Neuropsychological effects of exposure to naphtha among automotive workers

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Abstract

The association between exposure to naphtha and neurobehavioural measures was examined prospectively over one year among workers employed at an automotive plant that used naphtha to calibrate fuel injectors. The neurobehavioural tests included those that assess mood, basic intelligence, and functioning of the cerebral frontal lobes and limbic system and were designed so that acute, reversible, and chronic effects of solvent exposure could be assessed. Participants were 248 workers in June 1988, and the testing was repeated on 185 of these workers in 1989. Concentrations of naphtha at the plant ranged from six to 709 mg/m³, although exposure was greater in 1988 than in 1989. Duration of exposure for individual subjects ranged from 0·8 to 7·3 years. Cross sectional data analyses showed significant associations between level of exposure to naphtha and slower timed scores on trails A, and greater reports of negative affective symptoms on profile of mood states scales in 1988 but not 1989. Threshold model analyses of the 1989 data showed an association between score on visual reproductions immediate recall and daily exposure to naphtha at or above 1050 h × mg/m³. Models of chronic exposure showed no associations between chronic exposure and negative neurobehavioural outcome. Results suggest that naphtha produces mild acute reversible effects on function of the central nervous system at or above daily exposures of 540 h × mg/m³ (approximately 90 ppm/h).

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Although there is still much to be learned about the specific variables associated with adverse health outcomes after exposure to solvents,[1] there are several publications with different types of methodology that agree that solvents are neurotoxic.[2–4] For example, animal studies have verified the neurotoxicity of trichloroethylene[5–10] and benzene.[11] Human studies with acute exposure have confirmed central nervous system and behavioural effects of exposure to solvents,[12–14] as have case control studies of neuropsychiatric outcome,[15–22] retrospective comparisons of test performance in solvent exposed workers and controls,[23–28] and prospective assessments of the relations between exposure and neuropsychological outcome.[18 29–40]

Although naphtha, the solvent investigated in our study, has been described as a neurotoxicant and targeted as a solvent for neurobehavioural investigations,[41] there has been little scientific examination of the behavioural effects of naphtha in humans. In one study, acute exposure to Stoddard solvent in normal non-occupationally exposed subjects showed that olfactory thresholds for the solvent were low but irritative effects were none the less minimal at exposures of one to four times the threshold limit value (TLV) of 100 ppm.[42] These investigators found no dose effect relation between exposure and impaired performance on the Purdue pegboard (acute exposure to one TLV for 30 minutes), or the Michigan eye-hand coordination test, or choice reaction time (acute exposures of one to four times the TLV). An acute exposure study of a closely related solvent, white spirits, assessed effects of exposures ranging from 625–2500 mg/m³ over a 30 minute period.[43] Although nine of the 14 subjects reported subjective symptoms of intoxication such as dizziness, none showed performance decrements on the behavioural tests used (perceptual speed, visual reaction time, memory, manual dexterity, digit addition). When eight subjects were exposed to 4000 mg/m³, however, short term memory and measures of simple reaction time were negatively affected. A case study describing health effects of exposure to mineral spirits in a worker with respiratory and dermal exposure (he placed his hands in solvent several times a day) reported symptoms of the central nervous system such as nervousness and headaches after three years of exposure, when he left employment because of ill health.[44] One of us (RFW) has also seen a patient with clinical evidence of substantial damage to the central nervous system after more than 30 years of chronic occupational exposure to Stoddard solvent. Our review of publications on naphtha and related solvents suggested that naphtha is neurotoxic but substantial exposure may be required to produce acute or chronic effects.

Based on knowledge accumulated to date on the neuropsychological effects of exposure to solvents and our own research and clinical experience with subjects exposed to solvents, we have noted that exposure to solvents in adults particularly affects attention, executive function, visuospatial abilities, short term

Table 1   Neuropsychological tests used

Test	Functional domain	Cerebral localisation
	1988	
Trails A and B	Attention (A) Executive function (B)	Frontal system
Profile of mood states	Mood states	Frontal, limbic
Recognition span test	Short term memory	Limbic
Visual reproduction	Short term memory	Limbic
Vocabulary (NES)*	General intelligence	(Hold test-none)
Symbol-digit (NES)*	Motor, attention, scanning, visuospatial	?Motor strip
Pattern memory (NES)*	Short term memory	?Right hemisphere, limbic
Wisconsin card sorting test	Executive	Frontal
	1989	
As above except: No vocabulatory (NES) No Wisconsin card sorting test		
Rey-Osterreith complex figure	Executive, visuospatial short term memory	Frontal (planning), limbic

Tests from the neurobehavioural evaluation system (NES) have not yet been validated on patients with known localised brain damage; localisations are hypothesised based on studies with similar standard paper and pencil tests.

Table 2   Effects of solvents on the central nervous system. patterns of functional neuropsychological deficit

Effects	Acute	Chronic
Mild:		
Mood	Rev	Res
Attention	Rev	Res
Executive function	Rev	Res
Moderate:		
Mood	P to F rev	—
Attention	P to F rev	—
Executive function	P to F rev	—
Visuospatial	P to F rev	Res ME+
Short term memory	P to F rev	Res ME+
Motor	P to F rev	Res ME+
Severe:		
Amnestic syndrome	—	Res Mod E+

Rev = reversible; Res = residual; P to F rev = partially to fully reversible; Res ME+ = residual, mild effects plus; Res Mod E+ = residual moderate effects plus.

memory, and mood,[45] sparing functions such as language and retrograde memory. These findings suggest that solvents affect the brain in a focal manner, not diffusely as has been previously proposed. Specifically, we[3][46] and others[27] have theorised that solvents preferentially affect the frontal lobes and limbic system. In keeping with this prediction, the tests for our study were selected to include hold tests, that is—tests thought to be resistant to effects of solvents, as well as tasks specifically designed to assess frontal and limbic function (table 1). Also, our model of acute and chronic effects of exposure to solvents is based on prior work by one of us delineating the patterns of functional cognitive deficits expected in a model of acute and chronic effects of solvents (table 2).[47][48] The current study was designed to provide as sensitive a group of measures as possible to determine whether there are neuropsychological deficits associated with exposure to naphtha and to allow assessment of a broad range of potential outcomes of exposure to naphtha on the central nervous system in a working population, ranging from mild reversible signs of dysfunction to moderate effects of chronic exposure.

