no such difference was demonstrated.

The computer analysis (SPA) of the EEGs did not show any significant differences between the groups, but some tendencies were found which were in agreement with the results of AW's ranking: higher alpha power, smaller alpha bandwidth, lower delta power and larger delta bandwidth in the exposed group.

Visual evoked responses

Fig 16 shows the VER variables of the exposed group compared with those of the reference group. The latency was somewhat longer in the exposed group, especially in comparison with reference group 2, but the differences were not statistically significant. The mean amplitude of the exposed group was somewhat larger than that of the reference groups, particularly in comparison with reference group 1, for which the difference was statistically significant ($p < 0.05$). If the mean values of the latencies and amplitudes of the groups are divided into the five age strata, the difference in latency between the exposed subjects and the referents becomes present only in the older strata. The VER amplitudes did not show such an age dependence. However, a nonsignificant tendency towards larger differences was present in the youngest age stratum.

Electroneurography

The mean values and standard deviations for the electroneurographic (ENeG) variables are presented in table 10. Fig 17 shows the differences in these variables between the exposed group and the two reference groups. Seven of the 10 ENeG variables had significantly lower mean values for the exposed group in comparison with reference group 2. The differences in all the ENeG variables were the largest for the youngest age stratum.

Vibratory perception thresholds

As shown in fig 18, the exposed group had higher vibration thresholds than the reference groups. The difference was the most pronounced for the legs; it was similar in all age strata.

Discussion

Electroencephalography

No statistically significant differences between the exposed subjects and the referents were found in the visual evaluation of the EEGs. This result agrees with the findings of Seppäläinen et al (75) on a group of 102 car painters. However, other studies have revealed EEG differences between groups of subjects exposed to organic solvents and referents, but the type of EEG changes has been different in different studies. Knave et al (44) found a

smaller amount of alpha activity; Rosén et al (67) found increased beta activity; Ekberg et al (20) found (with a computer-based frequency analysis) a somewhat lower alpha frequency; and Seppäläinen et al (76) found an increased amount of theta activity in the exposed group. A difference between the groups was also found in our material after a ranking of the EEGs, performed by one of us (AW), showing a greater amount of alpha activity in the exposed group. The EEG changes found in the aforementioned studies have been subtle and noncharacteristic, and the differences between exposed subjects and referents have appeared as statistical differences between groups.

No definite dose-response relationships have been found in the aforementioned works, but in an earlier study on styrene-exposed workers Seppäläinen & Härkönen (74) found abnormal EEGs — mainly an increased amount of slow activity — in

Table 10. Electroneurographic results (mean $\pm$ standard deviation).

Variable ^a	Exposed group	Reference group 2
<i>Median nerve</i>		
Motor nerve conduction velocity (MCV)		
Distance 2-1 (m/s)	54.29 $\pm$ 3.93	55.91 $\pm$ 4.09 **
Distance 1-M (factor) ^b	1.85 $\pm$ 0.31	1.94 $\pm$ 0.26 *
Mixed nerve action potential (NAP), distance 1—2		
Conduction velocity (m/s)	61.46 $\pm$ 4.28	63.81 $\pm$ 4.82 ***
Amplitude (μ V)	26.74 $\pm$ 13.87	31.75 $\pm$ 15.81
Sensory nerve action potential (SNAP), distance D-1		
Conduction velocity (m/s)	53.13 $\pm$ 5.67	54.33 $\pm$ 5.79 *
Amplitude (μ V)	15.90 $\pm$ 8.34	17.75 $\pm$ 9.06
<i>Peroneal nerve</i>		
Motor nerve conduction velocity (MCV)		
Distance 2-1 (m/s)	46.32 $\pm$ 3.91	47.96 $\pm$ 5.44 *
Distance 1-M (factor) ^b	1.43 $\pm$ 0.29	1.45 $\pm$ 0.20
<i>Sural nerve</i>		
Sensory nerve action potential (SNAP), distance 1—2		
Conduction velocity (m/s)	40.32 $\pm$ 4.19	43.10 $\pm$ 4.77 ***
Amplitude (μ V)	7.23 $\pm$ 5.14	11.82 $\pm$ 7.95 ***

^a The distances given in the table are defined by the two points delimiting the distance in question. These points were placed as shown in fig 15. All recordings were performed with surface skin electrodes and concerning NAPs and SNAPs bipolarly with both electrodes along the nerve and with an interelectrode distance of 20 mm.

