Scand. j. work environ. & health 2 (1976) 14—20

A case-referent study on neuropsychiatric disorders among workers exposed to solvents

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AXELSON, O., HANE, M. and HOGSTEDT, C. A case-referent (case-control) study on neuropsychiatric disorders among workers exposed to solvents. *Scand. j. work environ. & health* 2 (1976) 14—20. Published reports give justification for the belief that long-term exposure to solvents might induce chronic but nonspecific neuropsychiatric conditions. This case-referent study of data from a regional Swedish pension fund register indicated a risk ratio of 1.8 in regard to nonspecific neuropsychiatric disorders among workers such as painters, varnishers and carpetlayers who are exposed to solvents as compared to workers not so exposed. Moreover a dose-response relationship seems to exist between exposure in terms of occupational years and neuropsychiatric conditions, the result being that persons affected are considered eligible for disability pensions.

Key words: Solvent exposure, neuropsychiatric disorders, case-referent (case-control) design, painters, varnishers, carpetlayers.

Although some knowledge exists of the acute effects of various industrial solvents upon the nervous system, comparatively little attention has been paid to the possible effects of long-term exposure. Nevertheless, numerous case reports in the literature [Browning (2) can be consulted for a review.] seem to indicate that conditions of impaired function in the nervous system, chronic to varying degrees, do in fact occur. These conditions are presumably often overlooked by reason of a nonspecific clinical picture. Disturbances in memory, thinking, and the affective state have thus been reported in workers exposed to trichloroethylene, carbon disulfide, and toluene (14), and trichloroethylene may influence visual attention (3). Lindström (6) found an impaired performance in psychological tests in a study of groups of workers with different types of solvent exposure (such as xylene, toluene and "thinners") in comparison with nonexposed controls. Recent reports on chronic poisoning by petroleum products (jet fuel and gasoline) (5, 16) have mentioned nonspecific symptoms of the central nervous system such as headache, giddiness and forgetfulness, insomnia, etc., although to a major extent these investigations were concerned with neuropathies. In a review of the applications of neurophysiological methods in occupational medicine, Seppäläinen (15) stated that at times symptoms in the nervous system are vague; consequently specific signs may be difficult to detect in purely clinical examinations. In view of these reports it seems reasonable to believe that possible mental and neurological disorders attributable to solvent exposure might be referred to different entities of neuropsychiatric disorders or simply regarded as "nervousness."

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These general aspects, along with our recent clinical experience of complaints from painters and workers undergoing similar exposure and our observations of the impaired performance of painters in psychological tests (1, Hane et al., to be published), have led us to undertake a retrospective case-referent (case-control) study (7, 13) on neuropsychiatric disorders in painters, varnishers, and carpetlayers, all of whom are workers with relatively intense exposure to turpentine and mixtures of aliphatic and aromatic hydrocarbons, especially since the early 1950s.

MATERIAL AND METHODS

Source of subjects. A regional pension fund register was used as the source of subjects for the study. Since the Swedish social security system provides a disability pension to all disabled persons, this register constitutes a complete source of information about all the individuals for whom pensions have been suggested by reason of disease. Moreover medical data, including diagnoses specified with varying degrees of detail, are available through the register. Information is included on the social situation and, to a large extent, also data on years of employment, etc., in various occupations.

An obvious drawback of the pension fund register for studies of mental disorders in relation to certain occupations is that those individuals who had never possessed the qualifications to become skilled workers such as painters, varnishers and carpetlayers would presumably be overrepresented among individuals considered for pension as a result of psychiatric disorders. Consequently in a case-referent study particular precautions must be taken in the selection of subjects to ensure comparability between cases and referents.

Subject selection. The characteristics of the pension fund register, as mentioned earlier, called for the subjects to be restricted so that they included only skilled workers in reasonably well-defined occupations, chosen so that they had some general connection with the construction industry. The different occupations studied are indicated in table 1. They correspond to the classification in Sweden's official statistics. The age limits were set at 35 and 64 years so that young individuals without pertinent exposure would not dilute the material. The time-span covered the years 1969 through 1973. Geographically the study was confined to the province of Örebro (total population about 275,000).