Materials and methods

STUDY DESIGN

The study was a prospective assessment of neuropsychological function in workers with relatively high exposure to naphtha and a comparison group with low exposure at two times separated by a one year interval. Subjects were recruited from among the 533 hourly production workers on first and second shift. Over 90% of these workers were successfully contacted by in plant recruiters in an attempt to enlist 250 workers, 125 each from the area of relatively high exposure to naphtha (inside the three calibration rooms) and the area of relatively low exposure (outside the calibration rooms). In June 1988, 248 workers participated, 119 from inside the calibration rooms and 129 from outside. Reasons for declining to participate were not collected on a systematic basis. The sex and seniority data of all hourly production workers were obtained. Seniority date was the date of hire at the plant, or if the worker had been employed previously at another plant in the corporation, an earlier date determined by contact, usually within one year of date of hire at any company plant.

In June 1989, 185 of the original 248 subjects participated again, 87 from inside the calibration rooms and 98 from outside. Among those lost to follow up, 33 refused outright, four were "busy", nine were on medical leave, seven were absent on two scheduled test dates, four were on vacation or training, and three had recently changed shift and could not be rescheduled.

EXPOSURE TO NAPHTHA

The blend of naphtha used at the plant consisted by weight of about 50% paraffins, 25% monocyclic naphthenes, 18% benzenes and <5% each of dicyclic naphthenes, indans or teralins, naphthalenes, and olefins. Trimethylbenzene, methylethylbenzene, and diethylbenzene were the most prevalent constituents in the aromatic fraction.

Methods of characterisation of exposure and calculation of cumulative measures of exposure have been described elswhere.[49] Briefly, cumulative exposure (years × mg/m³) was the product of the time worked in a naphtha exposure zone in a particular month and the mean naphtha air concentration in that zone that month, summed over the zones and months. Computerised work histories supplemented by personal interviews identified the dates worked in the zones. Mean naphtha air concentrations were calculated from 514 personal air samples for naphtha collected in June 1988, October 1988, December 1988, and June 1989. The sampling and analytical scheme was the National Institute of Occupational Safety and Health (NIOSH) method 1550.[50] Due to a strong association between air concentration and outdoor temperature, mean concentrations for each month between February 1982 (plant opening) to June 1988 were adjusted for monthly changes in outdoor temperature. Recent exposure was calculated as the mean

naphtha concentration of the exposure zone in which the employee worked currently adjusted for the mean temperature during that month.

Three alternative measures of the cumulative and recent exposure variables were calculated, based respectively on delineations of jobs at the plant into two, six, or 23 exposure zones.[49] Results from the three types of measures were similar; only results from the scheme with six zones are presented here.

An investigation of the potential effect of skin absorption of naphtha on total hydrocarbon and trimethylbenzene concentrations in exhaled breath among this study population failed to show any significant or consistent effects (unpublished data). Therefore, calculated exposures to naphtha were not adjusted for potential dermal absorption.

Two measures of acute exposure to naphtha were examined: the simple TWA concentration and the product of the TWA times the number of hours worked on the day of testing before undergoing the tests. Because a greater number of significant associations were present with the product term and because toxicokinetic considerations suggested that this measure was more likely to reflect acute dose to the target organ central nervous system, only the product term results are presented here.

IN PLANT EXPOSURE TO OTHER POTENTIAL NEUROTOXICANTS

As well as naphtha, subjects could be exposed to other potential neurotoxicants at the plant. These substances included 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113), low odour paraffin solvent, toluene, ethylene glycol monoethyl ether acetate, and cadmium. These exposures seemed unlikely to act as confounders because exposures were very low: in each case, $\leqslant 3 \cdot 0\%$ of the TLV designated by the American Conference of Governmental Industrial Hygienists (ACGIH).[50] Of these Freon 113 was the most prevalent. Freon 113 concentrations among 13 workers expected to have the highest exposures ranged from 32 to 230 mg/m³ (ACGIH TLV is 7670 mg/m³).[50] The sampling and analytical scheme used was NIOSH method 1020.[51]

MEASURES OF BEHAVIOURAL FUNCTION

During both data sampling periods, a questionnaire was given to each participant to assess medical history, including neurological and psychiatric disorders, renal disorders, hypertension, diabetes, use of medications, occupational history, educational history (including presence of learning problems), and history of alcohol consumption. The health questionnaire also included questions about the frequency and presence of transient and chronic symptoms associated with neurotoxic exposures. Pretesting and post-testing questionnaires were also given to assess subjective psychological and somatic symptoms experienced on the day of testing. Data were also collected from personnel records on the amount of overtime worked in the months

and week before testing. The number of hours worked before the test was noted. After giving the questionnaire, the formal neuropsychological tests were completed. These comprised:

profile of mood states, (POMS)[52]—This is a self administered measure of mood consisting of six scales: tension, depression, anger, fatigue, confusion, and vigour.

trail making test, (trails)[53]—This is a test of timed sequencing that requires the subject to complete a simple sequence (A) and alternate sequencing in a spatial array (B). It is sensitive to solvents[27 28 54] and to frontal lobe functions.[55]

delayed recognition span test[56]—This verbal and spatial learning test assesses both recognition and recall memory known to be sensitive to memory dysfunction. It requires pointing out new stimuli in an increasingly numerous array and incidental recall of verbal stimuli at 15 seconds and at two minutes.

visual reproductions—This is a subtest of the Wechsler memory scale,[57] a task of visual memory that requires the subject to draw designs from immediate and delayed recall. It is sensitive to damage of the limbic system.[58]

symbol-digit substitution test—This is a subtest of the neurobehavioural evaluation system (NES)[59 60] that assesses coding ability and motor speed. Its brain localisation is unknown at present but the task is sensitive to exposure to neurotoxicants.[61]

pattern memory,—This subtest of the NES uses visual stimulus arrays to assess visual memory. Its brain localisation is unknown but it is sensitive to exposure to neurotoxicants.[14]

vocabulary—This is an NES task designed to evaluate verbal knowledge and ability thought to be insensitive to neurotoxic exposures in adults. Because the subjects in this study objected to the task (they found it difficult and frustrating on the harder items), the Information subtest of the Wechsler adult intelligence scale revised (WAIS-R)[62] was substituted during 1989. This test also measures crystallised intelligence and is insensitive to moderate exposures to neurotoxicant in adults[45 63]:

Wisconsin card sorting test (WCST)[64]—This test assesses concept formation, cognitive flexibility, and cognitive tracking and requires inferring decision rules for a sorting task with minimal examiner feedback. It is known to be sensitive to frontal lobe function.[65] Because we believed that there would be a practice effect in repeating this task, it was only administered during 1988. In 1989, the following was used:

Rey-Osterreith complex figure task[66]—This test requires drawing an intricate visual design to copy and from immediate and delayed recall. It measures constructional function, strategy development, and memory.