^b Factor = (distance/latency for muscle response) $\cdot$ 0.1 if distance is given in millimeters and latency in milliseconds.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ between the two groups. It should be stressed that, for these significance calculations, standard deviations pooled within groups and age strata were used. The standard deviation values given in the table were not pooled.

one-third of the subjects with a urinary mandelic acid concentration of more than 700 mg/dm³, whereas the prevalence of abnormal EEGs among the workers with a lower level of mandelic acid was only about 10 %.

Visual evoked responses

Several different functions are tested by means of VER, ie, the transmission in the optic radiation, as well as synaptic transmissions in the retina, the lateral geniculate body, and the cerebral cortex. Abnormal delay of the responses is usually supposed to indicate a lesion of the optic nerve. In the exposed group, a tendency towards such a delay was found, though not on a statistically significant level. Organic solvents are not considered to produce the type of neuropathy (demyelination) associated with a marked reduction of conduction velocity. Thus, a pronounced delay of the VER was hardly to be expected. The difference found concerning the amplitude of the VER (a larger mean amplitude in the exposed group than in the reference groups) is difficult to explain. Seppäläinen et al (76) found differences in flash-evoked VER between a group of n-hexane exposed workers and a reference group. Their results partially agree with ours, but the comparison is a difficult one due to differences in the stimulation technique used.

Electroneurography

The earliest subjective symptoms of neuropathy caused by long-term low level exposure to organic solvents are sensory; they appear — in agreement with the distribution of the pathological-anatomical changes — in the distal parts of the limbs, beginning in the feet (70, 73). In agreement we found the most significant ($p < 0.001$) differences between the exposed group and the referents in the function of the purely sensory sural nerve distally on the lower leg. However, we did not find any distal-proximal gradient for the peroneal nerve or the arm nerves. Unexpectedly, in the arms, the conduction velocity of the sensory nerves was less influenced ($p < 0.05$) than that of the motor fibers ($p < 0.01$) and the mixed nerves ($p < 0.001$).

In general, it is surprising that the conduction velocities were significantly affected while the amplitudes of the median nerve action potentials did not show any significant differences between the groups (fig 16). Previous experimental work has shown that most neurotoxic compounds cause axonal degeneration (8, 18, 70, 71).

In this type of nerve lesion, the conduction velocity is only slightly or not at all affected while the action potential is reduced (32, 56). As a matter of fact, a decrease in amplitude and a change of the shape of the nerve action potential is considered to be the most sensitive sign of neuropathy (48, 68).

In our investigation, the action potential proved to be a less sensitive index of nerve lesion, possibly because we used surface electrodes instead of needle electrodes. Examination with needle electrodes is painful and would have rendered the recruitment of subjects more difficult. Presumably, surface electrodes give a larger scatter of the measured amplitude values, and thereby the sensitivity is lowered. The figures in table 10 lend some support to this assumption. The differences in the amplitudes of the nerve action potentials between the exposed and reference groups were proportionally greater than the differences in conduction velocities, but they were nevertheless not statistically significant due to the great dispersion of the values.

The observed slight decrease in conduction velocity in the exposed group (table 10) is consistent with axonal neuropathy. It has been considered that the primary changes in the axon — with, eg, paranodal swelling — causes a secondary degeneration of the myelin so that the conduction velocity is affected (48). Also in other studies on workers with long-term exposure to organic solvents, an affection of the nerve conduction velocity has been found (3, 67, 75). In our study, the observed differences between the exposed workers and the referents were in general the most pronounced in the lower age groups. This result can depend on the healthy worker effect (57), which means that those whose health deteriorates as a result of influence of the occupational environment leave their work for another type of work. Consequently, a majority of the remaining

workers — in higher age groups — have suffered no or only slight damage due either to higher resistance or to other factors.

Vibratory perception thresholds

The exposed group had significantly higher vibration thresholds than reference group 2. A vibration threshold examination tests the function of large sensory nerve fibers. In clinical work, impaired vibration sensibility has long been regarded as an early sign of peripheral neuropathy. Lindblom & Goldberg (50) found, in an examination of jet fuel-exposed workers, that vibration thresholds were more sensitive than ENeG as a test of peripheral neuropathy.

