ENVIRONMENTAL RESEARCH 61, 107–116 (1993)

Acute and Chronic Neurological Symptoms among Paint Workers Exposed to Mixtures of Organic Solvents[1]

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Received June 6, 1991

The purpose of this study was to determine the prevalence rates of acute and chronic neurologic symptoms among paint workers and the association of such symptoms with the severity of exposure to mixtures of solvents. Two paint manufacturing factories and 25 various kinds of spray painting factories were selected for study. Air concentrations of organic solvents were measured by personal samplers and were analyzed by gas chromatography. A total of 196 workers were given a screening neurological examination and a questionnaire on acute and chronic neurologic symptoms. A detailed personal medical history and a profile on alcohol consumption and medication were also included. The results showed that xylenes and toluene were the major solvents found in almost all the air samples with average contents of 50 and 24% on a weight basis of 73 air samples. We classified workers according to different exposure patterns and different air concentrations of breathing zones: high (8-hr hygienic effect, 0.25–9.86; median, 1.66), short-term high (hygienic effect, 0–3.38; median, 0.12), and low (hygienic effect, 0–0.38; median, 0.12). All workers showed no overt neurological signs such as ataxic gait, poor coordination, or muscle weakness. After excluding those workers who consumed more than 280 g of alcohol per week ($n = 8$), took antihypertensive medications ($n = 4$), or were treated with antipsychotic agents ($n = 1$), we found that the severity of exposure was associated with acute symptoms of headache and chest tightness and chronic symptoms of dizziness, easy fatigability, depressed mood, and palpitation. There was no association between peripheral neurological symptoms and the severity of exposure. Workers in the high exposure group were 2.7 times more likely to develop two or more acute symptoms and 3.3 times more likely to develop three or more chronic symptoms of the central nervous system than the low exposure group. After modeling by multiple logistic regression, we concluded that exposure to a medium level of mixtures of solvents (hygienic effect exceeding 1.66) may produce acute and chronic central neurological symptoms. © 1993 Academic Press, Inc.

INTRODUCTION

Organic solvents have been widely used in various industrial processes since the middle of the last century, and their neurotoxic effects were recognized early (Frost *et al.*, 1885). Although neurological symptoms are usually regarded as the earliest health effect from solvent exposure (Axelson and Hogstedt, 1988), they are very nonspecific and can be confounded by medication, alcohol consumption, smoking, psychological stress, etc. (Triebig *et al.*, 1988; Johnson, 1987; Estrin and Parry, 1990). Differences in case definition, methods of exposure assessment,

[1] Presented at the Fourth International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, July 8–11, 1991, Tokyo, Japan.

0013-9351/93 $5.00

study design, and strategy of analysis further complicated the interpretation of a causal association between subjective symptoms and solvent exposure. Thus, it is not surprising that subjective symptoms alone have not been regarded as a general tool for the early recognition of solvent hazards. Although neurobehavioral tests may be a more objective tool for detecting the health effects of solvent exposure, they also suffer from the similar drawback of being nonspecific (Rosenberg, 1990).

As questionnaires of subjective symptoms are very inexpensive and convenient to administer at the workplace, it may be worthwhile to develop a standardized questionnaire which, in combination with good epidemiological design and analysis, may be useful for the early detection of solvent neurotoxicity.

Because exhaust ventilation is generally not appropriately designed or installed in Taiwan, we are concerned that workers exposed to mixtures of solvents might suffer from neurotoxicity in the workplace. The purpose of this study is to determine the prevalence rate of abnormal neurological symptoms among paint workers and the relationship between such symptoms and exposure to solvents. In addition, to falsify this causal and dose–response relationship, we try to control possible confounding by various factors. In order to achieve this goal, we have enrolled a reference group with the same socioeconomic status, education, and life-style.

MATERIALS AND METHODS

In Taipei city, there were 2 factories of paint manufacturing, 3 factories of video terminal painting, 2 factories of aircraft painting, 1 factory of trailer spray painting, 2 factories of model spray painting, and 1 painting department of a car assembly factory. All workers who had been working in these factories for over 1 year were included in our study. There were over 200 car-painting factories in Taipei city from which a random sample of 16 of them were selected for our study (through random numbers). Thus, a total of 196 workers were enrolled in our study.