Selection of cases. Individuals considered for a disability pension because of some type of mental disorder, also in combination with somatic disorders, were selected as cases, except when primary debility, schizophrenia, or mano-depressive psychosis of the circular type was the diagnosis. Mental diseases of obvious somatic origin, such as dementia from a traumatic brain injury, encephalitis, etc.. were not accepted either. Since the diagnoses of cerebral atrophy and presenile dementia might represent the same condition, it seemed reasonable to include cerebral atrophy among the cases. In the light of current knowledge, as earlier outlined, a diagnosis of headache of unknown origin or unspecified vertigo was also accepted as a case.

Alcoholism was of particular interest in this context since symptoms arising from solvent exposure might easily be referred to the abuse of alcohol. Consequently alcoholism was also accepted as a "case" in this study. Moreover, if other neuropsychiatric diagnoses were combined with alcoholism, alcoholism was considered as the main diagnosis. Otherwise, the neuropsychiatric diagnosis reported first was taken as the main one. The cases were classified as indicated in table 2, following the WHO classification (17), although a divergent distribution could have been achieved, particularly as far as the nonspecific cases of "nervositas" are concerned. However it should be stressed that few problems arose in deciding whether an individual was acceptable as a case according to the particular neuropsychiatric diagnoses applied in the study (table 2).

Selection of referents. The referents were all skilled workers in the pension fund register who were completely free of any kind of mental disorder or social experience which might indicate mental disorder. No person with any type of brain injury was accepted as a referent.

Comparability of cases and referents. The application of these relatively strict principles in the selection of subjects makes it reasonable to believe in the achievement of an acceptable comparability of cases and referents. Further confirmation of this assumption was gained with the use of a random sample from the telephone directory and data from official statistics (Central Bureau of Statistics), as shown in table 1. However these data represent the cross-sectional view, and the table does not make any adjustment for age. Thus, although it is indicative, no full comparability exists in the figures listed in table 1, particularly between the longitudinal data (cases and referents) and the cross-sectional data. (Almost everyone in Sweden has a telephone.)

Assessment of exposure. Exposure was defined as years of painting, varnishing, or carpetlaying. It averaged about 30 years, the minimum being 6 months. The exposure was dichotomized at 30 years as indicated in tables 3 and 4.

When the duration of occupation as painters, varnishers, and carpetlayers is regarded as exposure, age becomes a confounding factor (9). This is hardly so if only the occupation as such is taken as the exposure since there is no reason to believe that skilled workers change jobs as they get older.

Statistical methods. The statistical analyses of the data were based upon the Mantel-Haenszel procedures (8) for the calculation of p-values and for the estimation of the overall risk ratio. The principles applied for the determination of the standardized risk ratios have been outlined by Miettinen (11) along with the method for calculating the confidence interval of the risk ratio (12).

Table 1. Percentage distribution of workers in different skilled occupations, unadjusted for age. (See text on comparability within table.)

Occupation	Cases		Referents	Telephone directory sample	Province of Örebro[a]
	Alcoholism excluded	Alcoholism included			
Mechanics, Machine fitters, Repairers	34.6	29.8	25.9	29.6	29.6[b]
Platers	5.1	5.8	7.0	7.2	7.7
Plumbers	9.0	12.5	4.3	3.6	6.1
Welders	12.8	10.5	9.2	7.2	10.1
Electric and telephone workers	11.5	11.5	11.4	16.2	19.1
Woodworkers	23.0	22.1	30.8	28.9	22.7
Painters, Varnishers, Carpetlayers	(33.3)[c]	(33.7)[c]	(18.9)[c]	(12.7)[c]	(9.3)[c]
Bricklayers	3.8	6.7	10.3	4.8	3.3
Concrete workers and similar types of workers	(11.5)[c]	(11.5)[c]	(15.1)[c]	— [d]	(12.8)[c]
Insulation workers	0.0	0.0	0.5	1.2	0.6
Glazers	0.0	1.0	0.5	1.2	0.9
Total	78	104	185	166	13091

[a] Source: Central Bureau of Statistics, Special communication, 1970.

