British Journal of Industrial Medicine 1991;48:750–761

Acute behavioural comparisons of toluene and ethanol in human subjects

Diana Echeverria, L Fine, G Langolf, T Schork, C Sampaio

Abstract

A comparison of toluene and ethanol (EtOH) induced changes in central nervous system (CNS) function and symptoms were evaluated in two studies, and when possible the effects of toluene were expressed in EtOH equivalent units. The toluene concentrations were 0, 75, and 150 ppm, bracketing the American Conference of Governmental Industrial Hygienists threshold limit value (ACGIH TLV) of 100 ppm. The socially relevant EtOH doses were 0·00, 0·33, and 0·66g EtOH/kg body weight, equivalent to two and four 3·5% 12 ounce beers. Forty two paid college students were used in each study. In the first study, subjects were exposed to toluene and an odour masking agent menthol (0·078 ppm) for seven hours over three days. In the second study EtOH or a placebo was administered at 1530 across three days also in the presence of menthol. Verbal and visual short term memory (Sternberg, digit span, Benton, pattern memory), perception (pattern recognition), psychomotor skill (simple reaction time, continuous performance, symbol-digit, hand-eye coordination, finger tapping, and critical tracking), manual dexterity (one hole), mood (profile on mood scales (POMS), fatigue (fatigue checklist), and verbal ability were evaluated at 0800, 1200, and 1600. Voluntary symptoms and observations of sleep were collected daily. A 3 × 3 latin square design evaluated solvent effects simultaneously controlling for learning and dose sequence. An analysis of variance and test for trend were performed on am-pm differences reflecting an eight hour workday and on pm scores for each solvent, in which subjects were their own control. Intersubject variation in absorbance was monitored in breath. A 5 to 10% decrement was considered meaningful if consistent with a linear trend at $p < 0·05$. At 150 ppm toluene, losses in performance were 6·0% for digit span, 12·1% for pattern recognition (latency), 5% for pattern memory (number correct), 6·5% for one hole, and 3% for critical tracking. The number of headaches and eye irritation also increased in a dose-response manner. The greatest effect was found for an increasing number of observations of sleep. A range of 2 to 7% decrements suggest the ACGIH TLV of 100 ppm toluene may be a good estimate of the biological threshold supporting a re-evaluation of the TLV. At 0·66g EtOH/kg body weight symptoms and performance decrements were 6·6% for digit span, 9·2% for pattern recognition, 4·0% for continuous performance, 7·9% for symbol-digit, 16·5% for finger tapping, 6·2% for critical tracking, and 5·2% for the one hole test. The EtOH equivalents at 150 ppm toluene for digit span (0·56g EtOH/kg/body weight), the latency for pattern recognition (0·66 g EtOH kg body weight), and the one hole element "move" (0·37 g EtOH kg body weight) show that the first two measures would be affected at or above the 50 mg% blood alcohol concentration. This concentration is recognised as the lowest alcohol concentration associated with increased numbers of automobile accidents. The results suggest that EtOH may be a useful acute standard to compare the effects of various industrial solvents and support investigating an association between exposure to solvents and increased risk to safety in industry.

The purpose of this study is to compare the acute behavioural effects of toluene with those of the well defined narcotic ethanol (EtOH). The effects of both solvents are assessed by changes in performance in a selection of behavioural tests. Whenever both solvents alter the same performance scores, the effect of the industrial solvent toluene is expressed in equivalent EtOH units (g EtOH/kg body weight). The toluene concentrations of 0, 75, and 150 ppm bracket the threshold limit value (TLV) of 100 ppm recommended by the American Conference of Governmental Industrial Hygienists. The EtOH

Battelle Seattle Research Center, 4000 NE 41st Street, Seattle, WA 98105, USA
D Echeverria, L Fine, G Langolf, T Schork, C Sampaio

concentrations of 0·00, 0·33, and 0·66g EtOH/kg body weight are above and below the legal impairment concentration of 50 mg%, equivalent to two or four domestic beers for a 70 kg person (a 12 ounce 3·5% wt/vol beer contains 12·42g EtOH).

Toluene and EtOH are both lipophilic and are absorbed through the lungs and distributed to the central nervous system (CNS), which is a lipid rich entity. The behavioural effects of low concentrations of both solvents appear non-specific. Therefore, at low doses a non-specific CNS depressive effect is the underlying hypothesis offered for observed effects of both solvents. Any change in behaviour is then a function of dose on a continuum of narcotic effects. Ethanol was chosen as a standard for acute effects because it is relatively non-toxic at doses producing performance decrements. Ethanol toxicity is well researched, and the results can be easily interpreted by health professionals, safety engineers, and legislators. It is also regulated by society for its effects on driving and by industry for its effects on productivity and safety.

Experimental studies evaluating toluene in human subjects have documented acute behavioural effects at levels of exposure that may cause dysfunction in the workplace.[1-3] For example, losses in manual dexterity and visual perception have been recorded at 100 ppm toluene[4 5] and increases in simple reaction time (SRT) have been found at a higher concentration of 300 ppm.[6] Simple reaction time may be less sensitive to acute exposure as it was not affected at 100 ppm,[7] a more common industrial level.

Consumption of low doses of EtOH has also increased simple reaction time[8 9] and critical tracking scores[10] between 0·24g EtOH/kg body weight and 0·76g EtOH/kg body weight. In a separate study, EtOH but not toluene impaired performance of manual dexterity and coordination tasks at 0·40g EtOH/kg body weight.[8] Attention, as measured by a WAIS digit span test, was also unaffected at 0·55g EtOH/kg body weight,[11] but was significantly affected at a higher dose of 1·1g EtOH/kg body weight.[12] These two doses approximate to 0·05 and 0·10 mg% blood alcohol concentrations, which are the legally impaired and intoxicated limits. Therefore, occupational exposure to toluene and the social consumption of alcohol may separately impair work performance and reduce adequate margins of safety.