We took a walk-through survey for each factory before we performed air sampling to determine exposure zones (Corn and Esmen, 1979). Air concentrations of organic solvents were measured by personal samplers and later analyzed by gas chromatography (GC) with a Perkin–Elmer Sigma 3B model and a flame ionization detector. The GC analytic conditions were as follows: the column, a Mega Bore OBWAX-30m with film thickness 1.0 μm, was programmed from 40 to 100°C with an incremental rise of 10°C/10 min. The injection temperature was 150°C, while the detector temperature was 200°C. The elevated nitrogen gas flow was set at 8 ml/min. Under this condition, we were unable to separate all isomers of xylenes, but were successful in distinguishing the major contaminants which were listed in Table 1. We took two to four air samplers at each factory according to the number of exposure zones. Because some factories were relatively small, only two exposure zones (e.g., paint spraying and filling and polishing) can be identified among them. Seventy-three air samples were collected, each representing at least 4 hr of continuous exposure during a complete workday. During the walk-through survey we found that car painters had the most serious exposure when working in a poorly ventilated painting booth; they must spend 0.5–1.5 hr in the painting booth every workday. Because the fluctuation of solvent exposure should be taken into account, we took 9 additional air samples which were randomly chosen from the above 16 car painting factories. All of the 9 air samples were collected from workers' breathing zones when car painters were actually working in the painting booth.

All the workers were given a subjective symptoms questionnaire, a comprehensive physical examination, and a liver function test. The subjective symptoms included in our questionnaire were translated and modified from Hogstedt *et al.* (1984). They include acute central nervous system (CNS) symptoms experienced during the workday, chronic CNS symptoms experienced during the past month, and symptoms of the peripheral nervous system. All the above symptoms were recognized as "positive" only when they occurred at least once per week independent of any other known medical problems such as the common cold. In addition, the questionnaire contains a detailed personal medical history including alcohol consumption and smoking and an extensive occupational history about previous exposures and duration of employment. All the interviews of the questionnaire were conducted by two standardized interviewers in the field during the medical examination. The association between the solvent exposure and biochemical alterations of liver function has been discussed in another paper (Chen *et al.*, 1991).

The workers were exposed to a mixture of solvents. Eight different solvents were detected in the air. The average contents of xylenes and toluene in these air samples were 50 and 24%, respectively. The air concentrations were expressed as an 8-hr time-weighted average (TWA) (Table 1). The hygienic effect is used as a measure of total solvent exposure and is defined as the sum of the fractions of the respective threshold limit values (TLV) (ACGIH, 1990) that each solvent represents. We divided workers into three groups according to their different exposure patterns and different categories of air concentrations in our analysis. These three groups are defined as follows:

TABLE 1

DETECTED SOLVENTS AND THEIR CONCENTRATIONS IN THE AIR SAMPLES OF PAINT WORKERS

Solvents	Range (ppm)	Median (ppm)	Mean ± SD (ppm)	TLV–TWA[a] (ppm)	Number of samples exceeding the TLV
Xylenes	0–365	18	33 ± 77	100	7
Toluene	0–540	10	16 ± 67	100	2
Acetone	0–124	3	8 ± 25	750	0
Benzene	0–20	1	2 ± 4	10	3
Methyl isobutyl ketone	0–68	0	2 ± 10	50	1
Methyl ethyl ketone	0–70	1	2 ± 9	200	0
Ethyl acetate	0–29	1	1 ± 4	400	0
Butyl acetate	0–41	0	2 ± 7	150	0

Note. All figures are expressed as an 8-hr time-weighted average. (Number of samples, 73; sampling period, 4 hr).

[a] TLV, threshold limit value recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1990.

Exposure index 0: This is the low exposure group, including 3 video terminal painting (39 workers), 2 aircraft painting (7 workers), 2 model painting factories (2 workers), and 1 painting department of a car assembly factory (10 workers). They were exposed to a relatively low level of organic solvents. The individual solvents detected in the personal samplers were all below ¼ TLV level of that recommended by the ACGIH (TLV–TWA) (ACGIH, 1990), while the 8-hr TWA hygienic effect of solvents ranged from 0 to 0.38; the median level was 0.12.