[b] Estimated value; official statistics seem to include several more occupations than do other sources.

[c] As percentage of other occupations, but excluding painters, varnishers, carpetlayers, and concrete workers and similar types of workers.

[d] Excluded from total number, as concrete workers and similar types of workers were unidentifiable in the telephone directory.

Table 2. Number of exposed and nonexposed cases, according to the type of diagnosis, and the corresponding classification of referents with regard to exposure.

Diagnosis (WHO)	Exposed	Nonexposed
Cases		
(290) Dementia senilis et presenilis	7	17
(296—297-excl. 296.10; 296.30) Psychosis affectiva et status paranoicus (excl. psychosis mano-depr., typus manicus et circularis)	1	5
(300—301) Neurosis (neurasthenia) et persona pathologica	6	34
(303) Alcoholismus	9	30
(309.20) Perturberationis mentis per laesionem cerebri	2	1
(347) Morbi cerebri alii (atrophia cerebri)	0	5
(780.50; 781.70) Vertigo; Encephalopathia	2	2
(790-excl. 790.19) Nervositas (excl. debilitas)	7	21
(791.99) Cephalalgia NUD	1	1
(290—791.99) Neuropsychiatric disorders	35	116
Referents	35	213

RESULTS

Table 3 illustrates that the study included 151 cases and 248 referents. A total of 35 individuals were found to have been exposed both among the cases and among the referents, i.e., they had a history of painting, varnishing, or carpetlaying. Thus 23 % of the cases and 14 % of the referents had a history of exposure according to the criteria adopted. The crude risk ratio was consequently 1.8 for neuropsychiatric disorders among the painters, etc., in relation to the "nonexposed," i.e., to the other categories of skilled workers in the study. In table 4 the cases of alcoholism have been excluded, but the relative frequency of exposure among the cases does not change. It seems unlikely that the distribution of exposed persons among the cases and referents is attributable to chance, as table 3 gives χ^2 (1) = 5.24; p $\doteq$ 0.01 (one-tailed) and table 4 gives χ^2 (1) = 4.28; p $\doteq$ 0.02 (one-tailed).

A dose-response relationship between the exposure and neuropsychiatric disorders is indicated by the elevated risk ratio with increasing years of exposure. This relationship is furthermore independent of the diagnosis of alcoholism.

DISCUSSION

Since mental disorders are problematic from the diagnostic standpoint, some of the diagnoses might be inadequate. However, there is little reason to believe that deficiencies in the diagnoses are related to the particular occupations studied. Therefore this type of observational bias will not invalidate the results obtained. Although classification of the different neuropsychiatric diagnoses in terms of table 2 is somewhat arbitrary, it does indicate the types of disorders which might bear a relationship to exposure in painting and similar activities.

Although a diagnosis such as "nervositas" might be regarded as weak, such diffuse conditions cannot be excluded as long as no definition exists of clear-cut syndromes induced by exposure to solvents. Again, there is no reason to be-

Table 3. Duration of solvent exposure, i.e., number of years employed as a painter, varnisher or carpetlayer (average 30.7 yr), according to age and with the cases of alcoholism included, along with various estimates of risk ratio.

Age	Cases/referents	Duration of solvent exposure			
		0	≤ 30	> 30	> 0
35—44	Cases	7	2	0	2
	Referents	4	1	0	1
45—54	Cases	28	4	2	6
	Referents	23	3	2	5
55—64	Cases	81	8	19	27
	Referents	186	13	16	29
35—64	Cases	116	14	21	35
	Referents	213	17	18	35
Crude risk ratio		(1.0)	1.5	2.1	1.8
Standard morbidity ratio		(1.0)	1.3	2.2	1.7
Standardized risk ratio[a]		(1.0)	1.3	2.1	1.8
Overall risk ratio (Mantel-Haenszel)					
— point estimate					1.8
— 95 % confidence interval					1.2—2.7

[a] With the nonexposed as the standard.

lieve that these diffuse conditions (under the null-hypothesis) bear any particular relationship to exposure or nonexposure (in terms of occupation or occupational years), which is the proper concern in case-referent studies.