According to Schaumburg & Spencer (72) light touch, pain ("pricking pain"), and temperature discrimination are more reduced than the vibration sense in cases of toxic occupational neuropathies. This possibility was not examined in our investigation, but the findings are unexpected since it is well known that the large fibers are those first affected while pain and temperature sensations are transmitted by small fibers.

An increased vibration threshold is not necessarily associated with sensory symptoms. On the other hand, it cannot be ruled out that an increased threshold can be related to impaired performance in tests requiring good tactile discrimination.

Conclusion

In conclusion, we wish to stress that the exposed group consisted of people in full daily work. A priori we do not have any reason to expect an overrepresentation of definitely pathological findings. Nevertheless, we found statistically significant differences between the exposed group and, in particular, reference group 2 that indicated a reduced function of peripheral nerves in the exposed group. However, the differences were small, and all the mean values were within normal limits. It is known that ENeG changes indicative of peripheral neuropathy can be found in patients (with, eg, diabetes, pernicious anemia, uremia) without symptoms or signs of sensory disturbances. The neurophysio-

logical findings from our subjects may therefore not be associated with obvious functional disturbances during ordinary daily activities.

NEURORADIOLOGICAL EXAMINATION

When this investigation was initiated, work in our department had recently indicated that degenerative changes of the brain of alcoholics can easily be detected by computed tomography (CT scanning) (60). This fact aroused an interest to determine whether changes of the same kind can be observed in industrial painters. CT scanning has the great advantage of being noninvasive, and the radiation dose is low, approximately of the same magnitude as that of an ordinary skull radiograph. The method is therefore, in contrast to pneumoencephalography, well suited for investigating large series of individuals.

Material and methods

The method and its theoretical principles will not be dealt with in detail. The reader can consult, for instance, Ambrose (4) and Hounsfield (41) for this information. Basically, an image of a slice of the brain (tomogram) is produced by computer calculations of data obtained from X-ray transmission recordings in the transversal plane. An accurate delineation of the anatomic structures is obtained, and at the same time the machine produces reliable values of the X-ray attenuation of the tissues incorporated in the slice.

An EMI-Mark I head unit was used. The whole brain was examined, usually requiring eight to ten tomographic cuts, each cut being 13-mm thick. The cuts were oriented parallel to the supraorbitomeatal plane. The pictures produced were composed of 160×160 picture elements.

The analysis of the CT scans was carried out on pictures obtained from the same terminal and all with the same window width and level of gray scale. Because of faulty tapes and other technical errors pictures with these specifications were not obtained for 18 individuals (evenly distributed in the different groups), and these CT scans were consequently not used for

the analysis of cortical changes or for direct measurements.

Furthermore all analyses were performed after a thorough random mixing of the individual scans and without access to any identification data whatsoever, ie, completely blindly. With the exception of cortical changes, which are reported for three separate investigators, no parameter was measured or estimated by more than one person.

Results

The analysis comprised three different parts. Part 1 consisted of an analysis of the frequency of calcifications and the incidence of local abnormalities in the shape of the ventricles and the cisterns (the fluid-filled cavities within and surrounding the brain). These parameters are listed in table 11. No significant differences could be demonstrated between the exposed and reference groups.

Part 2 comprised measurements carried out with vernier callipers directly from the CT scans of certain anatomic structures. The mean values of these variables, corrected for reduction in the scan, are

listed in table 12, which also includes a calculated anterior horn index (51). As seen from the table, a relatively large number of values were missing for the cerebral fissures. Often these structures cannot be delineated accurately with the technique used. However, since the number of missing values is of the same magnitude for the different groups, these mean values have been considered representative and have been included in fig 19, where the calculated differences for all linear variables are given as Z values. As seen from the figure, only one significant ($p < 0.05$) difference was obtained, ie, for inner transverse skull diameter (between the exposed group and reference group 1). It should be noticed, however, that all the mean values for the ventricular parameters were higher for the reference groups though the differences did not reach statistically significant levels.