Methods

SUBJECT SELECTION AND TRAINING

In accordance with the Declaration of Helsinki, 84 healthy University of Michigan students were selected and divided into two groups of 42 subjects for each solvent study. The groups were meant to be homogeneous with respect to age (18–35), education (at least one year of college), native English speaking, and in residence close to the school. Subjects were excluded if there was a history of exposure to solvents or if they drank more than 18 g alcohol/day (12·4 g EtOH = 12 ounces of a 3·5% wt/vol beer). Women who planned to be pregnant within one year or who were breast feeding were also excluded.

One training session was administered between 0700 and 0800 on the first day to reduce the effect of learning. Learning was also controlled by experimental design. To ensure more consistent performance, monetary payment was provided ($35·00 a day) and the odour of toluene and the taste of alcohol were masked for all doses. No alcohol or caffeine was permitted one night before or during the three days of testing.

EXPERIMENTAL DESIGN

Table 1 presents the experimental design for the EtOH and toluene studies.[13 14] Briefly, it is a balanced two way scheme (exposure or dose by day) for three permutations of one dose order in a standard 3 × 3 latin square. Fourteen subjects were randomly assigned to each group. They were tested at different exposures or doses on each of the three days. The independent factors were (1) solvent concentration, (2) learning, defined as improvement in performance scores over the three days, and (3) the solvent order.

This study compares acute effects of seven hour toluene exposures at 0, 75, and 150 ppm with the effects of 30–70 minute post-consumption of EtOH at 0·00, 0·33, and 0·66 g EtOH/kg body weight. The EtOH doses are equivalent to 0·03 mg% and 0·06 mg% peak blood alcohol concentrations, which encompass the legally impaired concentration.[15] The exposures in these experiments were masked with vapour from menthol crystals (0·078 ppm). Similarly, the taste of EtOH was masked by Kahlua, an aromatic spray. The study required a total of 252 exposures completed in 83 experimental days.

Four subjects were tested each day in two behavioural chambers that are described later. The subjects were administered the complete test battery at 0800 and 1600. Four of the tests were also given at 1200 for comparison with the toluene exposure study. The 0800 session serves as a control for the 1600 session for the toluene study. The 0800 and 1200 hour sessions serve as controls for the EtOH

Table 1 Experimental design for am–pm behavioural scores

	Toluene (ppm)			*EtOH dose (g/kg body weight)*		
Group	*A*	*B*	*C*	*A*	*B*	*C*
Day 1	150	75	0	0·00	0·33	0·66
Day 2	75	0	150	0·33	0·66	0·00
Day 3	0	150	75	0·66	0·00	0·33
No of subjects	14	14	14	14	14	14

study in which the subject received his or her dose at 1530. The control information is incorporated into the analysis by reporting the difference between a control and solvent score for each day—that is, noon–pm, or am–pm. The difference noon–pm reflects the afternoon acute EtOH effect and the difference am–pm is similar to testing before and after an eight hour workday.

At the end of the day symptoms and complaints were reported by subjects in response to the question "What are your reactions over the last four hours?" At the end of the three day experiment each subject was asked to rank the three days of exposure or dose as low, moderate, or high, in an effort to estimate the efficacy of masking either the smell of toluene or the taste of EtOH.

PERFORMANCE TESTS

A microcomputer (IBM PC) with a joystick (Ora Electronics) was used to administer the performance tests. The behavioural tests are a modification of a computer-administered test battery developed at the University of Michigan[16] and the neurobehavioural evaluation system (NES) developed at Harvard University.[17 18] The effects of solvents were compared on seven human performance functions: verbal skill (the vocabulary subtest of the armed forces qualifying test (AFQT) and the Mill Hill synonym test), verbal short term memory (the Sternberg test and digit span),[19] visual memory (pattern memory and Benton visual memory), perception (pattern recognition), psychomotor skill (simple reaction time, dynamic continuous performance (CPT), symbol-digit matching, and critical tracking),[20] manual dexterity (the one hole test,[21] hand-eye coordination and finger tapping), mood (profile on mood scale (POMS) and a fatigue checklist).[22] Table 2 presents the test order.

EXPOSURE TO TOLUENE AND MENTHOL

Exposures to toluene and menthol took place in two $6 \times 6 \times 7$ ft chambers. The exhaust was set to 60 m^3 min. The air temperature was maintained at 25°C, but humidity in the chamber varied throughout the day. The toluene concentration throughout the chamber was constant over the eight hour exposure (75 (SD 3·9) ppm and 150 (SD 7) ppm). Vapour from menthol crystals was introduced into the air stream at 0700 and maintained at 0·031 mM (0·079 ppm), sufficient to reduce detecting the difference between a high and low toluene dose. Exposure was from 0900 to 1700, with one hour from 1200 to 1300 outside the chamber for a prepared lunch.

INGESTION OF EtOH

Peak values of 0·03 and 0·06 mg% blood alcohol concentration were estimated using 0·33 and 0·66g EtOH/kg body weight.[15 26] Subjects were weighed daily, and their dose was diluted 1:5 in tonic water and orange juice with bitters. The placebo was laced with 3 ml EtOH and sprayed with Kahlua. Subjects were asked to drink it within 20 minutes at 1530, three hours after a light lunch. Subjects then waited 10 minutes until the 1600 test session began. Most tests were administered on the ascending side of the blood alcohol curve, which occurs about 45 minutes after ingestion. After the test session subjects were retained until their breath samples indicated one half of the absorbed dose of EtOH had been metabolised. It takes an estimated 45 minutes for the low dose and 2·5 hours for the high dose to remove 50% of the EtOH from the blood.