POTENTIAL CONFOUNDERS

The potential confounders considered in the regression models of outcomes on the central nervous system included age, sex,

handedness, native language, highest grade completed in school, hours of overtime in the previous week or day, self reported use of psychotropic medications, frequency of marijuana use, history of alcohol abuse, history of loss of consciousness, history of seizures, history of emotional illness, familiarity with video display terminals, history of repeating a grade in school, and histories of prior exposure to lead, mercury, or solvents. Multiple regression was stepwise, missing values were deleted pairwise, and the p value to enter was 0·1. The acute and cumulative measures of exposure were forced into the regression models as the final step.

The NES vocabulary scores were significantly negatively associated with cumulative exposure. Because vocabulary scores may be associated with several other neuropsychological scores and are expected to be highly resistant to solvent neurotoxic effects, key neuropsychological outcomes were re-examined in multiple regression models with vocabulary as a covariate.

STATISTICAL ANALYSES

Statistical analyses were conducted with SPSS-X version 3·0.[67] Participants in 1988 were compared with non-participants, and second year participants were compared with those lost to follow up by means of χ^2 tests (two tailed without Yates' correction) for dichotomous variables and the Mann-Whitney U test for continuous variables. A paired t test was used to examine differences in measures of neuropsychological function in 1988 and 1989.

For the cross sectional and longitudinal studies, the association between the measures of behavioural function and exposure to naphtha was examined with simple and multiple regression. Multiple regression was stepwise, the p value to enter was 0·1, and variables of exposure to naphtha were forced in as the final step. Independent variables included cumulative and recent exposure to naphtha and potential confounders. Multiple regression models including first order interaction terms between exposure to naphtha and potential confounders were also examined.

In view of the substantial differences found in regression models of neuropsychological outcomes in the two years of data collection and the substantially higher mean exposures in the first year, additional analyses were conducted. Firstly, the scores on all neuropsychological tests and symptom questions among the 185 subjects participating in both years were compared by paired t test. To investigate threshold effects, the multiple regression models for the two sets of data were re-examined with the first year's acute exposure 75th percentile (540 h × mg/m³), and separately the first year 90 percentile (1050 h × mg/m³) as thresholds. For these models, the measure of acute exposure was recalculated as follows:

Acute exposure (75th percentile threshold) = 0, if acute exposure ≤540 h x mg/m³

Acute exposure (75th percentile threshold) = acute exposure—540, if acute exposure >540 h × mg/m³

The acute exposure 90th percentile threshold was calculated in an analogous manner with a threshold of 1050 h × mg/m³. These models test the hypothesis that acute exposure has no effect on outcomes at or below the threshold but has a positive linear effect on outcomes above the threshold. All standard and threshold regression models were examined for the influence of outliers.

Table 3 Comparison of mean (SD) on neuropsychological tests in 1988 and 1989

Dependent variable	No	1988	1989	p Value (paired t test)	Year of poorer performance
Trails A:					
Response time (s)	185	30·9 (10·4)	28·5 (9·2)	0·002	1
Errors (n)	184	0·201 (0·510)	0·114 (0·381)	0·052	1
Trails B:					
Response time (s)	178	75·7 (39·5)	74·8 (45·8)	0·81	
Errors (n)	176	0·78 (1·68)	1·05 (2·80)	0·22	
Moss:					
Verbal scan	184	12·91 (2·45)	13·10 (2·18)	0·41	
Verbal span total score	184	13·56 (1·26)	13·75 (0·57)	0·053	1
15" Verbal recall	184	5·87 (1·58)	7·10 (2·25)	0·0005	1
2' Verbal recall	184	5·00 (1·74)	6·13 (2·17)	0·0005	1
Spatial scan	184	11·46 (2·56)	12·10 (2·22)	0·006	1
Spatial scan total score	184	12·74 (1·50)	13·16 (1·04)	0·001	1
Visual reproduction:					
Immediate recall	185	8·79 (2·45)	10·75 (2·42)	0·0005	1
Delayed recall	185	7·80 (2·75)	10·12 (2·55)	0·0005	1
Profile of moods states:					
Tension, t score	184	38·14 (6·85)	38·70 (6·75)	0·28	
Depression, t score	184	38·47 (4·84)	38·41 (4·41)	0·87	
Anger, t score	184	43·67 (6·45)	44·07 (6·44)	0·44	
Fatigue, t score	184	46·41 (7·18)	45·80 (6·92)	0·23	
Confusion, t score	184	38·99 (5·22)	39·56 (5·34)	0·14	
Pattern memory:					
% Correct	184	80·6 (11·9)	79·9 (11·4)	0·51	
Response time (s)	184	9·11 (2·46)	8·10 (2·23)	0·0005	1
Symbol-digit:					
% Correct	183	99·2 (2·7)	99·0 (3·1)	0·68	
Response time (s)	183	23·61 (6·22)	22·58 (4·82)	0·006	1

