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A neurological evaluation of workers exposed to mixtures of organic solvents

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ABSTRACT Workers with long term exposure to mixtures of organic solvents below regulatory limits have been reported to experience mild, but clinically detectable, sensory or sensorimotor polyneuropathies. In conjuction with a cross sectional study of behavioural performance a clinical neurological evaluation was conducted among printers and spray painters to examine dose response relations. All 240 subjects completed an occupational history and symptom questionnaire and underwent a clinical neurological examination. On average, subjects had been employed on their current job for six years. Classification of solvent exposure for each subject was based on exposed versus non-exposed job titles and observations during an industrial hygiene walk-through or on the measured concentration of solvents in full shift personal air samples. The average full shift solvent concentration was 302 ppm for printing plant workers and 6–13 ppm for workers at other plants. Isopropanol and hexane were the major constituents. Neurological abnormalities consistent with mild polyneuropathy were found in 16% of subjects; none was clinically significant. Exposed/non-exposed comparisons showed slightly higher frequency of symptoms in the exposed subjects which was not related to solvent level. Subjects categorised as exposed during the walk-through survey also had poorer vibratory sensation measured at the foot and diminished ankle reflexes. In multiple linear regression models, however, controlling for age, sex, alcohol intake, and examiner, no significant ($p < 0{\cdot}05$) relation was found between solvent concentration and poor neurological function except for two point discrimination measured at the foot. This investigation has not provided evidence for dose related adverse neurological effects from exposure to moderately low levels of solvent mixtures for a relatively short duration, although this may be due to the shortness of exposure duration, the type of solvent exposure, or to selection factors.

Impairment of the central and peripheral nervous systems has been documented in workers exposed to high concentrations of hexacarbon solvents and in solvent abusers.[1–3] Recent cross sectional epidemiological studies suggest that workers exposed to mixtures of solvents below recommended threshold limit values may have mild but clinically detectable sensory or sensorimotor polyneuropathies.[4–6] Findings have included decreased vibratory sensation in the feet and decreased sensory and motor nerve conduction velocities.[4–6] Quantitative exposure data have not been available to allow dose response relations to be characterised, however. The clinical study reported here was undertaken as part of a comprehensive neurobehavioural evaluation,[7] the object of which was to replicate previous cross sectional studies and to examine dose response with quantitative exposure data.

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Materials and methods

SELECTION OF STUDY SITES AND SUBJECTS

The selection of study sites and subjects has been described in detail elsewhere.[7] In brief, a cross sectional sample of subjects was selected from among hourly workers employed at four different plants (table 1). Each worker in the study population was

Table 1 *Description of study sites*

Plant	*Product*	*Processes involving solvents*	*Job classifications*		*Date(s) production started*
			*Exposed**	*Control*	
1	Office furniture	Spraying paint or glue	Sprayer (paint, glue), top trimmer, paint technician	Assembler, material handler, cutter, sewer	1963
2	Office furniture	Spraying lacquer or glue	Sprayer (glue, lacquer), rubber, wiper	Assembler, cutter, sewer, material handler	1970s
3	Automotive parts	Spraying paint or glue	Sprayer (paint, glue), spindle washer, booth cleaner, paint mixer	Assembler, material handler, machine operator	1973
4	Printed matter	Offset printing	Pressmen, feeder operator	Machine operator, material handler, plate preparer	1963

*Exposure category based on industrial hygiene walk-through survey.

assigned the status of "exposed" or "non-exposed," based on a walk-through inspection of jobs at each plant before the start of the study and on job classifications listed on employee rosters. A sample of exposed subjects was selected from the employee rosters (plants 2, 3, and 4) or from sign up sheets (plant 1) by matching a non-exposed subject's plant, sex, age (± 5 years), and educational level. Whenever possible, subjects who declined to participate or were otherwise unavailable for testing were replaced with other matched subjects.

SYMPTOM QUESTIONNAIRE AND CLINICAL EXAMINATION

Each subject completed a self administered questionnaire of symptoms, a 15 minute clinical neurological screening examination, a battery of psychometric tests, and blood and urine analyses. Each subject was examined either by a board certified neurologist (physician A) or by an occupational health physician (physician B) with training in the same examination protocol; both were blind with respect to the exposure of the subjects. Because of scheduling constraints, subjects could not be randomised to physicians, and only physician B was present at plant 4.

SYMPTOM QUESTIONNAIRE AND MEDICAL QUESTIONNAIRE

The symptom questionnaire included 21 items and the subjects indicated which had occurred within the past year. The symptoms were grouped into four categories based on similar groupings in previous studies[8]: sleep disturbances (wake up from sleep often, difficulty in falling asleep, night sweats); neuraesthenia (tire easily, anxious, depressed, personality change, irritable), intoxication (feeling high at work, difficulty concentrating, frequent headaches, lightheadedness on rising); and peripheral neuropathy (paraethesias, decreased sensation, weakness, and pain in hands and feet).

The medical questionnaire included items on demography, medical history, occupational history, past and current use or consumption of medication, alcohol, drugs, tobacco, caffeinated beverages, and chemicals used in hobbies.

NEUROLOGICAL EXAMINATION

The neurological examination[9] evaluated mental status, cranial nerves, motor function including strength, bulk, coordination, and gait; sensation; and reflexes. Abnormalities in either mental state or cranial nerve function were identified and described. Strength was graded on a five point scale (normal to severe impairment) and summarised for proximal and distal muscles after evaluating neck flexors, deltoids, biceps brachii, wrist extensors, hand intrinsics, iliopsoas, and anterior tibial muscles. Coordination (finger to nose, heel to shin), alternate motion rate of arms and legs, and tremor (resting and sustention) were also graded on a five point scale. Pin pain, joint position, and vibratory sensation were evaluated subjectively as in a conventional neurological examination, also using a five point scale. Muscle stretch reflexes (biceps brachii, brachioradialis, quadriceps, and ankle) were rated on a seven point scale (hyperactive to absent) and subjects were examined for the presence or absence of pathological reflexes (Babinski response, snout reflex, jaw jerk). A semiquantitative evaluation of peripheral neurological function was then performed, including evaluation of grip strength, touch pressure sensation, two point discrimination, vibration sensation, and pin pain sensation.