COLLECTION AND ANALYSIS OF SOLVENTS IN BREATH

Breath samples for toluene analysis were collected immediately upon leaving the chamber at 0, 5, 10, and 20 minutes post-exposure by exhaling a mixed

Table 2 The test order and corresponding blood alcohol concentrations at 30, 60, 75, and 120 minutes after ingestion

Test order	*Time taken for test (min)*	*Blood alcohol concentrations*	
		0·33 g/kg body weight	*0·66 g/kg body weight*
	0	0·00	0·00
(1) One hole test	12		
(2) Digit span test	20		
(3) POMS mood scale	2	0·030% (30 min)	0·063%
(4) Pattern recognition	2		
(5) Pattern memory	2		
(6) Hand-eye	4		
(7) Symbol digit	4		
(8) Sternberg test	7		
(9) Finger tapping	4		
(10) Reaction time	5	0·022% (60 min)	0·054%
(11) Continuous performance test	6		
(12) Critical tracking test	5		
		0·015% (75 min)	0·049%
		0·011% (120 min)	0·039%

breath sample into a 12 l teflon bag. Breath samples for EtOH analysis were collected in a similar manner but subjects were first instructed to drink water to remove alcohol from the mouth. Samples were collected pre-exposure at 0800 and 1530, and post-exposure at 30, 60, 75, and 120 minutes after ingestion. This assured points on both the ascending and descending limbs of the blood alcohol concentration curve. Samples were analysed by gas chromatography.[13 14]

STATISTICAL ANALYSIS

The main hypothesis is that EtOH and toluene cause a similar loss in performance in a dose-response manner and that the toluene effects can be expressed in equivalent EtOH units. This hypothesis is best evaluated while simultaneously controlling for the effects of practice of three sessions a day over three days and the sequence of dose. Thus the effects of exposure, day of exposure (learning), and sequence of exposure were evaluated for the am–pm difference scores and on the 1600 score alone with an analysis of variance for repeated measures within subjects (ANOVA).[23] The effect of solvents was similar for both dependent variables so that the increase in statistical power obtained by analysing the pm scores only does not alter the results. Also, the variation in control data across the three days was larger than the solvent effects; therefore, a within day difference score is the preferred dependent variable despite the added variation it introduces into the experiment.

Behaviour was considered to be significantly affected if an association was found at $p < 0{\cdot}05$ ($a = 0{\cdot}05$; $b = 0{\cdot}20$). The degrees of freedom were fixed for the effect of dose and day ($df = 2{\cdot}78$), and for trends ($df = 3{\cdot}39$). Significant differences between solvent concentrations were tested for consistency with a linear trend. Scheffe 95% confidence intervals identify the significant differences between scores at 0 and low, and 0 and high solvent concentrations. The probability of finding a statistically significant test score by chance is 1·6 out of the 31 performance scores ($31 \times 0{\cdot}05$). Therefore, the overall sensitivity of the test battery was only accepted if the number of affected variables exceeded the number attributable to chance.

Decrements in performance scores for each solvent were made comparable by expressing them as a % change from the mean am control performance scores. The am–pm difference scores for low and high solvent concentrations were subtracted from each subject's respective control am–pm different score. The corrected difference was then divided by the subject's mean am control score. The ratios were multiplied by 100 providing the mean % difference from a control score.

A parallel analysis examined the linear association between breath concentration of solvent at 1700 and the am–pm performance scores, the details of which are presented elsewhere.[13 14] The equations from this analysis were used in this study to express toluene decrements in EtOH equivalent units (g EtOH/kg body weight). Estimates of the mean loss in performance at 150 ppm toluene were based on each subject's regression equation. An ethanol equivalence for the mean toluene effect was determined by finding the same difference on the mean EtOH regression equation. Correlations between symptoms, mood, fatigue, age, sex, education level, and performance scores were checked for their influence on performance.

Estimates of statistical power for each performance measure were determined from the ratio of the observed difference over the standard deviation corrected for the degree of correlation.[24 25] The maximum difference $am\text{–}pm_{control}\text{–}am\text{–}pm_{high\ exposure}/am_{control}$ was divided by the largest standard deviation among the three am–pm scores. This ratio defines the detectable difference. The ratio and the degree of correlation for the three repeated measures were used to determine the statistical power.

Symptoms were tallied by solvent concentration and by day for headache, irritation, tiredness, and anxiousness or frustration. A dose-response relation is inferred for increasing marginal values. Subjects were also asked to rate their dose upon drinking by taste and later by effect into three categories of zero, low, or high.

Results

STUDY POPULATION

Small differences in age and education between the two study groups confirmed that the groups were homogenous (table 3). The population's vocabulary (84·8 (SD 9)% correct) and Mill Hill synonym test scores (84 (SD 9)% correct) were similar because most subjects achieved above 90% correct. The

Table 3 A comparison of the toluene and EtOH study populations

	Toluene	*EtOH*
Age (mean (SD))	22·6 (3·1)	21·9 (3·5)
Sex (% men)	54	50
Education:		
Graduate (%)	21·4	16·7
Undergraduate (%)	78·6	83·3
Vocabulary (No correct (SD))	87·72 (7·77)	84·76 (8·96)
Mill Hill synonym (No correct (SD))	87·18 (10·27)	83·97 (13·82)
% Correct guess of exposure or dose order:		
Exposure order	50	
Dose order by effect		78
Dose order by taste		5

Table 4 Control data for the mean of three am test sessions and the mean and the % difference am–pm within a control day (n=42 for each solvent group)