Exposure index 1: This is the short-term high exposure group, including 80 workers who were selected from 16 car-painting factories. They were exposed to a low level of organic solvents, the 8-hr TWA hygienic effects of solvents ranged from 0 to 3.38; the median level was 0.12. However, they must spend 0.5–1.5 hr in poorly ventilated painting booths every workday; the 15-min TWA hygienic effect of solvents while working in the painting booth ranged from 1.32 to 24.52 and the median level was 10.40. Because such a high level of exposure is usually limited to less than 1.5 hr among car painters, they are defined as the short-term high exposure group. While the kinds of major solvents detected inside and outside the painting booths were not different from each other, the concentration of toluene detected inside the booth is usually higher than that of xylenes (range, 11–948 vs 25–511 ppm; median, 354 vs 112 ppm).

Exposure index 2: This is the high exposure group, including 2 paint manufacturing (19 workers) and 1 trailer painting (39 workers) factories. Most of the workers are exposed to xylenes and toluene. The air concentrations of xylenes and toluene detected in the breathing zone are usually above the ½ TLV level recommended by the ACGIH. The 8-hr TWA hygienic effect of solvents ranged from 0.25 to 9.83; the median level was 1.66.

For comparison of each neurological symptom among different exposure indices, workers with or without a particular symptom were stratified by age and exposure indices and then analyzed by Mantel–Haenszel summary procedure (Mantel and Haenszel, 1959) and the Mantel extension for the test of trend (Mantel, 1963). Based on the 90th percentile for the numbers of the acute and chronic symptoms among workers of the low exposure group, a multiple logistic regression analysis and the Mantel–Haenszel procedure were performed to estimate the odds ratio and trends along the different exposure indices, simultaneously taking into consideration age and smoking effects.

RESULTS

A total of 196 workers were investigated. We divided workers into 3 groups according to their different exposure patterns and different categories of air concentrations as mentioned before. In general, workers with higher exposure were older and employed longer than the other 2 groups (Table 2).

All the workers showed no overt neurological signs such as ataxic gait, poor coordination, or muscle weakness. Workers who consumed more than 280 g of alcohol per week ($n = 8$), took antihypertensive medications ($n = 4$), or had a previous history of psychiatric disorder ($n = 1$) were excluded from the analysis to prevent any possible confounding effects.

We found that the severity of exposure was associated with acute symptoms of

TABLE 2

THE 8-hr TWA HYGIENIC EFFECT OF SOLVENTS, AGE, DURATION OF EMPLOYMENT, SMOKING, ALCOHOL CONSUMPTION, MEDICATION, AND PSYCHIATRIC DISORDER OF WORKERS WITH DIFFERENT EXPOSURE INDICES

	Index of exposure			
Term used in the text	0 (low)	1 (short-term high)	3 (high)	P of Kruskal–Wallis test
Total number of workers examined	58	80	58	
8-hr TWA hygienic effect of solvents				
Range	0–0.38	0–3.38 (1.3–24.5)[a]	0.25–9.83	$P < 0.0001$
Median	0.12	0.12	1.66	
Age (years)	29.7 ± 7.4	26.4 ± 8.7	41.0 ± 12.4	$P < 0.0001$
Duration of employment (years)	4.8 ± 6.4	6.4 ± 6.7	17.6 ± 13.3	$P < 0.0001$
No. of smokers (%)	26 (45.0)	52 (65.0)	40 (70.0)	
No. with alcohol consumption exceed 40 g/day (%)	0	4 (5.0)	4 (7.0)	
No. with antihypertensive in recent 2 weeks (%)[b]	0	0	4 (7.0)	
No. of workers with psychiatric disorder	0	0	1	

[a] The 15-min TWA hygienic effect of solvents in the painting booth.
[b] Taken antihypertensives during the past 2 weeks.

chest tightness and headaches and chronic symptoms of dizziness, easy fatigability, depressed mood, and palpitation. In addition, symptoms of irritability were only present in the high exposure group during the workday (Table 3). The number of symptoms in the peripheral nervous system showed no difference among different exposure categories. Table 4 shows that there was a trend toward an increased number of workers from the high exposure group who complained of two or more acute symptoms of the CNS. The analysis by multiple logistic regression also showed that the high exposure group had an increased risk (odds ratio = 2.7) of suffering from two or more acute symptoms of the CNS, while age, duration of employment, and smoking did not increase the frequency of acute symptoms of the CNS (Table 4).