The third part of the analysis consisted of an assessment of the cortical sulci, made by three independent investigators (two neuroradiologists, investigators 1 and 2 in fig 19, and one laboratory assistant with great experience with CT scan analysis, investigator number 3 in fig 19). The following rating scale was used: 1 = no

Table 11. Incidence of computed-tomography findings. (WTS = wide frontolateral sulci suggesting impeded cerebrospinal fluid circulation, PC = calcification of pineal gland, GCS = calcification of left glomus, GCD = calcification of right glomus, AL = calcification with other location, VFV = visualization of fourth ventricle, VTHS = visualization of left temporal horn, VTHD = visualization of right temporal horn, VCBC = wide cisterns in the posterior fossa)

Group	WTS	PC	GCS	GCD	AL	VFV	VTHS	VTHD	VCBC
Exposed	7	66	47	50	4	44	0	0	9
Reference 1	6	60	37	38	7	45	4	3	10
Reference 2	6	70	52	52	10	51	2	2	8

Table 12. Mean values of linear parameters of the computed-tomography analysis for the different groups.

Group	Left anterior horn		Right anterior horn		Anterior horn index		Largest inner skull diameter		Transverse diameter 3rd ventricle		Left sylvian fissure		Right sylvian fissure		Interhemispheric fissure	
	Number	Mean	Number	Mean	Number	Mean	Number	Mean	Number	Mean	Number	Mean	Number	Mean	Number	Mean
Exposed	73	16.95	73	16.29	73	0.26	73	130.12	62	4.40	30	4.62	27	5.07	48	6.59
Reference 1	70	17.01	70	16.79	69	0.27	70	128.41	60	4.71	27	4.67	24	4.92	49	6.42
Reference 2	74	17.39	74	17.14	74	0.27	74	129.57	70	4.77	39	4.88	46	5.11	51	5.96

changes = no widened sulci⁶; 2 = suspected degenerative changes = five to ten widened sulci in at least two tomographic cuts; 3 = clear-cut degenerative changes = wide sulci in most cuts; 4 = high grade degenerative changes = markedly widened sulci appearing in all lobes.

The ratings according to the classification were treated as continuous variables, and the results have been reported as mean values for each individual investigator (table 13). Calculated differences between the groups are reported as Z values (fig 19, lower part).

For two of the investigators there was a significant difference ($p < 0.05$) between the exposed group and reference group 2. The difference was negative (directed to the left in fig 19), which means a higher rating for the reference group. From table 13 it is furthermore obvious that the rating values were generally higher for the two reference groups.

An analysis of the ratings for different age strata in the exposed group and reference group 2 showed that the painters in the youngest age group generally had somewhat higher values than the referents, whereas the reverse was true for the older age groups. Furthermore, there was a tendency towards an increasing deviation between the groups with increasing age. For all three investigators, the difference between the painters and reference group 2 was the greatest in the oldest age group (56–65 a).

Discussion

Recent neuroradiological investigations have given evidence of brain atrophy in solvent-exposed workers with clinical cerebral symptoms (7, 36, 42).

The results obtained in our investigation showed certain differences in a direction opposite to those just referred to, ie, our results seem to indicate that our exposed workers had an increased relative brain volume when compared to the referents. It should be emphasized, however,

that the painters of the present study were clinically healthy and working when the examinations were undertaken, whereas the exposed workers of the other investigations referred to had been given neuroradiological examinations because of severe cerebral symptoms related to solvent exposure. Most of them were either retired on a disability pension or had had to change jobs.

One can only speculate as to the possible mechanisms behind our findings. The reason for an increased brain volume can be brain edema reflecting a low grade toxic effect of the organic solvents. It is, of course, not possible to decide whether the observed changes are reversible or not or whether they may pass into a stage with more degenerative characteristics.

Fig 19. Differences in the mean values of the linear computed-tomography variables of the exposed and reference groups expressed as Z values. Light bars represent reference group 1, and dark bars reference group 2.

Table 13. Rating of the cortical changes. Mean values for the different groups and different investigators.

Group	N	Investigator 1	Investigator 2	Investigator 3
Exposed	73	1.73	1.35	1.37
Reference 1	70	1.86	1.54	1.47
Reference 2	73	2.05	1.47	1.58

⁶ A sulcus is considered wide when its estimated width exceeds 1 mm in the CT scan, approximately corresponding to a real width of 4 mm.