	$Mean_{am}$	SD_x	$SD_{w/n}$	$Mean_{am-pm}$	SD_x	$\left[\frac{X\,(am-pm)}{X_{am}}\right]\times 100$	CV_{am}	CV_{am-pm}
Sternberg test:								
Yes intercept								
Toluene	432·0	4·0	3·0	21·0	83·0	0·46	0·12	3·95
EtOH	390·0	58·0	61·0	2·0	96·0	5·38	0·14	47·52
Slope								
Toluene	51·0	20·0	21·0	5·0	25·0	3·92	0·39	5·0
EtOH	51·0	24·0	19·0	2·0	26·0	7·80	0·47	13·0
Digit span:								
Toluene	7·97	1·19	0·80	−0·45	0·76	5·66	0·15	1·69
EtOH	8·04	1·30	0·77	−0·52	0·71	6·46	0·16	1·36
Benton visual memory:								
Number correct								
Toluene	10·96	1·01	0·53			2·55	0·09	3·78
EtOH	10·75	1·16	0·86			3·44	0·11	3·96
Pattern memory:								
Number correct								
Toluene	12·51	1·03	1·22	−0·88	1·66	7·03	0·08	1·88
EtOH	12·41	1·42	1·17	−0·14	1·84	−1·12	0·11	13·14
Latency (s)								
Toluene	5·12	1·53	1·04	0·364	0·230	−7·10	0·29	0·63
EtOH	3·43	1·10	0·75	0·056	0·198	1·66	0·32	3·00
Pattern recognition:								
Number correct								
Toluene	14·64	0·35	0·49	0·24	0·74	1·63	0·02	3·08
EtOH	14·66	0·35	0·38	0·07	0·65	−0·48	0·02	9·28
Latency (s)								
Toluene	2·31	0·60	0·58	0·432	0·537	18·70	0·26	1·26
EtOH	2·07	0·51	0·57	0·386	0·473	18·69	0·25	1·21
Simple reaction time (ms):								
Right								
Toluene	331·0	35·0	24·0	−5·0	35·0	−1·5	0·11	7·0
EtOH	326·0	27·0	23·0	−23·0	33·0	−7·05	0·08	1·43
Cont performance (ms):								
Toluene	447·0	35·0	19·0	5·0	24·0	1·11	0·08	4·8
EtOH	431·0	27·0	14·0	8·0	33·0	1·8	0·06	4·1
Symbol digit:								
Number incorrect								
Toluene	0·42	0·48	0·59	−0·19	1·38	−6·3	1·14	7·6
EtOH	0·47	0·61	0·58	0·00	1·26	0·0	1·29	0·00
Latency (s)								
Toluene	16·36	1·77	2·57		2·26	3·33	0·11	4·11
EtOH	16·38	2·92	2·23		2·00	1·77	0·18	2·04
Hand-eye coordination:								
Toluene	4·58	1·22	0·95	0·05	1·03	1·02	0·27	21·91
EtOH	4·80	3·18	0·83	0·01	0·96	0·27	0·66	73·84
Finger tapping:								
Right hand								
Toluene	58·8	7·2	4·8	−1·1	7·4	−1·82	0·12	6·49
EtOH	62·3	7·9	4·7	−1·3	5·3	−0·06	0·12	4·07
Left hand								
Toluene	66·1	8·0	0·1	0·3	5·4	1·72	0·11	20·07
EtOH	68·6	8·9	3·5	−1·0	15·1	−1·57	0·13	15·1
Alternating								
Toluene	58·3	9·1	7·1	−3·4	11·6	−4·59	0·15	3·41
EtOH	56·3	9·0	7·0	−2·5	9·8	−4·4	0·16	3·92
Critical tracking:								
Toluene	0·392	0·070	0·049		0·105	3·00	0·17	3·18
EtOH	0·408	0·061	0·045	−0·002	0·056	0·49	0·15	28·00
One hole test:								
Pin number								
Toluene	39·02	4·61	3·30	−2·62	4·35	6·71	0·12	1·66
EtOH	43·10	4·26	3·42	−0·40	8·38	0·90	0·10	20·95
Grasp								
Toluene	164·0	57·0	113·0	25·0	49·0	4·5	0·34	1·96
EtOH	153·0	49·0	27·0	10·0	43·0	2·67	0·32	4·3
Move								
Toluene	510·0	59·0	46·0	33·0	36·0	2·15	0·11	1·09
EtOH	479·0	48·0	31·0	18·0	39·0	0·84	0·10	2·17
Position								
Toluene	382·0	71·0	79·0	−2·5	75·0	10·76	0·18	30·00
EtOH	350·0	69·0	68·0	26·0	135·0	2·17	0·20	5·19
Reach								
Toluene	355·0	86·0	29·0	27·0	51·0	2·35	0·24	1·88
EtOH	309·0	65·0	31·0	15·0	34·0	4·93	0·21	2·26

Table 4 Continued

	$Mean_{am}$	SD_x	$SD_{w/n}$	$Mean_{am-pm}$	SD_x	$\left[\frac{X\,(am-pm)}{X_{am}}\right] \times 100$	CV_{am}	CV_{am-pm}
Fatigue checklist:								
Toluene	11·2	4·4	3·2	1·7	12·80	15·00	0·39	7·52
EtOH	10·5	4·9	2·9	2·1	12·05	20·00	0·46	5·73
Mood:								
Tension								
Toluene	2·4	0·6	0·4	−0·005	1·80	0·20	0·25	36·00
EtOH	2·45	0·8	0·5	0·15	0·36	6·10	0·32	2·40
Depression								
Toluene	1·87	0·6	0·4	−0·033	0·86	1·80	0·32	26·10
EtOH	1·88	0·6	0·4	−0·033	0·44	1·80	0·32	13·33
Fatigue								
Toluene	1·7	0·5	0·4	−0·043	1·05	2·50	0·29	24·42
EtOH	1·8	0·6	0·3	0·09	0·29	5·00	0·33	3·22
Anger								
Toluene	2·8	0·7	0·5	0·21	0·93	7·50	0·25	4·43
EtOH	2·8	0·6	0·5	−0·009	0·54	0·30	0·21	60·00
Confusion								
Toluene	2·4	0·6	0·6	0·25	0·87	0·10	0·25	3·48
EtOH	2·6	1·0	0·8	0·09	0·87	0·03	0·38	9·66

average % correct for the two tests for the toluene group was 87·5%, slightly better than the 84·3% for the EtOH group. The 3·09% difference is not statistically significant. These scores are considerably higher than industrial populations scores, which are typically about 65% correct.[28] Subjects in both groups obeyed the restrictions, and had no difficulty using the computer.