Table 4   Comparison of mean (SD) symptom scores in 1988 and 1989

Dependent variable	No	1988	1989	p Value (paired t test)	Year of poorer performance
Feeling tired	180	2·77* (0·86)†	2·53 (0·87)†	0·0005	1
Difficulty concentrating	180	1·81 (0·76)	1·86 (0·70)	0·36	
Having headaches	180	1·93 (0·94)	1·93 (0·88)	0·93	
Difficulty falling asleep	180	1·44 (0·74)	1·59 (0·85)	0·02	2
Diminished sexual desire	179	1·38 (0·70)	1·41 (0·67)	0·51	
Tingling in fingers, toes	179	1·44 (0·80)	1·38 (0·70)	0·36	
Facial numbness	180	1·07 (0·35)	1·07 (0·34)	0·99	
Diminished appetite	180	1·29 (0·63)	1·27 (0·61)	0·72	
Diarrhoea	179	1·40 (0·67)	1·33 (0·63)	0·13	
Dry mouth	182	1·66 (0·88)	1·52 (0·71)	0·03	1
Confusion	180	1·23 (0·52)	1·35 (0·63)	0·007	2
Feeling depressed with or without reason	181	1·50 (0·75)	1·40 (0·63)	0·08	1
Have to take notes to remember	182	1·80 (0·88)	1·93 (0·90)	0·06	2
Hallucinations	182	1·02 (0·08)	1·07 (0·28)	0·02	2
Heart palpitations	179	1·30 (0·70)	1·29 (0·63)	0·89	
Experienced lack of coordination	180	1·24 (0·59)	1·25 (0·52)	0·88	
Sleeping more than usual	182	1·50 (0·84)	1·32 (0·64)	0·001	1
Skin dryness	182	1·82 (0·97)	1·81 (0·92)	0·93	
Unexplained weight loss	181	1·08 (0·37)	1·11 (0·42)	0·49	
Indigestion	180	1·62 (0·85)	1·49 (0·77)	0·009	1
Excessive salivation	178	1·14 (0·45)	1·11 (0·41)	0·36	
Feeling irritable	181	1·90 (0·82)	1·77 (0·79)	0·04	1
Light headedness	181	1·40 (0·69)	1·31 (0·59)	0·05	1
Lack of muscle strength	180	1·33 (0·65)	1·33 (0·59)	0·91	
Feeling excitable	182	1·53 (0·73)	1·58 (0·71)	0·38	
Tightness in chest	182	1·38 (0·73)	1·29 (0·61)	0·06	1
Nausea	182	1·31 (0·61)	1·27 (0·61)	0·15	
Inflamed gums	181	1·27 (0·44)	1·10 (0·34)	0·54	
Tremor in fingers	180	1·17 (0·46)	1·14 (0·42)	0·56	
Feeling anxious	180	1·57 (0·77)	1·58 (0·75)	0·85	
Loose teeth	179	1·03 (0·25)	1·04 (0·19)	0·53	
Trembling eyelids, lips, tongue	181	1·22 (0·52)	1·19 (0·51)	0·64	

Mean symptom score in past month: 1 = not at all; 2 = a little; 3 = a moderate amount; 4 = quite a lot.
†SEM.

Table 5   Demographic variables and mean (SD) test scores stratified by acute naphtha exposure groups 1988

	Acute naphtha exposure group		
Dependent variable	75th Percentile (<550 mg/h/m³) (n = 186)	75th-90th Percentile (n = 36)	>90th Percentile (>1060mg/h/m³) (n = 25)
% Men	64·0	61·1	60·0
Age (y)	36·0 (0·7)*	35·1 (1·2)*	36·0 (1·8)*
Education (y)	12·4 (0·1)	12·5 (0·2)	12·6 (0·3)
Overtime in week before testing (h)	9·1 (0·6)	5·7 (1·2)	5·1 (0·9)
Trails A:			
Response time (s)	31·1 (0·9)	29·3 (1·2)	37·8 (4·4)
Errors (n)	0·20 (0·04)	0·14 (0·06)	0·12 (0·07)
Trails B:			
Response time (s)	79·8 (3·6)	78·1 (5·5)	76·5 (4·9)
Errors (n)	0·85 (0·14)	1·12 (0·42)	0·58 (0·27)
Wisconsin card sorting test:			
Correct sets (n)	3·16 (0·10)	3·36 (0·20)	3·59 (0·23)
Errors (n)	13·3 (0·8)	12·1 (1·5)	11·0 (1·8)
Times sets lost (n)	2·04 (0·14)	1·78 (0·29)	1·73 (0·30)
Moss:			
Verbal span	12·9 (0·2)	13·7 (0·2)	12·7 (0·5)
Verbal span total score	13·6 (0·1)	13·8 (0·1)	13·6 (0·2)
15" Verbal recall	5·86 (0·12)	5·94 (0·28)	6·79 (0·46)
2' Verbal recall	4·93 (0·14)	5·31 (0·25)	5·75 (0·46)
Spatial span	11·3 (0·2)	11·3 (0·4)	11·8 (0·5)
Spatial span total score	12·8 (0·1)	12·7 (0·2)	13·0 (0·3)
Visual reproduction:			
Immediate recall	8·67 (0·19)	7·89 (0·46)	8·88 (0·49)
Delayed recall	7·75 (0·20)	6·83 (0·53)	7·48 (0·53)
POMS:			
Tension, t score	37·8 (0·5)	38·3(1·3)	42·1 (1·7)
Depression, t score	38·3 (0·3)	38·5 (0·9)	40·4 (1·1)
Anger, t score	43·5 (0·5)	43·8(1·3)	45·4 (1·7)
Fatigue, t score	45·7 (0·5)	47·0(1·4)	47·7 (1·9)
Confusion, t score	38·5 (0·3)	38·9(1·0)	42·8 (1·5)
Pattern memory:			
Percentage correct	79·9 (1·0)	77·8 (1·8)	78·6 (1·8)
Response time (s)	9·02 (0·18)	9·00 (0·40)	9·18 (0·49)
Vocabulary	71·0 (1·1)	74·3 (2·5)	72·2 (3·1)
Symbol-digit: % Correct	99·0 (0·2)	99·1 (0·6)	99·3 (0·3)
Response time (s)	23·7 (0·5)	22·5 (0·6)	25·5 (1·5)

*Mean (SEM).