Grip strength was determined in the dominant hand using a Jamar hand dynamometer. Subjects were asked to squeeze the handle as hard as possible for five seconds. The maximum force in three five second trials was recorded.

Touch pressure sensation was recorded using a

pressure aesthesiometer (Research Media, Inc). Stimuli were delivered to the dorsum of the dominant index finger and great toe. Subjects were asked to identify in which of two three second time intervals the stimulus was delivered. Progressively smaller stimuli were presented until the subject made an error. The protocol was then repeated (three trials), randomly presenting stimuli in either the first or second time interval. If all responses were correct the next smaller stimulus was applied and the sequence repeated until one or more responses was incorrectly reported. The next largest stimuli was then repeated and recorded as the threshold value if the subject correctly identified all three trials.

Two point discrimination was measured on the dorsum of the dominant index finger and dorsolateral aspect of the ipsilateral foot using a Sweet's two point compass. Begining with the index finger, subjects were given a recognisable stimulus of 10 mm. Separation was decreased by about 1 mm per trial until three consecutive responses of one point were obtained at the same distance. This was considered a threshold value if the subject correctly identified the next increment of 0·5 mm. The protocol was repeated on the foot beginning with a 30 mm separation, decreasing by about 2·5 mm per trial as above. Once the descending threshold was defined, the subject had to recognise correctly the next increase of 2·5 mm, otherwise that portion of the protocol was repeated.

Vibratory sensation was determined for the dominant index finger and great toe using a 128 Hz tuning fork. Subjects were asked to indicate when vibration could no longer be felt. The difference (sec) between the subject's and examiner's threshold for the index finger was recorded as the average of the last two of four consecutive trials. This was repeated at the toe, recording the difference between the subject's toe threshold and the examiner's index finger threshold as above.

Pin pain was graded subjectively and subjects were asked to determine whether a single stimulus at the index finger was equal to, less than, or greater than a stimulus of about equal intensity presented on the upper forearm. Subjects were then asked subjectively to estimate the percentage that the smaller response was of the greater, if they differed. This was repeated for the dorsum of the great toe and the upper calf. Responses were recorded as the ratio of the proximal to distal intensity (%).

At the conclusion of the neurological examination, an overall clinical impression was recorded as normal, abnormal, or equivocal. If abnormal the physician determined whether there was an identifiable peripheral nervous system abnormality. Unequivocal clinical abnormalities were specifically identified and recorded.

Blood and urine analyses

Blood (non-fasting) was analysed for 22 indicators of organ and haematological function and for ethanol. The analyses included: glucose, urea nitrogen, creatinine, total bilirubin, direct bilirubin, serum enzymes of possible liver origin (SGOT, SGPT, GGPT), lactate dehydrogenase, alkaline phosphatase, cholesterol, white cell count, red cell count, haemoglobin, and haematrocrit. Urine was screened for the presence of barbiturates, tranquillisers, and amphetamines. Blood and urine specimens were analysed by an accredited commercial laboratory.

DESCRIPTION OF WORK PROCESS AND EXPOSURE

The materials and work processes were similar at plants 1, 2, and 3 and have been described by Whitehead *et al.*[10] Paint vehicles contained alkyd resins and mixtures of aromatic solvents, chlorinated and oxygenated aliphatic solvents, alcohols, and acetates. Fillers contained various pigments but lead pigments were used infrequently. The paints also contained various additives including biocides, stabilisers, and antiskinning agents. Glues contained toluene, hexane, and chlorinated hydrocarbon solvents. The original ventilation systems were still in use at each plant at the time of the study. The ventilation system at plant 4 recirculated contaminated pressroom air which led to heavy contamination of all production areas. No workers engaged in solvent operations wore solvent collecting respirators.

Solvent concentrations in the breathing zone were measured for a full shift during the week of the physical examination with personal air monitors for 159 subjects (66%). Mean total solvent concentrations (table 2) at the furniture and automotive parts plants (plants 1–3) were low. At the printing plant (plant 4), the mean total solvent concentration, which was dominated by isopropanol, naphtha, hexane, and xylene exceeded 300 ppm. The mean total concentration among the *non-exposed* at plant 4 was about eight times greater than that of the *exposed* at the other plants (table 2, row 3–5). This finding indicates that the exposed/non-exposed classification scheme introduces a considerable degree of misclassification with respect to demonstrable solvent exposures. Further analyses rely primarily on the quantitative solvent measurements. To maintain consistency with previous studies, comparisons of "exposed" and "non-exposed" will also be presented.

In addition to total solvent concentration, other exposure variables were constructed from measurements of airborne solvents and duration of employment. Each of these exposure variables was highly correlated with total solvent concentration and with each other. For analytical purposes, only the

Table 2 *Per cent cumulative TLV[11] and mean concentration (ppm) of solvents in breathing zone air by plant**

Solvent†	*Plants 1–4*	*Plant 1*	*Plant 2*	*Plant 3*	*Plant 4*
% TVL‡	40	6	13	9	170
Total solvent:	68	9	17	12	302
Exposed	96	17	24	20	385
Non-exposed	37	1	9	5	193
Isopropanol	31	0‖	0	1	161
Acetone	4	1	1	2	15
Naphtha§	10	0	1	0	50
Toluene	3	2	5	2	6
Xylene	4	1	1	0	20
Ethylbenzene	1	0	0	0	5
Hexane	8	1	1	1	39

*Includes assumed values of unsampled subjects.
†Methylene chloride, trichloroethylene, 2-butanone (MEK), methyl isobutyl ketone (MiBK), propyl benzene, cumene, heptane, butyl acetate, isobutyl acetate, isopropyl acetate, isobutyl butyrate, butyl cellosolve, and residual solvents were present at mean concentrations of less than 5 ppm.
‡% TLV = $100 \times \Sigma\, C_n/T_n$, where C is the concentration of the nth solvent in a mixture and T is the threshold limit value for that solvent.
§Assumes an average molecular weight of 100.
‖0 = <0·5 ppm.

total solvent concentration will be presented, although the other exposure variables, including concentration of n-hexane, yielded similar results.