BREATH DATA

Breath concentrations at 75 ppm and 150 ppm toluene in air averaged 7·65 (SD 3·37) ppm and 16·05 (SD 7·16) ppm respectively. Twenty minutes post-exposure, the average breath concentrations for both exposures dropped to 2·2 (SD 1·04) ppm and 4·05 (SD 1·57) ppm.

Ethanol breath concentrations were also a linear function of dose. At 0·33 g/kg body weight and 0·66 g EtOH/kg body weight, breath concentrations were 56·07 (SD 12·84) ppm and 118·10 (SD 36·38) ppm. Estimates of mean blood alcohol concentrations at 30 and 60 minutes after administration of 0·33 g EtOH/kg body weight were 0·030 (SD 0·006) mg% and 0·022 (SD 0·007) mg%. The blood alcohol concentrations at 30 and 60 minutes after administration of 0·66 g EtOH/kg body weight were 0·063 (SD 0·019) mg% and 0·054 (SD 0·015) mg%. As seen in table 2, peak blood alcohol concentrations occur about 40 minutes into the test session. Therefore, over half of the behavioural battery was administered on the ascending side on the blood alcohol curve. The test session was finished 75 minutes after consuming the dose corresponding to 0·015 (SD 0·0004) mg% and 0·039 (SD 0·012) mg% blood alcohol concentration.

COMPARISON OF VARIATION BETWEEN THE CONTROL DATA FOR THE SOLVENT GROUPS

The mean am control scores for the toluene and EtOH groups were similar for all behavioural tests (table 4). The mean within day difference scores varied between groups for pattern memory and pattern recognition, symbol-digit, critical tracking, and the pin number for the one hole test, which supported a separate analysis for the two solvent exposed populations.

The reduction in variation by repeatedly testing the same subject improved latency measures but not accuracy measures. The toluene and EtOH group averaged a 37 (SD 19)% net reduction in variation by eliminating the across subject component. The CPT test benefited the most with a 48% reduction in variation.

The degree of daily am–pm variation was generally below 8% of the mean am control score. Out of the 25 performance measures, only the latency of the pattern recognition test (18·7%) and the element "position" from the one hole test (10·7%) exceeded an 8% daily fluctuation in performance for both solvent groups.

The coefficients of variation for the within day am–pm difference scores had a substantial decrease in stability. Performance measures for which coefficients of variation exceeded 5·0 were too unstable and were not affected by either solvent.

COMPARISON BETWEEN TOLUENE AND EtOH BEHAVIOURAL RESULTS

Toluene and EtOH significantly affected performance on three tests in a dose-response manner—namely, digit span, pattern recognition, and the one hole test (upper left quadrant, table 5). Toluene but not EtOH significantly affected performance on pat-

tern memory (number correct) and symbol-digit substitution (number incorrect). The last was inconsistent with a dose-response. Performance improved at 75 ppm and was 22·4% worse at 150 ppm. Ethanol also significantly affected performance on pattern memory (latency), continuous performance, symbol-digit substitute, finger tapping (alternating), critical tracking, and a fatigue checklist. The remaining tests were unaffected by either solvent.

Figures 1–3 show estimates of the relative sensitivity for each solvent. For the toluene study, pattern memory (number correct) at 9·4% and pattern recognition (latency) at 12·0% had the largest % decrements. The remaining four tests were more consistent, with an average % decrement of 3·7 (SD 1·6)%. For EtOH, finger tapping (alternate) had the largest decrement (16·6%) and the remaining tests averaged 7·5 (SD 2·5)%.

Among tests affected by both solvents, the magnitude of the effect of 150 ppm toluene was expressed in equivalent EtOH units (g EtOH/kg body weight). For digit span the equivalent 6% loss in performance at 150 ppm toluene was 0·56g EtOH/kg body weight. For pattern recognition (latency) the equivalent 12% loss in performance for toluene and EtOH was statistically the same at 0·66g EtOH/kg body weight, as the apparent difference of 2·1% was not significant. Among the one hole measures, the element "move" was more sensitive than "pin number" with 5% and 3% losses in performance. Their respective equivalents were 0·40g EtOH/kg body weight and 0·37g EtOH/kg body weight.

STATISTICAL POWER OF THE BEHAVIOURAL TESTS

The statistical power of each behavioural measure was used to determine whether negative performance results were due to lack of a solvent effect or due to an inability to detect a difference (table 6). Test retest correlations were the same for the toluene and EtOH groups so that, for example, the differences in statistical power for CPT and critical tracking between the two separate studies were caused by either an increase in observed difference or an increase in standard deviation. Variables showing at least a 5% minimum detectable difference in performance were considered sensitive to the effects of solvents.

Among tests unaffected by toluene or EtOH the Benton visual memory test, the latency for symbol digit substitution, and the critical tracking task had sufficient statistical power to detect an effect and thus appear insensitive to low toluene exposures or EtOH doses. Table 6 shows that apart from these three exceptions the non-significant measures (lower right quadrant, table 5) were insensitive because they were either too stable, as seen with measures of accuracy (number correct); or were too variable, as found for hand-eye coordination and the one hole elements "grasp, position, and reach". For example, the

Table 5 Behavioural results for toluene and EtOH

EtOH	Toluene: Significant	Toluene: Non-significant
Significant	Digit span One hole: pin, move Pattern recognition: latency	Pattern memory: latency$_{nl}$ Continuous performance Symbol digit: latency Finger tap: alternating Critical tracking† Fatigue checklist
Non-significant	Pattern memory: No correct Symbol digit: No incorrect$_{nl}$†	Sternberg memory scan Benton visual memory† Pattern recognition: No correct Finger tapping: right, left Hand-eye coordination One hole test: grasp, position, reach Mood

*Significant when ANOVA and test for linear trend statistic had $p < 0.05$.
†Sufficient statistical power, therefore performance was unaffected by the specified solvent.

number correct for the Benton visual memory test, pattern memory, pattern recognition, symbol-digit, finger tapping (left and right), and mood scales did not vary much within or across days. Even with the increased statistical power afforded by just analysing the pm scores, the results were not improved. Generally, the number correct remained unaffected and this, therefore, may not be a sensitive solvent measure in homogenous populations exposed to low solvent concentrations.