Results

Air concentrations of naphtha ranged from 9 to 590 mg/m³ in June 1988 and 4 to 790 mg/m³ in June 1989. Mean (SD) naphtha concentrations were significantly higher inside the calibration rooms than outside the calibration rooms and higher in June 1988 than in June 1989—namely, in June 1988 177(71) mg/m³ inside and 40(39) mg/m³ outside and in June 1989 127(55) mg/m³ inside and 31(14) mg/m³ outside. (As naphtha is a complex mixture of compounds of varying molecular weight, the relation of concentration in mg/m³ to parts per million (ppm) may vary from one naphtha sample to another; however, division of mg/m³ by six to obtain ppm is a reasonable approximation.) The calculated cumulative exposure to naphtha among participants averaged 216 (range 18–834) × mg/m³ in June 1988 and 269 (range 37–905) × mg/m³ in June 1989. Duration of exposure averaged 2·8 (range 0·8–6·3) years in June 1988 and 3·9 (range 1·8–7·3) years in June 1989.

Compared with eligible non-participants, participants in 1988 had lower mean seniority (5·04 v 6·53 years, p < 0·0005) but did not differ significantly with regard to sex (66% men v 57% women). Those lost to follow up in 1989 did not differ from those who participated in 1988 on potential confounding variables or exposure to naphtha except that second year participants were somewhat older in 1988 (37·1 v 34·7 years, p = 0·08) and had more exposure to organic solvents in jobs held before working at the plant (3·8 v 0·1 years, p < 0·0005).

COMPARISON OF SCORES IN 1988 AND 1989
Tables 3 and 4 compare the mean test and symptom scores for the two years. The mean

Table 6 Mean scores for selected symptoms stratified by acute naphtha exposure groups 1988

Symptom	Acute naphtha exposure group		
	<75th Percentile (<550 h/mg/m³) (n = 186)	75th-90th Percentile (n = 36)	>90th Percentile (>1060 h/mg/m³) (n = 25)
Feeling tired	2·79* (0·07)†	2·28 (0·14)†	2·64 (0·20)
Difficulty concentrating	1·80 (0·05)	1·83 (0·15)	2·00 (0·15)
Having headaches	1·92 (0·07)	2·19 (0·19)	2·17 (0·25)
Dry mouth	1·55 (0·06)	1·81 (0·17)	2·00 (0·22)
Confusion	1·19 (0·03)	1·22 (0·10)	1·46 (0·18)
Feeling depressed without reason	1·50 (0·05)	1·42 (0·12)	1·96 (0·20)
Lack of coordination	1·20 (0·04)	1·42 (0·15)	1·38 (0·16)
Sleeping more than usual	1·42 (0·06)	1·44 (0·14)	1·75 (0·22)
Feeling irritable	1·87 (0·06)	1·72 (0·15)	2·17 (1·01)
Light headedness	1·40 (0·05)	1·39 (0·14)	1·54 (0·18)
Lack of muscle strength	1·30 (0·04)	1·39 (0·12)	1·67 (0·21)
Tightness in chest	1·28 (0·05)	1·53 (0·14)	1·54 (0·18)

*Mean symptom score in past month: 1 = not at all; 2 = a little; 3 = a moderate amount; 4 = quite a lot.
†SEM.

test scores on the neuropsychological measures are generally within expected norms for a subject group with a mean age of 36 and a mean educational level of 12 years. Among the tests, in all cases of significant difference, the poorer performance was in 1988. Tests showing significant differences included trails A (response time and number of errors), most of the Moss verbal and spatial scores, visual reproductions (immediate and delayed recall), pattern memory response time, and

Table 7 Cross sectional multiple regression* analysis of neuropsychological outcomes for 1988

Dependent variable	Acute exposure			Cumulative exposure		
	Coeff	SEM	p Value	Coeff	SEM	p Value
Trails A:						
Response time (s)	0·005	0·002	0·024	−0·009	0·006	0·12†
Errors (n)			0·27			0·95
Trails B:						
Response time (s)			0·98			0·85
Errors (n)			0·93			0·58
Wisconsin card sorting test:						
Correct sets (n)			0·75			0·36
Errors (n)			0·76	−0·008	0·005	0·10†
Times sets lost (n)			0·25			0·86
Moss:						
Verbal span			0·36			0·55
Verbal span total score			0·90			0·43
15″ Verbal recall	0·0004	0·0003	0·11†			0·96
2′ Verbal recall			0·36			0·36
Spatial span			0·32			0·63
Spatial span total score			0·68			0·59
Visual reproduction:						
Immediate recall			0·63	0·0018	0·0012	0·13†
Delayed recall			0·36	0·0021	0·0012	0·09†
POMS:						
Tension, t score	0·0022	0·0011	0·042			0·77
Depression, t score	0·0016	0·0008	0·043			0·31
Anger, t score	0·0020	0·0010	0·055			0·38
Fatigue, t score			0·16			0·35
Confusion, t score	0·0031	0·0008	0·0004			0·22
Pattern memory:						
% Correct			0·38			0·37
Response time (s)			0·62			0·41
Vocabulary				0·014	0·006	0·02†
Symbol-digit:						
% Correct			0·52			0·48
Response time (s)			0·41			0·98

*Each line in the table represents a single regression model. Acute and cumulative exposure measures were included in each model. Covariates included if p value <0·1. Covariates considered included overtime worked in past week, age, sex, handedness, self report of effort, sleep in past 24 hours, caffeine in past 24 hours, alcohol in past 24 hours, use of marijuana, use of alcohol, history of loss of consciousness, history of seizures, history of emotional problems, familiarity with video games, first language, education, repeated grades in school, history of mercury exposure, history of lead exposure, and history of solvent exposure. The only covariate shown is overtime worked in past week.
†Effect in counterintuitive direction.

symbol digit response time. The findings for symptoms (table 4) were mixed. Among the 12 symptoms for which there were significant differences, eight were more frequent in 1988 and four in 1989.

COMPARISON OF DEMOGRAPHIC VARIABLES AND MEAN TEST AND SYMPTOM SCORES ACROSS ACUTE NAPHTHA EXPOSURE GROUPS

Table 5 shows that participants with acute exposure to naphtha less than the 75th percentile in 1988 were similar to higher exposed participants with respect to age, sex, and years of education but had worked more overtime in the week before testing. Among the tests examined, trails A response time and five POMS scores showed the most consistent trends of poorer performance with increasing exposure. Timed performance was somewhat slowed on trails A in the highest exposed group (average time for 20 to 39 year olds is 32 seconds[65]). The Moss DRST 15 second verbal recall showed the strongest trend in a counter intuitive direction (improved performance with increasing exposure). Similar analyses of the 1989 data showed fewer apparent trends in test scores (not shown). Only for visual reproductions immediate recall and for symbol digit response times were there trends in the expected direction.