Finally it should be mentioned that no consistent differences in the width of the Sylvian and intrahemispheric fissures were demonstrated between the groups, and the results do not indicate any derangement of the cerebrospinal fluid circulation in the exposed group.

nish epidemiologic study published by Raitta et al in 1976 (66). They found more lens opacities in a group of car painters than in a reference group of railway engineers, matched with respect to age. Because of this observation an ophthalmologic examination was included in the present study, special attention being paid to the possible occurrence of lens opacities.

OPHTHALMOLOGIC INVESTIGATION

It is well known that high concentrations of vapors from organic solvents can cause an acute transient irritation of the eyes with conjunctival redness and tearing. Some case reports also describe changes of the retina and the optic nerve in workers exposed to organic solvents (35, 86). It is likely that the levels of exposure have been relatively high, certainly higher than the levels measured in contemporary workshops. With these exceptions, no studies suggesting injury to the eyes from occupational exposure to organic solvents have been published until recently. Much attention was therefore drawn to a Fin-

Method

The eye examinations were performed by two ophthalmologists. The first 56 persons were examined and the findings evaluated by both ophthalmologists together. The following 14 persons were also examined by both ophthalmologists, but the findings were evaluated independently. The evaluation of the findings of the two ophthalmologists showed good reliability, and therefore the remaining 168 persons were examined only by one of the two. The workers came in pairs so that one exposed person and one person out of the first reference group were examined on the same occasion by the same doctor. The exposure

Table 14. Contents of the examination of the lens.

Item number	Object of examination	Evaluation
1	Capsule: Presence of coating material on or changes in the anterior lens capsule	Graded: 1 = absence, 2 = presence
2	Anterior subcapsular opacities (except vacuoles)	Graded from 1 to 5
3	Anterior subcapsular vacuoles	Graded: 1 = no vacuoles, 2 = one small vacuole, 3 = more than one small or one big vacuole
4	Posterior subcapsular opacities	Graded from 1 to 5
5	Posterior subcapsular vacuoles	Graded: 1 = no vacuoles, 2 = one small vacuole, 3 = more than one small vacuole or one big vacuole
6	Zones of discontinuity, zones with a slightly increased light scattering in the superficial lens cortex	Counted
7	Punctate opacities in the lens cortex	Counted in a 0.2-mm wide central slit light beam
8	Larger cortical opacities	Graded after their extension
9	Light scattering in the deepest part of the anterior cortex, the supranuclear zone	Graded from 1 to 5
10	Transparency of the nucleus	Graded from 1 to 5
11	Color of the nucleus	Graded from 1 to 5
12	Punctate opacities close to the suture lines in the nucleus	Graded: 1 absence, 2 = presence

was not known to the examiner. The second reference group was examined separately.

The corrected visual acuity of each eye was determined. The pupils were dilated to 7–8 mm with 1% Cyclogyl® and 10% Neosynfrine®. The anterior segment of the eye was examined with a Haag-Streit 900 slit lamp microscope. The central fundus was inspected with direct ophthalmoscopy. The intraocular pressure was measured with applanation tonometry in persons over 40 a of age. The slit lamp examination comprised, in particular, a thorough examination of the lens. The lens opacities found were photographed with a Nikon photo slit lamp and marked in a schematic drawing of the lens. The form used for the lens examination is shown in table 14.

Results

The occurrence of clinical pathological ophthalmologic findings was of the same proportion among both the exposed and the nonexposed workers (table 15). The suspected or clearly pathological lens changes are presented in table 16. There was no predominance of lens changes in the exposed group. The lens opacities were in no case big enough to cause reduced visual acuity. The intraocular pressure in persons over 40 a of age was of the same order of magnitude in all the three groups.

The statistical analysis of the lens data and the visual acuity showed only small differences between the exposed and reference groups (fig 20). The number of posterior subcapsular vacuoles was slightly higher in reference group 1 than in the exposed group (see also table 16). The diffuse opacity and the yellow color of the nucleus were more pronounced ($p < 0.05$) in reference group 2 than in the exposed group. Punctate opacities close to the suture lines in the lens nucleus showed significant differences between the exposed and both of the nonexposed groups. These opacities were found more frequently in the exposed persons than in the nonexposed ($p < 0.05$ and < 0.001 for reference groups 1 and 2, respectively).