The association of chronic symptoms of the CNS with the severity of exposure had results similar to the acute symptoms. Workers in the high exposure group were 3.9 times more likely to develop three or more chronic symptoms of the CNS than the low exposure group (Table 5). The multiple logistic model also showed a similar result with no effect found for age, duration of employment, and smoking on chronic symptoms of CNS.

DISCUSSION

Although CNS symptoms resulting from organic solvent exposures were well documented (Baker *et al.*, 1985; Spencer and Schaumburg, 1985; Waldon, 1986;

TABLE 3
NUMBERS OF WORKERS SUFFERING FROM ACUTE AND CHRONIC SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM AT LEAST ONCE PER WEEK UNDER DIFFERENT EXPOSURE INDICES

	Exposure indices			
	0 (low, $n = 58$)	1 (short-term high, $n = 76$)	2 (high, $n = 49$)	*P* value of M–H test for trend
Acute symptoms				
1. Chest tightness or compressed feeling over upper chest	1	7	11	
M–H odds ratio	1	5.8	25.6	0.001
2. Headaches	1	4	8	
M–H odds ratio	1	3.2	13.1	0.018
3. Irritability	0	0	3	
M–H odds ratio	—	—	—	0.161
4. Soreness of knee joint[a]	1	3	5	
M–H odds ratio	1	2.1	8.3	0.066
Chronic symptoms				
1. Have you felt lightheaded or dizzy?	4	2	18	
M–H odds ratio	1	0.4	7.8	0.001
2. Have you tired more easily than expected for the amount of activity you do?	7	13	21	
M–H odds ratio	1	1.5	5.5	0.001
3. Have you felt depressed?	2	7	8	
M–H odds ratio	1	2.9	4.6	0.03
4. Have you had heart palpitation even when not exerting yourself	1	3	6	
M—H odds ratio	1	2.1	10.9	0.023
5. Have you felt "high" from the chemicals you use at work?	1	1	5	
M—H odds ratio	1	0.7	8.3	0.059
6. Have you found it hard to understand the meaning of magazine newspaper and books you have read?	1	5	5	
M–H odds ratio	1	3.7	7.0	0.109
7. Have you had difficulty concentrating?	5	2	11	
M–H odds ratio	1	0.3	2.6	0.129
8. Have you had an episode of diarrhea?[a]	3	1	3	
M–H odds ratio	1	0.2	2.0	0.741
9. Have you had an episode of tinnitus?[a]	6	5	5	
M–H odds ratio	1	0.6	1.1	0.897

Note. Frequencies for each symptom were stratified by age (>35 and ≤35 years old) and later summarized by Mantel–Haenszel procedure (M–H), which tested a linear trend along with the exposure severity among workers.

[a] Dummy symptom.

TABLE 4

NUMBERS OF WORKERS WITH TWO OR MORE ACUTE SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM STRATIFIED BY AGE AND INDICES OF EXPOSURE (ANALYSIS BY MULTIPLE LOGISTIC REGRESSION IS ALSO SHOWN)

		Exposure indices		
Age	No. of symptoms	0 (n = 58)	1 (n = 76)	2 (n = 49)
≤35	≥2	9	8	9
	<2	39	59	16
>35	≥2	0	3	6
	<2	10	6	18
Total	≥2	9	11	15
	<2	49	65	34
Standardized odds ratio		1	0.93	3.33
Mantel extension for trend			χ^2 = 3.81 P = 0.055	

	Modeling by logistic regression		
	Odds ratio	95%CI	P value
Age (>35 vs ≤35)	0.77	0.30–1.98	0.586
Exposure index 1	1.03	0.40–2.68	0.955
Exposure index 2	2.72	1.00–7.41	0.050
Smoke 10–19 cig./day	0.80	0.31–2.05	0.645
Smoke ≥20 cig./day	0.89	0.34–2.34	0.807