STATISTICAL METHODS

Dose response relations were investigated with univariate plots of performance versus total solvent concentration, simple linear regression, and stepwise, forward multiple regression models[12] in which total solvent concentration (ppm), plant, age, sex, examiner, mean daily alcohol intake, regular medications, prior job (as a painter or printer), and hobby (involving potential exposure to lead, solvents, or pesticides) were candidate variables. The significance level for including a term was $p < 0{\cdot}1$.

Age, sex, alcohol intake, and examiner were considered to be the most important potential confounders of neurological function and were examined by correlation analysis (table 3). Because sensory modalities generally decline with age[13 14] and possibly with alcohol intake, a slight decline in function due to age or alcohol intake may be positively confounded with solvent exposure. Physician B, who examined subjects at plant 4, was associated with increasing solvent levels ($r = 0{\cdot}36$) and older subjects ($r = 0{\cdot}11$) due to the higher solvent levels and older ages at plant 4. Proportionately more men were examined by physician B (73%) than by physician A (55%). Each physician, however, examined about the same proportion (50%) of subjects classified as exposed at walk-through.

Mean performance on the semiquantitative tests of neurological function between those classified as exposed and non-exposed on the walk-through survey was compared using two tailed *t* tests for unpaired data. To estimate the relative risk of an abnormal clinical impression, subjects with equivocal impressions were combined with normal subjects. This yielded a conservative estimate of risk in statistical analyses.

Table 3 *Correlation between solvent exposure and demographic variables by plant*†

	Solvent level (ppm) v:			
Plant	*Age*	*Sex*‡	*Alcohol*	*Physician*§
1–4	0·09	−0·31**	0·16*	0·36**
1	−0·10	−0·18	0·03	0·13
2	0·26	−0·38**	0·10	−0·01
3	0·01	−0·14	−0·13	0·17
4	−0·46**	—	0·17	—

†No = 236, four cases with missing data excluded.
‡Binary variable: 0 = M, 1 = F.
§Binary variable: 0 = A, 1 = B.
*$p < 0{\cdot}05$; **$p < 0{\cdot}01$.

One subject with confirmed juvenile onset diabetes was excluded from the statistical analyses of the clinical examination. Five other individuals with recent limb injuries were excluded from the statistical analyses of sensory function and reflexes for the affected limb. Data on strength testing were not included in the statistical analyses because of equipment malfunctions.

The association between the results of the biochemical tests and airborne solvent levels was examined with stepwise forward multiple linear regression analyses. Age, sex, mean daily alcohol intake, plant, cigarette smoking, and solvent exposure on the current job were candidate variables, and were allowed to enter the models at $p < 0{\cdot}10$.

Results

CHARACTERISTICS OF SUBJECTS

The demographic characteristics of the study group

(n = 240) are presented in table 4. The subjects were young (mean 35 years), mostly male (66%) and white (90%), high school educated (mean 11th grade), and employed both in their current job (6 years) and at the plant (7 years) for a short time. Mean daily alcohol intake was low; 31% reported consuming more than one alcoholic beverage a day, usually as beer. Sixteen per cent reported having had a former job as a painter or printer. Subjects at plant 3 were mostly female; at plants 1 and 4 more than 96% were male.

The overall response rate was 42%, with a low of 28% at plant 1 and high of 89% at plant 2. Non-respondents were similar to respondents with respect to age and sex distribution.[7]

SYMPTOMS

The mean number of symptoms per person was approximately three (table 5). Women reported on average about twice the number of symptoms than men for all symptoms and for sleep disturbances and neuraesthenic, intoxication, and peripheral symptoms. Mean symptoms and distributions (not shown) did not monotonically increase with increasing solvent level but rather peaked in the 5–24 ppm category (table 6). A significant excess in total symptoms was associated with the exposed (at walk-through); a small increase in the mean number of symptoms in each symptom category accounted for the overall excess among the exposed.

Physical examination

Clinical abnormalities in mental status, cranial nerves, proximal strength, distal strength, coordination, tremor, alternating motion rate, gait, pin/temperature sensation, joint position sensation, and dual simultaneous stimulation were not detected.

SENSORY TESTS

Sensory thresholds for selected tests are plotted against total solvent concentration by plant in figs 1–4. The results of stepwise, forward multiple linear regression models are summarised in table 7, and the means of the sensory tests by plant are presented in table 8.