Exposure was recorded by the same method for both cases and referents since the pension fund register provided notes on the numbers of years spent by cases and referents in the different types of occupations.

Apart from observational problems, attention should be given to the question of whether people in certain occupations might have been more readily considered for disability pension because of neuropsychiatric disorders or alternatively for other types of disease. Individuals suffering from, say, mental retardation and schizophrenia seemingly tend to remain unskilled, the result being a possible overrepresentation of such diagnoses among individuals in unskilled occupations. Accordingly these diagnoses and occupations were excluded from the study. Similarly the possibility exists that some occupations could demand great physical exertion, causing individuals suffering from heart disease, osteoarthrosis, etc., to become ready candidates for a disability pension. If such physically demanding occupations were overrepresented among the referents, a relative underrepresentation of exposed persons would occur in the referent group, with a consequent increase in the risk ratio. Examination of table 1 indicates however that the physical strain involved in painting, varnishing, and carpetlaying corresponds to that experienced in the other occupations. Table 1 also illustrates reasonable consistency in the relative distribution of the different occupations among the cases and referents. When a comparison is made of the relative distribution of various occupations among both people with telephones and Sweden's official statistics, it is noteworthy that the painters, etc., might even be overrepresented among the referents, i.e., the actual risk ratio of neuropsychiatric disorders found in this study could be an underestimate of the true situation.

Consideration is also due to confounding factors, but only age was accounted for by stratification in the analysis of the data. Tables 3 and 4 indicate that age

Table 4. Duration of solvent exposure, i.e., number of years employed as a painter, varnisher or carpetlayer (average 30.5 yr), according to age and with the cases of alcoholism excluded, along with various estimates of risk ratio.

Age	Cases/referents	Duration of solvent exposure			
		0	≤ 30	> 30	> 0
35—44	Cases	3	1	0	1
	Referents	4	1	0	1
45—54	Cases	21	3	2	5
	Referents	23	3	2	5
55—64	Cases	62	5	15	20
	Referents	186	13	16	29
35—64	Cases	86	9	17	26
	Referents	213	17	18	35
Crude risk ratio		(1.0)	1.3	2.3	1.8
Standard morbidity ratio		(1.0)	1.1	2.4	1.7
Standardized risk ratio[a]		(1.0)	1.1	2.3	1.8
Overall risk ratio (Mantel-Haenszel)					
— point estimate					1.8
— 95 % confidence interval					1.0—3.2

[a] With the nonexposed as the standard.

only introduces weak confounding since the standard morbidity ratio differs little from the crude risk ratio (10) even when the exposure takes the form of occupational years. It is apparent that when the occupation as such is used as a measure of exposure, age will not introduce a confounding of any importance, as skilled workers do not tend to change professions as they age. Confounding factors other than age can hardly be strong enough to cause a serious bias in the study. Moreover it was thought unnecessary to consider the influence of age in categories of less than 10 years.

The observations initially discussed in this paper make it seem likely that the exposure to solvents involved in these particular occupations might have had an etiological significance. The most common solvents are turpentine and mixtures of aliphatic and aromatic hydrocarbons within the C_6-C_{10} range, but little is known of the amount of exposure by inhalation or skin absorption. Our experience has shown that amounts of several hundred parts-per-million of such hydrocarbon solvents are not uncommon, and similar results have been found in an experimental study (4). The exposure to paint pigments is probably of minor importance, and, for Swedish painters at least, exposure to lead is rather unusual because of the special regulations for the utilization of lead pigments in paints. Other exposures, such as to components of modern plastic paints, substances for wood preservation, and so on, should be kept in mind, but currently too little is known of such exposures to permit a relevant discussion.

One conclusion which might reasonably be drawn from this study is that neuropsychiatric disorders bear some relation to exposure in such occupations as painting, varnishing and carpetlaying. In the light of previous reports it is likely that exposures to different solvents play an etiological role.

ACKNOWLEDGMENTS

This investigation was supported by Arbetarskyddsfonden (The Swedish Workers' Protection Fund), grant 75/3.

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Received for publication: 1975-08-19