NIOSH, 1987), and the issue was extensively reviewed by the expert committee organized by WHO (WHO, 1985), it has still been relatively difficult for an occupational physician to make a diagnosis based on symptoms alone owing to the nonspecificity of these symptoms. Similarly, our finding that there was an association between the increase of exposure indices and the presence of acute and chronic CNS symptoms did not necessarily indicate that the symptoms were caused by solvent exposure. However, we argue strongly for the causal association based on following reasons: first, workers who consumed alcohol in excess of 280 g per week, took antihypertensive medicine, or had a previous history of psychiatric disorder were excluded from the analysis. Therefore, the association could not be explained by alcohol abuse, medications, or psychiatric disorder. Second, we have considered age, duration of employment, and smoking by stratified and modeling analysis. All showed a consistent and independent association between exposure and CNS symptoms. Third, all three groups came from the same socioeconomic class with similar educations, incomes, and occupational skills. Thus, their work stress and social life were very similar and cannot explain the difference in prevalence of CNS symptoms among the three groups. Fourth, because we selected workers of low exposure instead of no exposure as the reference group, our estimates of the prevalence rates of CNS symptoms among workers could only underestimate the real figure. Last, the results of our three dummy questions (soreness of knee joint, diarrhea, and tinnitus in Table 3) did not show any statistical association to solvent exposure. Thus, we conclude that the association between increased exposure to organic solvents and a high prevalence of acute and chronic CNS symptoms in high exposure group was probably causal.

TABLE 5

NUMBERS OF WORKERS WITH THREE OR MORE CHRONIC SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM STRATIFIED BY AGE, AND INDICES OF EXPOSURE (ANALYSIS BY MULTIPLE LOGISTIC REGRESSION IS ALSO SHOWN)

		Exposure indices		
Age	No. of symptoms	0 (n = 58)	1 (n = 76)	2 (n = 49)
≤35	≥3	6	7	9
	<3	42	60	16
<35	≥3	1	3	7
	<3	9	6	17
Total	≥3	7	10	16
	<3	51	66	33
Standardized odds ratio		1	1.15	3.87
Mantel extension for trend			χ^2 = 4.86 P = 0.027	

	Modeling by logistic regression		
	Odds ratio	95%CI	P value
Age (>35 vs ≤35)	1.17	0.48–2.94	0.715
Exposure index 1	1.06	0.40–3.14	0.387
Exposure index 2	3.27	1.19–9.39	0.022
Smoke 10–19 cig./day	0.63	0.22–1.80	0.388
Smoke ≥20 cig./day	1.30	0.50–3.39	0.588

Since organic solvents are widely used in various industrial processes, developing an inexpensive and simple method for early detection of adverse solvent-induced health effect, especially neurotoxicity, is an urgent priority. CNS symptoms were the earliest form of chronic toxicity resulting from organic solvent exposure (Axelson and Hogstedt, 1988). However, the nonspecific nature of these symptoms has prevented them from being widely used as a simple tool for the early recognition of occupational hazard. To solve this problem, a falsification attitude plus a multivariate analysis to exclude alternative explanations such as age, smoking, alcohol, and medication is necessary to successfully document the hazard. We, therefore, recommend that a constructive and standardized questionnaire followed by careful epidemiological study design and analysis be used to reach the goal of early detection of neurotoxicity caused by organic solvents. It can also be supplementary to environmental measurements. Moreover, an internationally standardized questionnaire such as the one by Hogstedt *et al.* might be needed to collect and compare the information of solvent-induced neurotoxicity from different exposure levels in different countries.

Our results showed that workers exposed to a medium level of 1.66 of TWA hygienic effects of solvents would be 2.7 times more likely to develop two or more acute symptoms and 3.3 times more likely to develop three or more chronic symptoms of CNS than workers with low exposure. We tentatively concluded that an exposure level exceeding 1.66 of TWA hygienic effect of solvents would increase the risk of solvent-induced neurotoxicity. A long-term followup of symptoms and/or batteries of objective neuropsychologic performance tests would also be useful to test the causal association. In addition, routine environmental or biological monitoring plus engineering controls should be performed to assure the safety of the exposure level and to prevent any possible adverse health effects caused by solvents.

Smoking was once proposed to be a confounder and/or cofactor to the CNS symptoms (Johnson, 1987) because it could increase the inhalation of solvents and elevate the level of carboxyhemoglobin, which in turn would result in CNS symptoms (Ferris, 1978). However, we could not document any effects due to smoking in our study even by multivariate logistic regression. The reason might be that smoking is generally prohibited at the workplace of spray painting, and few workers have enough time to smoke a great deal.

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