Among tests affected by EtOH but not toluene (upper right quadrant, table 5) only critical tracking was truly unaffected as the remaining four tests lacked sufficient statistical power to detect a significant decrement. Table 6 shows that an increase in variability accounts for pattern memory (latency) and

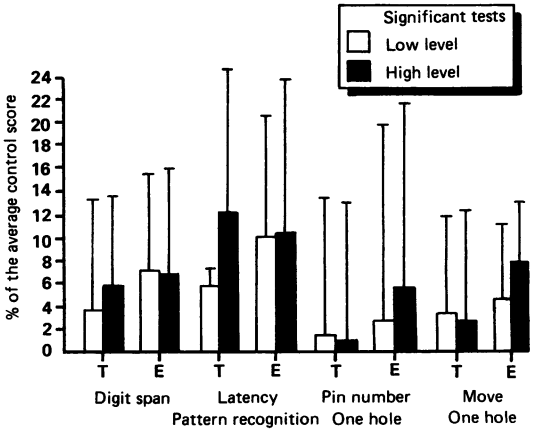

Figure 1 Significant tests for toluene and EtOH.

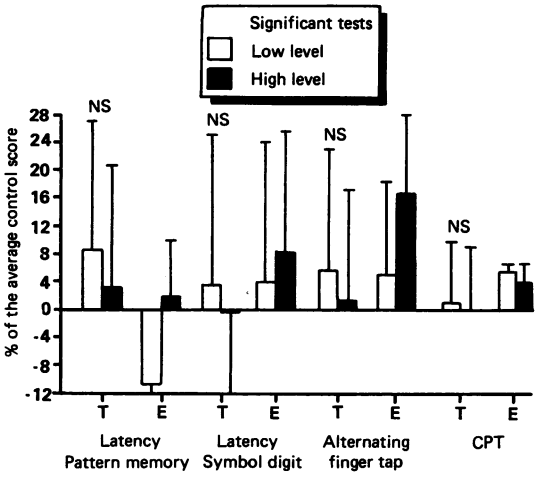

Figure 2 Comparison of tests where only EtOH affected performance (T = toluene; E = EtOH).

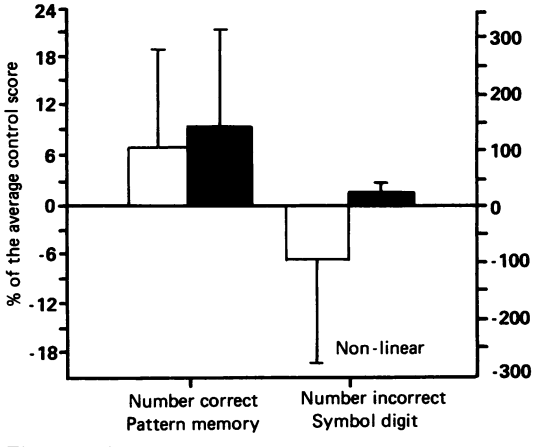

Figure 3 Significant tests for toluene but not EtOH.

a smaller observed difference accounts for CPT, symbol-digit (latency), and finger tapping (alternating).

The two tests significantly affected by toluene but not EtOH (lower left quadrant, table 5) were unaffected for different reasons. As seen in table 6, pattern memory (number correct) was too stable and symbol-digit (number incorrect) was too variable in the EtOH study. The positive toluene effect was not convincing as performance improved at 75 ppm and deteriorated at 150 ppm toluene.

A COMPARISON OF MOOD, FATIGUE, SYMPTOMS, AND MOTIVATION FOR TOLUENE AND EtOH

The POMS were not significantly affected by toluene or EtOH. The fatigue checklist was significantly affected by EtOH. At 0·33 and 0·66g EtOH/kg body weight fatigue scores increased from 4·98 (SD 31·0)% to 17·34 (SD 30·3)%. The correlation of the EtOH fatigue scores with other solvent affected measures was not sufficient to improve the ANOVA model.

Volunteered symptoms and complaints differed between toluene and EtOH (fig 4). Complaints of headaches and eye irritation increased in an exposure-effect manner among subjects exposed to toluene. Among subjects who consumed EtOH, an inverse relation existed between complaints of being tired and complaints of being frustrated. The more tired the EtOH group were, the less frustrated they became. The pattern for the toluene group was not as consistent. Complaints of being tired or frustrated did not conform to an exposure effect curve, but both varied in the same way suggesting that they might be measuring the same thing.

Consistent motivation in performance was partially controlled by masking the difference in odour of toluene and taste of EtOH between none, low, and high concentrations. In the toluene study, half of the subjects correctly guessed their order of exposure indicating only a partial success of the masking agent menthol. A comparison of performance between the two groups, however, showed no significant differences. In the EtOH study, subjects could not identify the dose by taste, but could identify it by effect at the end of the three day session.