Table 6 shows that for subjective symptoms fatigue was the most intensely endorsed at all threshold levels. There were trends suggesting increasing frequencies of several symptoms with increasing exposure in 1988, particularly if the highest exposure group was compared with the other two groups. Trends were particularly notable for dry mouth, confusion, feeling depressed without reason, sleeping more than usual, and lack of muscle strength. Substantially fewer such trends were present for symptoms reported in 1989 (not shown).

CROSS SECTIONAL MULTIPLE REGRESSION ANALYSES
Neuropsychological test scores
Table 7 presents the results of the cross sectional multiple linear regression models of the neuropsychological outcomes in 1988. Trails A (number of errors and response time) and t scores on four of the POMS affective scales (depression, anger, tension, and confusion) were significantly associated with the measure of acute exposure in 1988, although the significant association for trails A errors was due to an outlier. The Moss (Delayed Recognition Span Test) 15 second verbal recall was marginally associated with acute exposure in a counter intuitive direction. In 1989 (not shown), only the symbol digit subtest was significantly associated with the measure of acute exposure (coefficient 0·0026 (0·0011); p = 0·014).

None of the tests was associated with the measure of cumulative exposure in the expected direction in either year. In 1988, trails A (response time and number of errors), Wisconsin card sort (number of errors) and

Table 8   Cross sectional multiple regression* analysis of neuropsychological outcomes for 1988

Dependent variable	Acute exposure			Cumulative exposure		
	Coeff	SEM	p Value	Coeff	SEM	p Value
Feeling tired			0·40			0·38
Difficulty concentrating			0·56			0·16
Having headaches	0·00023	0·00015	0·12			0·32
Difficulty falling asleep			0·45			0·50
Diminished sexual desire			0·86			0·32
Tingling in fingers, toes			0·99			0·78
Facial numbness	0·00014	0·00006	0·01			0·83
Diminished appetite			0·49			0·59
Diarrhoea			0·16			0·96
Dry mouth	0·00041	0·00013	0·002			0·95
Confusion	0·00041	0·00008	0·09			0·94
Feeling depressed without reason	0·00018	0·00012	0·15			0·48
Have to make notes to remember			0·91			0·83
Hallucinations			0·82			0·88
Heart palpitations			0·16			0·57
Experienced lack of coordination			0·33	0·00040	0·00026	0·13
Sleeping more than usual	0·00019	0·00013	0·12			0·99
Skin dryness	0·00025	0·00016	0·11	0·00064	0·00043	0·15
Unexplained weight loss			0·60			0·62
Indigestion	0·00024	0·00014	0·14			0·35
Excessive salivation			0·96			0·36
Feeling irritable			0·84			0·37
Light headedness			0·44			0·52
Lack of muscle strength	0·00021	0·00011	0·05			0·22
Feeling excitable			0·72			0·91
Tightness in chest	0·00026	0·00011	0·02			0·63
Nausea			0·78	0·00041	0·00028	0·015
Inflamed gums			0·37	0·00043	0·00020	0·04
Tremor in fingers			0·92			0·77
Feeling anxious			0·27			0·44
Loose teeth			0·90			0·35
Trembling eyelids, lips, tongue	0·00022	0·00008	0·009			0·98

*As for table 7.

visual reproductions (immediate and delayed recall) were marginally associated with estimated cumulative exposure in the counter intuitive direction. Vocabulary scores were significantly negatively associated with exposure (those who had the highest exposure had the better vocabulary scores). Because vocabulary scores may be associated with other scores and are expected to be highly resistant to neurotoxic effects, key outcomes were re-examined in multiple regression models including vocabulary as a covariate. In no case, however, did this adjustment have a meaningful effect on the association between the measure of exposure and outcomes.

Symptoms

Table 8 presents the results of cross sectional multiple linear regression analyses of subjective symptomatic complaints in 1988. Self reported symptoms showing significant associations with the measure of acute exposure during 1988 included facial numbness, dry mouth, lack of muscle strength, tightness in chest, facial trembling, and, marginally, confusion. Only a few subjective symptoms were associated with the measure of acute exposure in 1989—namely, diarrhoea, headache, and, marginally, difficulty concentrating (data not shown).

Table 9   1988 Cross sectional multiple regression *models of association of acute exposure measures† with neuropsychological outcomes

Dependent Variable	No threshold‡				Threshold at 75th percentile §				Threshold at 90th percentile ¶			
	Coeff	SEM	p Value	Model r²	Coeff	SEM	p Value	Model r²	Coeff	SE	p Value	Model r²
Trails A:												
Response time (s)	0·0050	0·0020	0·022	0·154	0·0101	0·0031	0·0014	0·173	0·0314	0·0070	<0·0001	0·207
Errors (n)			0·27				0·65				0·95	
Trails B:												
Response time (s)			0·97				0·99				0·88	
Errors (n)			0·89				0·70				0·91	
Wisconsin card sorting test:												
Correct sets (n)			0·75				0·38				0·60	
Errors (n)			0·76				0·84				0·84	
Times sets lost (n)			0·25				0·42				0·34	
Moss:												
Verbal span			0·36				0·64				0·78	
Verbal span total score			0·90				0·55				0·46	
15" Verbal recall	0·0004	0·0003	0·109**	0·118	0·0007	0·0004	0·080**	0·12	0·0011	0·0010	0·26	0·125
2' Verbal recall			0·40				0·20				0·29	
Spatial span			0·32				0·50				0·98	
Spatial span total score			0·68				0·64				0·40	
Visual reproduction:												
Immediate recall			0·61				0·85				0·63	
Delayed recall			0·44				0·45				0·70	
POMS:												
Tension, t score	0·0022	0·0011	0·040	0·137	0·0040	0·0017	0·018	0·143	0·0078	0·0038	0·041	0·137
Depression, t score	0·0016	0·0008	0·043	0·15	0·0028	0·0012	0·019	0·156	0·0046	0·0029	0·087	0·146
Anger, t score	0·0020	0·0010	0·055	0·166	0·0033	0·0016	0·039	0·169	0·0079	0·0036	0·030	0·170
Fatigue, t score			0·15				0·18				0·32	
Confusion, t score	0·0027	0·0008	0·002	0·132	0·0053	0·0013	0·0001	0·159††	0·0110	0·0029	0·0002	0·146
Pattern memory:												
% Correct			0·38				0·25				0·32	
Response time (s)			0·62				0·99				0·52	
Symbol-digit:												
% Correct			0·52				0·60				0·94	
Response time (s)	0·0006	0·0009	0·49	0·257	0·0020	0·0014	0·16	0·262	0·0068	0·0033	0·037	0·270