Table 4 *Characteristics of the study group*

Item	*Plants 1–4 (n = 240)**	*Plant 1 (n = 72)**	*Plant 2 (n = 51)**	*Plant 3 (n = 71)**	*Plant 4 (n = 46)**
Mean age ± SD	35 ± 11	36 ± 10	30 ± 12	36 ± 10	39 ± 9
Mean years eduction ± SD	11 ± 2	12 ± 2	11 ± 2	11 ± 2	12 ± 1
Mean years on current job ± SD	6 ± 6	7 ± 6	3 ± 5	4 ± 3	12 ± 8
Mean alcoholic drinks/day ± SD	1 ± 2	1 ± 2	1 ± 1	1 ± 2	2 ± 2
Men (%)	66	96	61	18	100
Caucasian (%)	90	96	96	79	93
Cigarette smoking:					
Never smokers (%)	32	29	53	29	22
Current smokers (%)	50	49	31	63	56
Ex-smokers (%)	18	23	16	8	22
> 1 Alcoholic drink/day (%)	31	43	20	25	41
Former job as a printer or painter (%)	16	15	4	13	35
Hobby chemical user (%)†	7	6	8	0	17
Regular medicine takers (%)‡	18	15	18	23	15
Response rate (%):§	42	28	89	72	59
Exposed (%)	50	30	96	75	60
Non-exposed (%)	38	27	82	69	57

*Missing data excluded from calculations. No more than five missing cases for any item.
†Hobby chemical included solvents, lead, or pesticides.
‡Of 53 reports of medicine taken during 24 hours before testing, 25% were taking aspirin or other analgesics, 13% antihypertensive medications, and the remainder were uniformly divided between 11 different categories.
§Response rate = (respondents/sample) × 100.

Table 5 *Mean number of symptoms by plant and sex*

Symptom category (No)	*Sex**		*Plant†*				
	M	*F*	*1*	*2*	*3*	*4*	*1–4*
All symptoms (21):	2·5	4·9	2·1	3·1	5·2	2·5	3·2
Sleep disturbances (3)	0·4	0·7	0·3	0·5	0·7	0·5	0·5
Neuraesthenic (6)	1·0	1·8	0·7	1·1	2·0	1·0	1·2
Intoxication (5)	0·5	1·1	0·4	0·8	1·1	0·5	0·7
Peripheral (4)	0·3	0·9	0·3	0·4	0·9	0·2	0·5

*Means between sexes overall and in each symptom category significantly different ($p < 0·05$, 2 sided unpaired t test).
†Means between plants overall and in each symptom category significantly different ($p < 0·05$, ANOVA).

Table 6 *Mean number of symptoms by plant and solvent exposure*

Symptom category (No)	*Exposure category*		*Solvent level (ppm)*			
	Exposed	*Non-exposed*	*0–*	*5–*	*25–*	*⩾125*
All symptoms (21):	3·8	2·8*	3·0	4·4	3·4	2·5
Sleep disturbances (3)	0·5	0·4	0·4	0·6	0·5	0·5
Neuraesthenic (6)	1·3	1·1	1·2	1·5	1·3	1·0
Intoxication (5)	0·8	0·6	0·6	1·0	0·8	0·5
Peripheral (4)	0·6	0·4	0·4	0·7	0·5	0·3

*Means between exposed and non-exposed significantly different ($p < 0·05$, 2 sided unpaired t test).

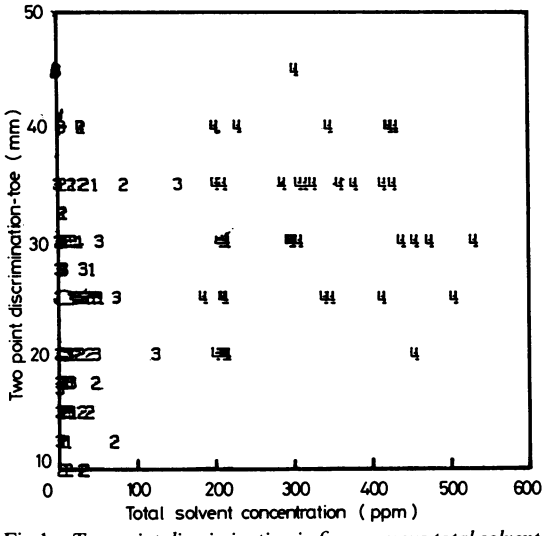

Fig 1 *Two point discrimination in finger versus total solvent concentration (ppm) by plant.*

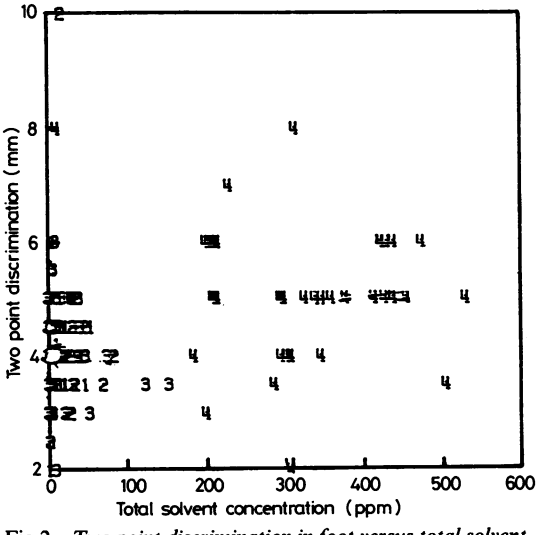

Fig 2 *Two point discrimination in foot versus total solvent concentration (ppm) by plant.*

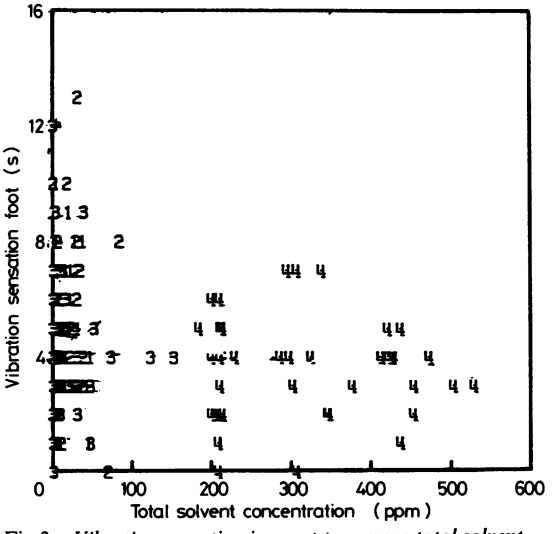

Fig 3 *Vibration sensation in great toe versus total solvent concentration (ppm) by plant.*