When the material was divided into age groups, no additional significant differ-

Table 15. Number of persons in the examined groups with pathological eye changes.

Pathological finding	Exposed group	Reference group 1	Reference group 2
Amblyopia of one eye	5	1	1
Keratoconus		1	
Central chorioretinal scars		2	
Degenerative maculopathy	1	2	1
Diabetic retinopathy	1		1
Congenital atrophy of the optic nerve	1	1	
Glaucoma	1		
Grave myopia			1

Table 16. Number of persons in the examined groups with suspected or clearly pathological lens changes in at least one eye.

Pathological finding	Exposed group	Reference group 1	Reference group 2
Anterior subcapsular opacities			1
Anterior subcapsular vacuoles	1	1	2
Posterior subcapsular opacities	3	5	2
Posterior subcapsular vacuoles	11	18	16
Small cortical opacities (except punctate)	11	16	20
Larger cortical opacities	5	6	6
Punctate opacities in the nucleus	43	29	20

Fig 20. Differences between the exposed and reference groups in regard to the mean values of visual acuity and lens parameters according to the description in table 15. The differences are expressed in Z values. Light bars refer to reference group 1, and dark bars to reference group 2.

ences were found between the exposed and reference groups. However, in the whole material, there was, as could be expected, a distinct correlation between age and some parameters. With increasing age, visual acuity was reduced, the number of opacities in the lens cortex increased, the degree of light scattering in the supranuclear zone increased, the transparency of the nucleus decreased, and its yellow-brown pigmentation increased.

Discussion

Toxic cataract is primarily known as a side effect of treatment with corticosteroids (13) and cholinesterase inhibitors (10, 64). The drugs that were first described to cause cataracts were dinitrophenol and dinitrochresol. These drugs were given for reducing purposes in the 1930s and were found to cause a cataract in 1% of the persons treated (40). Other substances that have been reported to cause cataracts in humans are triparanol (43), a cholesterol-lowering drug now withdrawn from the market, naphthalene (31), myleran (65), and phenothiazines (78).

Recently, organic solvents used in car paint have been strongly suspected to induce lens changes (66). Nau et al (62) have shown experimentally that the inhalation of high concentrations of some fractions of petroleum distillates can cause cataracts in rats. This result must be interpreted with a certain amount of caution as the general condition of the animals was poor at the onset of cataract.

The first lens change due to toxic influence on the lens is very frequently the appearance of subcapsular vacuoles and subcapsular opacities. Disturbed function of the lens epithelium has been shown experimentally to be an important pathogenic factor in toxic cataracts (69).

In the present study, all visible subcapsular changes and opacities in the cortex and the nucleus of the lens were registered. The diffuse light scattering in the zones of discontinuity, the supranuclear zone, and the nucleus was also estimated. The mean values for the diffuse opacity and yellow color of the nucleus in reference group 2 were 0.14 and 0.16 units higher, respectively, than for the

exposed group. This grading from 1 to 5 was performed without any objective reference system. Consequently it contains a relatively large subjective factor which is minimized when one exposed person and one referent are examined at the same time. This was the case for reference group 1. Reference group 2 was examined later and the larger difference in values for diffuse scattering and yellow color of the nucleus can possibly be explained by a small change in the grading scale.

The most likely effect of organic solvents on the nucleus would have been opacification. This is a known effect of dimethylsulfoxide (DMSO) which, after oral intake, causes an increased nuclear density in several experimental animals (46). The only parameter for which a significant difference was found with respect to both reference groups was microopacities in the suture area of the nucleus (fig 20).

These opacities, due to their position in the lens, can be expected to be congenital changes. However, the distinct predominance for these opacities in the exposed group (table 16) makes it obvious that an effect of the solvents cannot be excluded. The microopacities were vacuoles close to the sutures, ie, at the ends of the lens fibers. Fagerholm (23) has shown experimentally that the ends of lens fibers are sensitive to changes in the ionic environment, resulting in formation of vacuoles. The influence of organic solvents may cause osmotic disturbances in the central parts of the lens and lead to a similar formation of vacuoles.

Our results differ from the results of the Finnish study (66) in which significantly more lens opacities were found among car painters than among referents when age-matched pairs were compared.