*Each line in the table represents three separate regression models. Acute and cumulative exposure measures were included in each model. Covariates included if p value <0·1. Covariates considered included overtime worked in past week, age, sex, handedness, self report of effort, sleep in past 24 hours, caffeine in past 24 hours, alcohol in past 24 hours, marijuana use, alcohol use, history of loss of consciousness, history of seizures, history of emotional problems, familiarity with video games, first language, education, repeated grades in school, history of mercury exposure, history of lead exposure, history of solvent exposure, and vocabulary. Only the results for the acute exposure measure are shown.
†Acute exposure = measured concentration of naphtha on day of testing (mg/m³) × on job before testing.
‡Acute exposure treated as a standard continuous variable.
§Acute exposure = 0, if ≤540 h × mg/m³ (n = 188). Acute exposure = measured value -540, if > 540 h × mg/m³ (n = 61).
¶Acute exposure = 0, if ≤1050 h × mg/m³ (n = 222). Acute exposure = measured value—1050, if >1050 h × mg/m³ (n = 25).
**Effect in counterintuitive direction.
††Model r² not directly comparable to r² for no threshold because different set of covariates entered model.

Table 10   Longitudinal multiple regression analysis of association of change in neurobehavioral outcomes with change in acute and cumulative exposures between 1988 and 1989

Dependent variable: (difference in)	Difference in acute exposure			Difference in cumulative exposure			Cumulative exposure up to 1988		
	Coeff	SE	p Value	Coeff	SE	p Value	Coeff	SE	p Value
Trail A:									
Response time(s)	0·0036	0·0023	0·11			0·43			0·83
Errors(n)			0·27			0·76			0·54
Trails B:									
Response time(s)			0·66			0·36			0·95
Errors(n)			0·66			0·73			0·44
Moss:									
Verbal span			0·41	0·014	0·08	0·06§			0·72
Verbal span total score			0·35			0·42			0·87
15″ Verbal recall			0·25			0·48			0·19
2′ Verbal recall			0·50			0·98			0·20
Spatial span			0·20			0·31			0·30
Spatial span total score			0·21			0·87			0·47
Visual reproduction:									
Immediate recall			0·65			0·38			0·67
Delayed recall			0·42			0·77			0·92
POMS:									
Tension, t-score	0·0039	0·0016	0·02			0·77			0·53
Depression, t score	0·0025	0·0011	0·02			0·66			0·79
Anger, t score	0·0027	0·0016	0·09			0·67			0·68
Fatigue, t score	0·0036	0·0015	0·02			0·58			0·17
Confusion, t score			0·23			0·63			0·59
Pattern memory:									
% Correct			0·64			0·71			0·82
Response time(s)			0·41			0·87			0·60
Symbol-digit:									
% Correct			0·32			0·59			0·95
Response time(s)	0·0030	0·0011	0·008			0·62			0·99

*Each line in the table represents a single regression model. Difference in acute exposure, difference in cumulative exposure, and cumulative exposure up to 1988 were included in each model. Covariates included if p value < 1. Covariates considered included difference in self report of effort, effect of medication, marijuana use, history of loss of consciousness, history of seizures, history of emotional problems, overtime worked in past week.
†All differences are 1989 value minus 1988 value.
‡Value in 1989 minus value in 1988.
§In counterintuitive direction.

Only the symptoms of nausea and inflamed gums were significantly associated with the estimate of cumulative exposure in 1988 and there were only two marginal associations in 1989 (skin dryness and excessive salivation).

Threshold models
Table 9 compares the association between measures of acute exposure and neuropsychological outcomes for the 1988 cross sectional data in a no threshold model and in models examining possible thresholds at the 75th and 90th percentile of 1988 exposure. Decreased p values and increased r^2 values for the threshold models compared with the no threshold models suggest a threshold effect. The test for which the results most strongly suggested a threshold effect was trails A (response time and number of errors), with the 90th percentile showing the strongest associations. Again, the results for trails A errors are explained completely by a single outlier. Although less obvious than the case of trails A, for each of the other tests showing significant associations in the no threshold model (POMS depression, tension, anger, and fatigue), there was some decrease in the p value and increase in r^2 for the 75th percentile threshold model. Except for the anger t score, results for the 90th percentile threshold model were less significant on the POMS tests than results for the 75th percentile model. Finally, for the symbol-digit response time, there was a statistically significant asso-ciation only in the 90th percentile threshold model.

When the same analyses were conducted on the 1989 data (not shown), the only test with a significant association in the no threshold model, symbol-digit response time, showed some increase in significance, particularly in the 90th percentile threshold model. The only other significant association was for visual reproductions immediate recall in the 90th percentile threshold model.

LONGITUDINAL MULTIPLE REGRESSION MODELS
Table 10 presents the results of longitudinal regression analyses of the difference in results on neurobehavioural tests in 1988 and 1989 with the differences in acute and cumulative exposure. The differences in test scores were significantly associated with acute exposure in the expected direction for three of the measures of POMS (tension, depression, fatigue) and for symbol-digit response time, with marginal significance for trails A response time and POMS anger. There were no associations in the expected direction with the difference in estimates of cumulative exposure.