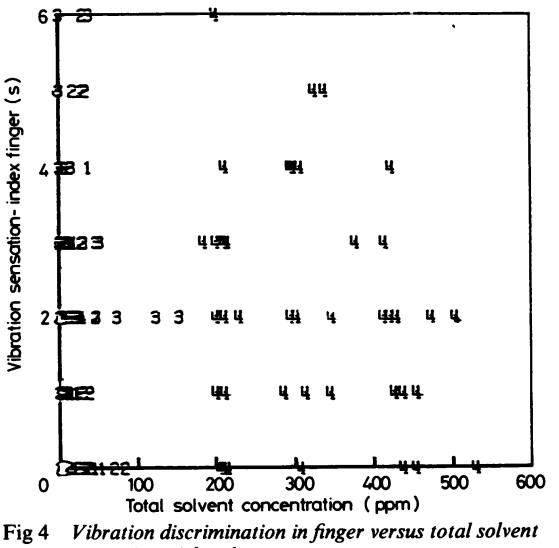

Fig 4 *Vibration discrimination in finger versus total solvent concentration (ppm) by plant.*

Table 7 *Summary of stepwise forward, multiple linear regressions of sensory and reflex tests: poorer (−) or better (+) function associated with demographic variables and increasing solvent exposure**

	Two point discrimination		*Vibration sensation*		*Touch pressure sensation*			*Pin pain sensation*	
Variable†	*Foot*	*Finger*	*Toe*	*Finger*	*Toe*	*Finger*	*Ankle reflex*	*Arm*	*Leg*
Age	−	−	−	−	−	−	−	−	−
Physician	−	−	−	−	+	+		−	−
Alcohol	−								
Plant 2		−	−	−	+	+		−	
Plant 3				−	+	+			−
Plant 4		−	+		+	+			
Former job‡			−	−					
Regular medication						−			
Total solvent concentration	−								+
r^2	0·30	0·23	0·25	0·32	0·47	0·34	0·02	0·06	0·08

*All + or − significant at $p < 0·1$.
†Candidate variables included: age, sex (0 = M, 1 = F), physician (0 = A, 1 = B), mean daily alcohol intake (drinks/day), plant (3 dummy variables relative to plant 1), regular medication, former job as a printer or painter, hobby chemical exposure (0 = no, 1 = yes) and solvent exposure (time weighted full shift sample of current job).
‡Former job as a painter or printer.

Table 8 *Mean sensory and reflex function by plant. (Standard deviation in parentheses)*

Test	*Plants 1–4 (n = 240)*	*Plant 1 (n = 72)*	*Plant 2 (n = 51)*	*Plant 3 (n = 71)*	*Plant 4 (n = 46)*
Two point discrim (mm):					
Finger*	4·3 (1·0)	4·1 (0·7)	4·2 (1·0)	4·0 (0·8)	5·2 (1·1)
Foot*	24·8 (7·0)	23·6 (5·7)	21·7 (7·3)	24·1 (5·8)	31·1 (6·6)
Vibration sensation (sec):					
Finger*	1·7 (1·5)	1·2 (1·2)	1·7 (1·7)	2·0 (1·5)	2·1 (1·6)
Toe	4·1 (2·2)	4·1 (2·0)	4·3 (2·6)	4·1 (2·1)	3·9 (2·1)
Touch pressure (mg):					
Finger*	3·1 (0·6)	3·5 (0·5)	3·0 (0·5)	2·7 (0·6)	3·2 (0·5)
Toe*	3·0 (0·8)	3·5 (0·5)	2·9 (0·8)	2·7 (0·8)	2·7 (0·6)
Pin pain (proximal/distal):					
Arm	0·92 (0·2)	0·94 (0·2)	0·88 (0·2)	0·93 (0·2)	0·89 (0·2)
Leg	0·91 (0·2)	0·91 (0·2)	0·88 (0·2)	0·95 (0·6)	0·89 (0·2)
Ankle reflex					
(5 = normal, 0 = hypo, 7 = hyper)	4·8 (0·9)	4·7 (1·2)	4·9 (0·6)	4·8 (0·9)	4·9 (0·4)

n = Maximum number, no more than four cases excluded on all tests except pin pain (arm), which had nine cases excluded.
*Means between plants significantly different at $p < 0·01$ (F-test, ANOVA).

Two point discrimination

Plots of two point discrimination measured at the foot (fig 1) and index finger (fig 2) against solvent level show highly variable responses. In multivariate models (table 7, column 2) two point discrimination at the foot was significantly related to increasing solvent levels ($p < 0·001$), age ($p < 0·001$), physician ($p = 0·07$), and alcohol intake ($p = 0·03$). Two point discrimination measured at the index finger was significantly associated with age ($p < 0·001$), physician ($p = 0·07$), and plants 2 and 4 but was not significantly associated with solvent level (fig 2).

The mean two point discrimination threshold at the foot was significantly greater among the exposed than the non-exposed examined by physician B but, combining over plants and physicians, this increase was not statistically significant (table 9). Significantly higher mean thresholds for two point discrimination at the index finger were found among exposed subjects examined by physician A but, overall, the difference between exposure groups was not statistically significant (table 9).