Discussion

PERFORMANCE AFFECTED BY TOLUENE AND EtOH

The response time for pattern recognition was the most sensitive behavioural measure to exposure to either solvent, followed by digit span and the elements "move" and "pin number" from the manual dexterity one hole test. Within the control day the effect of practice on pattern recognition response time improved performance by 18%, which is more than for any other test. At the highest exposure or dose, toluene and EtOH reduced this improvement by 12% and 10·5% respectively. The solvent sensitivity of this measure is in part due to enough natural variability to detect a significant decrement using 42 subjects. On the other hand, the number correct was not affected by either solvent as few mistakes occurred. Its stability accounts for its insensitivity to either solvent at these low levels of exposure. In previous toluene and EtOH studies,[5 24-28] the number correct was also unaffected at 100 ppm toluene and at 0·73g EtOH/kg body weight.

Consistent with other study results, manual dexterity was affected by both solvents. The element "move" was more sensitive to both solvents than the summary measure "pin number" using the one hole test. Significant effects had also been found using its

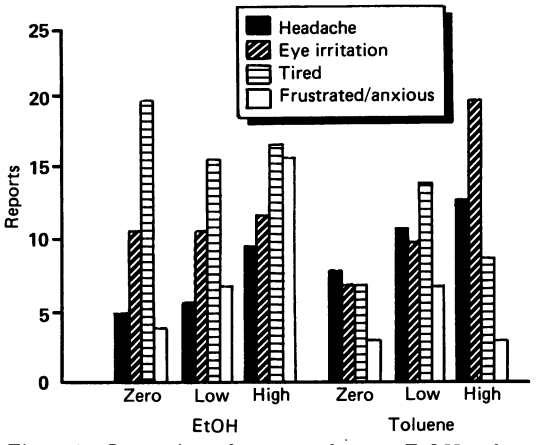

Figure 4 Comparison of symptoms between EtOH and toluene.

predecessor, the Purdue peg board test at 0·35 and 0·58g EtOH/kg body weight[29 30] and at 100 ppm toluene,[4] but the one hole test has not been previously used in acute behavioural studies. The other elements of the one hole test, "grasp," "position," and "reach," were too variable, accounting for their poor statistical power.

The 6% loss of performance on the digit span test was comparable in magnitude to the effect of the solvents on manual dexterity. This version of a digit span test also has not been used in previous acute solvent studies and the common WAIS digit span was unaffected at comparable concentrations of 0·55g EtOH/kg body weight.[11 31] It is likely that improved accuracy, by using a pre-test range finding sequence, and substantial reduction in variation may explain the increased sensitivity of this version of a digit span test as compared with the WAIS digit span. The digit

Table 6 Statistical power

		Detectable difference (Delta/sigma = ratio)	*% am–pm$_{max}$/ am control*	*No*
Sternberg test:				
Yes slope	T	3·0/27·0 = 0·11	5·6	295
	E	5·0/28·0 = 0·32	9·8	132
Digit span	T	0·44/0·67 = 0·65	5·8	37
	E	0·53/0·71 = 0·75	6·6	28
Benton visual memory:				
No correct	T	0·28	2·5	273
	E	0·37	3·4	206
Pattern memory:				
No correct	T	1·15/1·74 = 0·66	9·4	37
	E	0·19/1·84 = 0·10	1·0	352
Latency	T	0·430/1·11 = 0·39	5·1	78
	E	0·423/0·72 = 0·59	11·0	39
Pattern recognition:				
No correct	T	0·17/0·53 = 0·33	5·7	127
	E	0·03/0·64 = 0·05	9·9	1352
Latency	T	0·290/0·53 = 0·55	12·1	41
	E	0·212/0·45 = 0·47	9·2	39
Reaction time	T	8·0/45·0 = 0·18	2·0	521
	E	12·0/44·0 = 0·27	3·0	378
Continuous performance	T	3·0/25·0 = 0·12	0·8	1200
	E	18·0/25·0 = 0·73	4·2	42
Symbol digit:				
No correct	T	0·52/0·67 = 0·77	95·2	34
	E	0·30/1·11 = 0·27	145·2	194
Latency	T	0·640/2·2 = 0·29	0·2	823
	E	1·310/2·0 = 0·66	8·0	35
Hand eye coordination	T	0·194/0·74 = 0·26	4·2	219
	E	0·280/0·67 = 0·41	6·1	82
Finger tapping:				
Right	T	2·21/6·1 = 0·36	3·9	99
	E	2·39/5·3 = 0·45	3·5	67
Left	T	2·50/5·2 = 0·48	3·5	66
	E	0·42/6·2 = 0·06	1·0	135
Alternating	T	2·60/6·6 = 0·39	5·3	48
	E	8·26/8·4 = 0·98	16·5	13
Critical tracking	T	0·037/0·059 = 0·62	11·5	41
	E	0·035/0·059 = 0·59	9·5	39
One hole test:				
Pin No	T	2·5/2·74 = 0·91	6·5	25
	E	2·8/3·83 = 0·73	5·2	40
Move	T	39·0/71·0 = 0·54	4·2	39
	E	33·0/40·0 = 0·82	7·0	30

T = Toluene; E = EtOH.

span test provided sufficient statistical power to detect a half digit decrement using 42 subjects, which is reasonable as the loss of half a digit is equivalent to losses incurred over a 20 year lifespan.[32]

PERFORMANCE AFFECTED BY EtOH

Ethanol was more potent than toluene using the am–pm score as EtOH consumption significantly affected six other tests—namely, pattern memory $(latency)_{nl}$, CPT, symbol-digit (latency), finger tapping (alternating), critical tracking, and a fatigue checklist. The effect of EtOH on the CNS may actually differ from the effect of toluene only on the critical tracking task because it was the only test that truly remained unaffected by toluene despite sufficient statistical power to detect a decrement in performance. The remaining tests were probably not sensitive to low concentrations of toluene either, as even when increasing the statistical power to a sufficient level by analysing the pm scores alone over the three exposure days, no evidence of a toluene effect was found.