Discussion
The finding in the 1988 cross sectional analyses of a significant association between acute exposure and neuropsychological outcome on trails A and POMS is intriguing and is

supported by the threshold analyses. Threshold analysis suggests that the daily exposure threshold that best fits the data for trails A performance (a measure of attention and simple sequencing) is $1050 \, h \times mg/m^3$ whereas a threshold daily exposure of 540 $h \times mg/m^3$ fits most of the POMS data best. Few findings emerged from the 1989 data, with only one task (symbol-digit response time) showing a significant association in the no threshold model and an effect at 1050 $h \times mg/m^3$ in the threshold model analyses. The 1989 data, however, must be interpreted with caution because mean exposure was significantly lower in 1989 than in 1988 and there were many fewer subjects experiencing higher exposures: only six subjects in 1989 had daily exposures at the level of the 1988 90th percentile ($1050 \, h \times mg/m^3$). The discrepancy in exposure was due to a significant difference in outside temperature between the two years: 1988 was much warmer, necessitating greater use of air conditioning and therefore more recirculation of solvent in plant air. The presence of more symptoms in 1988 than 1989 is also consistent with effects related to higher exposures in the first year.

With regard to the longitudinal data, the finding of statistically significant associations between the difference in acute exposure and the difference in three of the POMS scale scores, as well as borderline significance for the difference in trails A response time and another POMS scale, is also consistent with the occurrence of greater effects related to exposure in 1988. The finding for trails must be interpreted with some caution given the likelihood that practice effects could in themselves improve test performance. Practice effects, however, cannot be invoked to explain differences in POMS. It is also unlikely that subjects consciously or unconsciously deliberately skewed POMS data as they were unaware of the results of measures of personal exposure at the time of neuropsychological testing.

In past studies of neuropsychological effects of solvents, exposure has been shown to be associated with decrements in performance on trails A in subjects exposed to mixtures of solvents[27] as well as overall trails response and error scores with subjects exposed to carbon disulphide.[28] In a third study,[54] trails A was performed more slowly in workers exposed to toluene and paint solvents than controls, although the difference was not significant. The discrepancy between performance on trails A and trails B in this group was interesting and cannot be directly compared with prior reports. It is likely to reflect the subjects' ability to overcome mild tracking problems and to inhibit impulsive responses when faced with a more challenging task. This explanation is consistent with negative findings on trails B and coupled with negative findings on the Wisconsin card sorting test, another task that challenges tracking capacity.

The POMS subtests seem to be especially sensitive to the effects of solvents at low levels of exposure. We have found a positive association between acute exposure to mixed silk screening solvents and the depression and anger scales on POMS,[31] and performance on the NES version of the POMS (computerised version of the standard POMS but lacking the vigour scale items) has been found to be associated with exposure to mixed solvents in painters.[68 69]

The concurrence of findings of attentional and mood decrements at higher levels of exposure to naphtha is consistent with our prediction that the earliest manifestations of exposure would be in the functional domains of attention and mood. Given this clustering, we do not believe that the positive results from 1988 are due to chance. They are typical of the mild, acute, reversible effects of exposure to solvents described in previous work,[47] and are consistent with those seen clinically in patients exposed to solvents.[4] Furthermore, the results support the hypothesis of frontal (as measured by trails) and limbic system (as measured by POMS) dysfunction predicted at the outset of the study.

The strength of the effects found after acute exposure to naphtha at daily concentrations around $540 \, h \times mg/m^3$ deserves more investigation. Past studies of acute exposure done on humans in exposure chambers have suggested that this exposure level would be too low to produce effects. For example, Gamberale et al concluded that there is a "risk...in workers exposed to 2500 mg/m^3 doing light work",[43] and Stokholm showed that exposure to 400 ppm (2100–2400 mg/m^3) of white spirits resulted in performance deficits tests.[70] These conclusions, however, are based on performance measures, not mood, and it seems likely that affective changes are among the earliest manifestations of solvent intoxication.[4 48] Also, the occupational exposure situation is significantly different from the experimental setting in that acute and chronic exposures are intertwined and exposure occurs for longer.

The negative findings on effects of cumulative exposure must be interpreted with caution. Whereas they seem to support the conclusion that the effects of exposure to naphtha at this level are only mild, acute, and transitory, the plant had been open only eight years at the time of the study. The opportunity for studying subjects with extensive exposure at a chronic low dose was thus limited. Also, it is notoriously difficult to estimate cumulative lifetime exposures for subjects in a manner that produces strong findings. Anecdotally, the workers in the plant studied were themselves convinced that there was no doubt about the occasional occurrence of acute symptoms after exposure and were concerned about the potential for subacute chronic effects of exposure.

Based on this study, it was recommended that the plant ventilation system be upgraded to limit daily exposure to naphtha to less than 540 $mg/h/m^3$ (about 90 ppmh).

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NOTICE

Wellness Forum
keeping business healthy

MAJOR NEW UK AWARD LAUNCHED TO PROMOTE HEALTH AT WORK

A group of top companies and leading health organisations in the UK are joining together today to launch a major new award to promote the health and wellbeing of working people across the country. The first PPP/ Wellness Forum, *Working For Health Award* will be presented to the UK company judged to be carrying out the best practices to promote the health and wellbeing of its employees.

Chairman of the Wellness Forum Dr Robert Smith said: "The search is now underway to find the UK company which is doing the best for the health of its employees. With 350 million working days lost in the UK through illness each year, there is a clear incentive for companies to promote the health of their workforce."

The Wellness Forum is a group of some of the best known companies and health organisations in the UK. The founder members are Grand Metropolitan; J Sainsbury; Glaxo Group; The Institute of Personnel Management; and The English National Board for Nursing, Midwifery and Health Visiting. Other members include Marks and Spencer, IBM, and the Industrial Orthopaedic Society. The Forum meets regularly to develop programmes for improving health in the workplace, to share best practice, and to influence areas for research and training initiatives.

Andrew Randall, General Manager, PPP Corporate Division, said that: "By sponsoring this award, we hope to encourage UK employers to help employees to improve their health. Better morale, lower absenteeism and staff retention are just some of the benefits of wellness programmes."

UK companies who want to win the new PPP/Wellness Forum, *Working for Health Award* will have to prove that they have a strategy for achieving optimum physical and mental health for their staff and that their programmes for the wellness of employees are established and implemented to the maximum capability of the company. The winner will be announced in April 1994.

For details of how to enter (closing date 15 March 1994), companies should write to Jenny Marshall, Wellness Forum, Priory House, 8 Battersea Park Road, London SW8 4BG.