Vibration sensation

The plot of vibration sensation at the dorsum of foot (fig 3) and index finger (fig 4) against solvent level indicated highly variable responses. In mulitvariate models (table 7) vibration threshold at the foot was significantly related to age ($p < 0·001$), physician ($p < 0·001$), plants 2 and 4 ($p = 0·01$), and former job

)le 9 *Mean sensory and reflex function by exposure status (walk-through) and physician. (SD in parentheses)*

	Total		*Physician A*		*Physician B*	
	Exposed (n = 124)	*Non-exposed (n = 116)*	*Exposed (n = 47)*	*Non-exposed (n = 48)*	*Exposed (n = 77)*	*Non-exposed (n = 88)*
) point discrimination (mm):						
ıdex finger	4·3 (0·9)	4·3 (1·0)	4·4 (0·6)**	3·9 (0·6)	4·3 (1·0)	4·5 (1·3)
)orsum of foot	25·4 (7·2)	24·1 (6·7)	22·3 (5·1)	22·5 (5·4)	27·4 (7·5)*	24·4 (7·0)
ration (sec):						
ıdex finger	1·7 (1·5)	1·7 (1·5)	0·9 (1·0)	1·1 (1·4)	2·2 (1·5)	2·0 (1·5)
ireat toe	4·5 (2·1)**	3·7 (2·2)	4·2 (1·7)**	3·1 (1·8)	4·7 (2·3)*	4·0 (2·2)
ıch pressure (mg):						
ndex finger	3·1 (0·6)	3·1 (0·6)	3·4 (0·5)**	3·1 (0·5)	3·0 (0·7)	3·1 (0·7)
ireat toe	3·0 (0·8)	3·0 (0·7)	3·6 (0·5)**	3·3 (0·5)	2·6 (0·7)	2·7 (0·8)
pain (proximal/distal):						
ırm	0·93 (0·2)	0·90 (0·2)	0·98 (0·2)	0·95 (0·2)	0·91 (0·2)	0·87 (0·2)
.eg	0·93 (0·2)	0·90 (0·2)	0·96 (0·1)	0·94 (0·1)	0·90 (0·2)	0·86 (0·2)
ıkle reflexes:						
5 = normal, 0 = hypo, = hyper)	4·7 (0·9)*	4·9 (0·8)	4·5 (1·1)**	5·0 (0·8)	4·8 (0·8)	4·9 (0·9)

: Maximum number, no more than four cases excluded on all tests except pin pain (arm) which had nine cases excluded.
< 0·05, 2 sided unpaired *t* test; **p < 0·01.

as a painter or printer (p = 0·002). Vibration threshold at the index finger was also significantly related to age (p < 0·001), physician (p < 0·001), plants 2 and 3 (p < 0·002), and former job (p = 0·045).

Overall, the mean vibratory threshold at the foot was significantly greater (p = 0·008) among the exposed than the non-exposed. This difference was consistently found by both physicians and greater thresholds among the exposed were also observed at each plant. Significant differences between exposure groups were not found for mean vibratory threshold at the index finger (table 9).

Pressure touch sensation

In multivariate models touch pressure thresholds at the foot were significantly related to age (p < 0·001), physician (p < 0·001), and plants 2, 3, and 4 (p ⩽ 0·001) (table 7). Touch pressure thresholds at the index finger were significantly associated with age (p = 0·003), physician (p = 0·002), plant 2, 3, and 4 (p ⩽ 0·05), and medications (p = 0·09).

Significantly higher touch pressure thresholds at the finger and foot were found among the exposed subjects examined by physician A (table 9). Overall, and at each plant, no significant differences (p < 0·05) were found between exposed (at walk-through) and non-exposed for mean touch pressure thresholds at the foot or index finger (table 9).

Pin pain

Increasing solvent level was associated with an *improvement* in pin pain threshold at the leg (p = 0·05) in multivariate models (table 7). Increasing age (p = 0·03), physician (p = 0·002), and plant 3 (p = 0·007) were associated with decreased pin pain thresholds in the leg. Age (p = 0·09), physician (p = 0·01), and plant 2 (p = 0·02) were significant predictors of pin pain threshold in the arm.

Overall, significant differences in mean pin pain thresholds were not found between the exposed walk-through and the non-exposed (table 9).

Muscle stretch reflexes

Solvent level was not associated with muscle stretch reflexes (biceps, brachioradialis, quadriceps, and ankle) in multivariate models (table 7). Ankle reflex significantly diminished with increasing age (p = 0·03). Overall, small, but significantly diminished, ankle reflexes (p = 0·04) were associated with the exposed group at walk-through (table 9). Diminished reflexes among the exposed subjects examined by physician A accounted for the significant difference.

Overall clinical impression

Abnormal clinical impressions were reported by the examiners in 24% of all subjects (table 10), although the abnormalities were not judged to be of clinical significance. Presumed signs of peripheral neuropathy—diminished pin pain and vibratory sensation, or diminished ankle reflexes—were found in 16% of subjects and accounted for two thirds of the abnormal impressions. The frequency of abnormal impressions was slightly less among the subjects examined by physician A than by physician B. The frequency of decreased pin pain, however, was about seven times greater in the subjects examined by physician B than in those examined by physician A; the finding of diminished ankle reflexes was five times more frequent among the subjects examined by physi-

Table 10 *Prevalence (%) of abnormal impressions on neurological examination by plant and physician (A or B)*

Cause	Plants 1–4 (n = 240)	Plants 1–4		Plant 1		Plant 2		Plant 3		Plant 4
		A (n = 95)	B (n = 145)	A (n = 42)	B (n = 30)	A (n = 26)	B (n = 25)	A (n = 27)	B (n = 44)	B (n = 46
Findings consistent with polyneuropathy:										
Decreased pin pain (%)	9	1	14	0	13	4	24	0	7	17
Decreased vibration (%)	4	1	6	0	10	0	8	4	5	2
Decreased ankle reflex (%)	3	5	1	7	3	0	0	7	2	0
Other causes:										
Possible carpal tunnel syndrome (%)	3	5	2	0	3	8	0	11	5	0
Other abnormalities* (%)	5	8	3	12	7	4	4	7	2	0
Total prevalence of abnormal impressions (%)	24	21	26	19	37	15	36	30	20	20

*Other abnormal impressions included injuries (1); surgery (2); diabetic (1), adult (1) and alcoholic (1) polyneuropathy; Grave's disease (1); muscle atro unspecified diminished reflexes (2); decreased pressure touch sensation (1); and unspecified peripheral abnormality.

cian A than by physician B.