In our study a similar comparison of pairs composed of one person from the exposed group and one from reference group 1 produced 18 pairs in which the exposed person had more lens opacities, 23 pairs in which the nonexposed had more opacities, and 35 pairs without any observed difference. When reference group 2 was used for the same comparison, the following results were obtained: in 24 pairs the exposed person had more lens changes, in 24 pairs the nonexposed had more, and in 28 pairs no difference was found. These numbers do not show any

significant differences. In our own, as well as in Raitta's Finnish investigation, the small opacities in the center of the lens were not considered. The Finnish reference group consisted of railway engineers, who are a group with high demands on vision, a fact which might influence the result. Other differences between the two investigations might be the method of documenting minimal lens opacities.

To summarize, we have found an increased frequency of microopacities in the central parts of the lenses of the exposed persons. On the other hand, there were no indications that prolonged exposure to solvent vapors, at the levels in question, causes reduced vision or induces cataract formation. Acute effects of solvents on the conjunctiva and the cornea were not studied.

SUMMARY

As indicated in the introductory sections, the purpose of this investigation was to ascertain whether a group of workers with long-term occupational exposure to solvents differed from other, analogous groups of unexposed workers in regard to the nervous system and sensory functions. Both the car painters and industrial painters, as well as the industrial workers in the reference groups, were fully fit for work, and there was no reason to expect any grave clinical abnormalities among them. It was therefore necessary to use methods which, as far as was possible, would permit differentiation within the clinically "normal" range.

The results from the occupational hygiene study yielded a time-weighted mean value of 0.21 for the hygienic effect for both the car and industrial painters. The same mean value for two individuals need not imply the same biological effect: a steady exposure to levels near the mean value could have another (and perhaps milder) effect than exposure to extremely high levels alternating with low levels, or periods of no exposure. It should also be noted that, when the hygienic effect is being evaluated, a purely additive effect from the various solvents is presumed. However, a potentiating synergism among

different solvents cannot be ruled out. These problems were not examined in our investigation.

The painters were also exposed to lead, although usually in relatively low doses (exposure levels below one-fifth of the accepted limit). The industrial painters were considered to have been less exposed to lead than the car painters; this has definitely been the case at any rate over the past 20 a. Since the same effects were found among younger industrial workers as among the group of painters as a whole, it is our view that solvent exposure has been the most important factor responsible for the observed difference between the exposed group and the reference groups.

It has recently been demonstrated that certain solvents have a relatively long half-time (days) as regards elimination from the human body (22). The painters in our study were definitely unexposed to solvents for only 18–24 h prior to examination. We therefore do not know to what extent the observed effects were or were not reversible. Presumably, several months without exposure would be necessary to shed light on this question. However, the question is but of secondary importance for standard setting (TLV). As long as painters work under exposure to the solvent concentrations found in this investigation they are affected, regardless of whether the symptoms are reversible or not.

We approached the problem of the neurotoxic effect of occupational exposure to solvents in this study from a number of perspectives, employing methods from various disciplines. It should be stressed that the different results all point in the same direction. In the questionnaires and the controlled psychiatric evaluations, the exposed subjects exhibited more neuroathenic symptoms than the reference subjects; they performed more poorly on psychological tests of memory, manual dexterity, perceptual speed, and reaction capability; and in neurophysiological tests they had slower nerve conduction velocities, lower nerve action potentials, and higher vibratory perception thresholds. In addition the results from computed tomography and eye examinations revealed certain differences among the groups.

Since the study was designed so that

only exposure to solvents should distinguish the exposed group from the reference groups and since lead exposure was not felt to be an adequate explanation for the observed differences among the groups, the conclusion seems to be warranted that solvent exposure was the cause of these differences.

We have not been able to demonstrate a correlation between degree of exposure and extent of effect (dose-response correlation). The measure of exposure defined proved to have a very high correlation with age. Some correlation between age and effect was demonstrated in some of the studies although not without ambiguity. Indeed, it is probably very difficult in an investigation of this nature to ascertain a dose-response relationship on account of the healthy worker effect.

In conclusion, it should be pointed out that the measured solvent concentrations — both the current levels and the levels from the reconstructed model of a workplace of 25 a ago — were less than half of the TLV of the current Swedish standard. The same was true for Finnish car painter studies (see the introduction).

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