Overall, the increased relative risk (RR 1·4) of presumed signs of peripheral neuropathy (diminished pin pain, vibratory sensation, and ankle reflex) in the exposed subjects was not significant (table 11), nor were diminished vibratory sensation and ankle reflex alone (RR = 2·8, $p > 0·05$) often the earliest signs of peripheral neuropathy. The increase in risk in the exposed was observed in both the subjects examined by physician A (RR = 2·6, $p > 0·05$) and by physician B (RR = 1·2, $p > 0·05$).

Blood and urine analyses

All 228 blood samples tested were negative (< 1 μg/ml) for ethyl alcohol. Urine analyses detected one subject with a positive drug screen who also reported taking tranquillisers on the medical questionnaire.

In multivariate models of the biochemical and haematological tests (table 12) decreasing red blood cell count was significantly associated with increasing solvent level. Increasing solvent level was unexpectedly related to *decreasing* concentrations of SGOT and SGPT and to *increasing* levels of serum albumin.

Discussion

Mild sensory deficits and a diminished ankle reflex suggestive of a mild polyneuropathy were found in approximately 16% of the study group, but these deficits were not considered to be of clinical significance.

The lack of a dose response relation in this study does not reinforce previous reports of mild sensory and motor deficits among workers exposed to mixtures of organic solvents below recommended limits. As in previous studies, comparisons of solvent exposed and non-exposed groups showed a significant increase in symptoms,[6 8 15 16] and diminished vibration sensation[4–6] in the exposed group. Neither number of symptoms nor vibration thresholds were consistently related to solvent level, however. A dose response relation indicating poor discriminatory function was found for two point discrimination in the foot. This finding was not expected, based on clinical experience and previous reports that vibration sensation threshold is likely to be more sensitive to solvent exposure than two point discrimination in the foot.[4–6]

Table 11 *Prevalence (%) of abnormal impressions with polyneuropathy by physician, plant, and exposure status at walk-throu*

Cause	Plants 1–4		Physician A		Physician B	
	Exposed (n = 124)	Non-exposed (n = 116)	Exposed (n = 47)	Non-exposed (n = 48)	Exposed (n = 77)	Non-exposed (n = 68)
Decreased pin pain (%)	9	9	0	2	14	15
Decreased vibration (%)	6	2	2	0	8	3
Decreased ankle reflex (%)	4	2	9	2	1	1
Total	19	13	11	4	23	19
Relative risk (95% confidence limit)	1·4 (0·8, 2·6)		2·6 (0·5, 12·5)		1·2 (0·7, 2·3)	

The prevalence of abnormal clinical impressions attributable to presumed signs of peripheral polyneuropathy (decreased pin pain, vibration sensation, and ankle reflex) was 1·4 times greater among the exposed than the non-exposed, classified at walk-through. This finding was not observed in analyses of dose response.

The reasons for the increase in the prevalence of abnormal impressions consistent with peripheral polyneuropathy in the exposed group are not readily explained by solvent exposure, nor are they explained by potentially confounding by age or sex (because of frequency matching in the sample design). Mean daily alcohol intake was not controlled in the comparisons of exposed and non-exposed, but alcohol was not strongly or consistently associated with impaired sensory function in multiple linear regression models. Both solvent level and mean daily alcohol intake were independent risk factors for two point discrimination measured at the foot (table 11).

The increased prevalence of abnormal clinical impressions among the exposed does not appear to be an artifact of, or confounding by, physician effects; the distribution of exposed and non-exposed subjects was approximately 50% for both physicians (table 11). An increased risk among the exposed subjects was found by both physicians, although the risk of findings consistent with peripheral neuropathy was greater in the subjects examined by physician A. The physicians also differed in frequency and types of clinical findings (table 10). In semiquantitative measurements of sensory function and ankle reflex (table 9) the variability (as indicated by the standard deviation) was generally smaller for physician A. This is not surprising since physician A was a neurologist and physician B was not.

The results of blood tests showed a decline in red cell count with increasing solvent level. Serum enzymes suggestive of altered liver function were either not associated with solvent level (GGPT) or were unexpectedly associated with lower solvent levels. The validity of the blood tests is strengthened by the confirmation of previously identified relations with sex (RBC),[17] cigarette smoking (WCC),[18] alcohol intake (SGPT, SGOT),[17] and age (creatinine, albumin).[17]

COMPARABILITY OF STUDIES

There are important differences between previous studies and the one reported here. Firstly, the average duration of employment (exposure) was seven years in the present study compared with 14 years in other studies involving solvent mixtures.[4-6] Secondly, the main component of solvent exposure in previous studies was toluene, whereas isopropanol, which is probably less potent, was the dominant exposure in this study (table 2). Thus short exposure duration and less potent components in the exposure may contribute to the lack of associations.

The inability to replicate previous studies may also reflect differences in the protocol of the neurological examination. The present and past studies have included the same range of neurological functions but differ in the methods of delivering the stimuli and of grading the responses. The present study used a pressure aesthesiometer similar to von Frey hairs to quantitate light touch rather than touching a piece of cotton to the skin, as was done in previous studies. As the measure of discriminatory ability in previous studies, subjects identified Arabic numerals written with a blunt tool on the dorsum of the foot. The present study differed considerably in that a compass was used to deliver a focal stimulus reported by subjects as either one or two points. Vibration sensation in previous studies was determined with a 100 to 109 Hz stimulus presented by either a tuning fork or pressure bioaesthesiometer. In the present study a tuning fork was used to deliver a slightly higher stimulus of 128 Hz. Pin pain measurements of the present and Scandinavian studies used similar pin stimuli but subject responses were graded differently.

ANALYTICAL METHODOLOGY

It was assumed that sensory thresholds and reflexes were accurately described by linear-additive models in which confounding was adequately controlled. The models identified age as the most consistent predictor of sensory thresholds, as previously reported.[4 13 14]

Plant 1		*Plant 2*		*Plant 3*		*Plant 4*	
Exposed (n = 35)	*Non-exposed (n = 37)*	*Exposed (n = 27)*	*Non-exposed (n = 24)*	*Exposed (n = 36)*	*Non-exposed (n = 35)*	*Exposed (n = 26)*	*Non-exposed (n = 20)*
3	8	22	4	3	6	12	25
8	0	4	4	6	3	4	0
8	3	0	0	6	3	0	0
20	11	26	8	14	11	15	25
1·9 (0·6, 5·8)		3·1 (0·7, 13·6)		1·2 (0·4, 4·2)		0·58 (0·2, 1·9)	

Table 12 *Stepwise forward multiple linear regression of blood tests against age (AGE), sex (SEX), mean daily alcohol intake (DRINKDLY), current cigarette smoking (CIGSDLY), plant (PLANT), and solvent exposure on the current job (PPM JBNW)**

Blood test,† units	*Model*	r^2
Creatinine (mg/dl)	Creatinine = 1·3 − 0·28 SEX + 0·12 PLANT 3 − 0·12 PLANT 4	0·26
Albumin (g/dl)	Albumin = 4·8 − 0·07 AGE − 0·21 SEX − 0·02 DRINKDLY + 0·001 PPM JBNW	0·22
SGOT (IU/l)	SGOT = 21·5 + 0·27 AGE − 5·8 SEX + 1·1 DRINKDLY − 0·03 PPM JBNW	0·14
SGPT (IU/l)	SGPT = 21·7 + 0·42 AGE − 16·0 SEX + 9·6 PLANT 3 − 0·02 PPM JBNW	0·11
LDH (IU/l)	LDH = 184·2 + 0·46 AGE − 20·4 SEX − 0·31 CIGSDLY − 0·08 PPM JBNW	0·12
GGPT (units/l)	GGPT = 4·9 + 0·34 AGE − 5·0 SEX + 1·6 DRINKDLY	0·17
WBC (10/mm)	WBC = 6·1 + 0·04 CIGSDLY + 0·6 PLANT 3	0·12
RBC (10/mm)	RBC = 5·2 − 0·66 SEX − 0·001 PPM JBNW	0·42

*Sex coded as 0 = M, 1 = F; plant dummy variables relative to plant 1.
†SGOT = Serum glutamic oxalic transaminase, SGPT = serum glutamic pyruvic transaminase, LDH = lactic dehydrogenase, GGPT = gamma glutamic pyruvic transaminase, WBC = white blood cell count, RBC = red blood cell count.
All terms significant at $p < 0·05$.

This finding provides the consensual validity of the tests in general. Sex was an important predicator of the frequency of symptoms. This is consistent with observations that women generally report morbid conditions more frequently than men.[19 20]

Several potentially confounding relations including age, sex, alcohol, physician, and plant were identified (table 3). Positive associations, however, were not found between sensory modalities and solvent level except for two point discrimination in the foot. Because differences in physicians were indicated by linear regression models (table 11) and stratified analyses (tables 9–11), and increasing solvent level was associated with physician B, multiple linear regression analyses were repeated, restricting observations to subjects examined by physician B. The significant finding of increased two point discrimination thresholds in the foot persisted after restriction. This finding will require confirmation in future studies since chance may also account for it, given the large number of relations investigated.

Of additional concern are selection biases, subject motivation, nature of past exposures, and observer/subject bias.

Non-response and "healthy worker" selection were considered as sources of selection biases. More than one third of the eligible subjects at plants 1 and 4 were non-responders. Because subjects at plant 1 were self selected, more interested or better informed individuals probably participated. Data other than age and sex (which were unrevealing) were not available to investigate whether healthy or exposure related factors influenced self selection. Twenty of the 30 non-responders at plant 4 were interviewed; 12 did not cite a specific reason for non-participation and five said they were "too busy." These data are insufficient to rule out the possibility of a bias due to non-response.

Cross sectional studies are vulnerable to an underestimation of risk because affected individuals leave the workplace or select themselves out of exposed jobs within the workplace (healthy worker selection). This has been asserted in several neurobehavioural investigations and documented in one study.[5] It is not known whether the population in the present study underwent this type of selection. Many of the "exposed" jobs in this study were higher paying, high seniority jobs. Moreover, the small difference between duration of the current job (6 years) and total employment at the plant (7 years) suggests that migration between jobs was not a significant factor.

A further limitation of cross sectional studies is inherent in the study design; subjects were not followed over time and it is not known whether their neurological function deteriorated beyond that attributable to the normal aging process.

It is not likely that quantitative measurements of current solvent levels misrepresented current or past exposures. Also, the plants were relatively new, having been opened in the 1960s and 1970s. Leaded paints were infrequently used; moreover, lead would have contributed to an association of adverse solvent related effects rather than masked it. It is not likely that other neurotoxic exposures were overlooked.

Through the consent procedure subjects were informed that the focus of the study was to examine possible effects of solvents. Compared with exposed subjects non-exposed subjects may have been less motivated, believing that their participation was secondary. The lower response rate in non-exposed (38%) than exposed subjects (50%) suggests that this may have occurred. Symptom reporting and tests of sensory function may also have been vulnerable to bias because the subjective responses of the participants were used to quantitate the measurements.

In conclusion, this investigation has not provided evidence of dose related adverse neurological effects from exposure to moderately low levels of solvent mixtures for a relatively short duration. The concern about the adverse effects of longer term, low level solvent exposure cannot be completely mitigated, how-

ever, because of the finding of diminished vibratory sensation and ankle reflexes among the exposed group at walk-through and because of limitations in the study design. Periodical monitoring of workplace solvent exposures and of neurological function may provide longitudinal data on which definitive conclusions may be based.

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