The tests affected by EtOH are consistent with results of other studies. Symbol-digit (latency), CPT, and finger tapping for the alternating button have also been affected by 20% nitrous oxide.[33] The CPT is a forced choice test with an attention component. Both forced choice tests and vigilance tests have been affected above 0·6g EtOH/kg body weight.[20] Finger tapping has also been affected at a higher dose of 1·1g EtOH/kg body weight.[12]

The pattern memory test was statistically significant but not in a solvent related manner as subjects improved at 0·33g EtOH/kg body weight and got slightly worse at 0·66g EtOH/kg body weight. The number correct was unaffected by EtOH. Insufficient statistical power accounted for the EtOH result in this study, but other experiments have also reported negative results at 0·3g EtOH/kg body weight,[34] 0·69g EtOH/kg body weight,[8] and 1·1g EtOH/kg body weight.[12] This strongly suggests that visual memory may not be sensitive to EtOH but it was not satisfactorily substantiated in this study.

PERFORMANCE AFFECTED BY TOLUENE

By comparison with the EtOH group, exposure to toluene did affect the number correct for the pattern memory test due to a larger observed difference, even though the standard deviations were the same for both groups. Latency was too variable to be statistically significant. The partial positive toluene result for the visual memory test is the only one in publications concerning toluene. Two other acute toluene experiments reported no effects for a more complex memory reproduction test using fewer subjects at lower exposures (12 and 16 subjects at 80 ppm).[8 35] It is not known whether these negative results were due to a lack of statistical power or whether toluene would have affected this test at higher exposures.

The symbol-digit substitution test (number incorrect) was not convincingly affected by acute exposure to toluene as experimental error probably accounts for improvement at 75 ppm and a small decrement at 150 ppm toluene. The number incorrect has been reported to be affected in epidemiological studies, however, examining chronic effects of toluene and paint solvents.[36–38]

PERFORMANCE UNAFFECTED BY EITHER SOLVENT

The Sternberg memory scanning test, pattern recognition (number correct), finger tapping (right, left), hand-eye coordination, the one hole test (grasp, position, reach), and mood were unaffected by either solvent due to poor stability and limited statistical power. The Benton visual memory test (number correct) was also unaffected although it had sufficient statistical power to detect a 6% difference in performance for either solvent. This test showed a ceiling effect for both solvent groups as the average number correct was 91 (SD 5)%. Some of the insensitivity of the test battery may be due to the experimental population, which has shown ceiling effects for most measures of accuracy (the number correct or incorrect). The profile of behavioural deficits may change for an industrial population. With increased use of these tests in the future, better calibration of the test battery for select populations may be possible.

Given the use of 42 subjects and the strength of this study design, the insensitivity to solvents and poor stability shown by some performance variables support the need for a renewed effort to re-examine test measures. The enhancement of some of these measures may not be as productive as selecting other measures that are sensitive under the time and learning constraints found in industrial field studies. Such measures, for example, could be based upon more useful laboratory paradigms such as well defined information processing measures used in a dual task approach,[39] or, alternatively, the ability to switch between tasks.[40] These measures may potentially better explain detectable decrements in performance using fewer subjects. This point is particularly important as the NES battery has not been validated by determining test profiles for clinically defined populations. Therefore, selecting behavioural measures based on other sound psychological theory is an appropriate alternative approach.

THE PATTERN OF BEHAVIOURAL RESULTS

The most striking pattern characterising the behavioural results is that the treatment effect for both solvents is smaller than the variation across subjects about the mean. Further, the exposure effect is comparable with the within day am–pm control

difference. Using the pm scores alone would have overcome the problem of limited statistical power introduced by using the am–pm difference score. The am–pm within day scores, however, were of equal or even greater magnitude as the variation across days for the control scores, which is one reason for using the within day difference score as the preferred dependent variable. A non-statistical consideration was that a difference score more accurately represents changes in performance over an eight hour workday. Further, using each subject as his or her own control also eliminated an average of one third of the variation found across subjects. These factors contributed to detecting significant toluene effects despite substantial decreases in stability and consequent statistical power, as noted by the coefficients of variation for the within day differences in am–pm.

Toluene and EtOH effects only differ in magnitude, as they affect the test battery qualitatively in the same way. The ability to determine a difference between EtOH and toluene toxicity on the CNS was only possible for the critical tracking task, but EtOH did affect a greater range of psychomotor tests indicating greater potency. Other differences between the solvents may yet be found since some important functions have not been tested. For example, using a dual task paradigm,[39] switching between tasks,[40] or more complex reasoning skills[26] may prove to be even more sensitive measures.

Both solvents have significant but small acute behavioural effects. A range of 2 to 7% decrements suggest the ACGIH TLV of 100 ppm toluene may be a good estimate of the biological threshold of detectable behavioural effects. The EtOH equivalents at 150 ppm toluene for digit span (0·56g EtOH/kg body weight), the latency for pattern recognition (0·66g EtOH/kg body weight), and the one hole element "move" (0·37g EtOH/kg body weight) show that the first two measures are affected at or above 50 mg% blood alcohol concentration. This concentration is recognised as the lowest associated with increased numbers of automobile accidents.[41] As yet the association between industrial solvents and increased risk of safety has not been investigated. Future research may establish if exposure to toluene at 150 ppm increases the accident rates in industry.

We gratefully acknowledge the National Institute for Occupational Safety and Health (contract No OH02071–02) for making this research possible.

Requests for reprints to: Diana Echeverria, Battelle Seattle Research Center, 4000 NE 41st Street, Seattle, WA, 98105, USA.

1 Anger WK. Neurobehavioral testing of chemicals: impact on recommended standards. *Neurobehavioural Toxicology and Teratology* 1984;6:147–53.
2 Otto DA, Eckerman D, eds. Workshop on neurotoxicity testing in human populations. *Neurobehavioural Toxicology and Teratology* 1985;7:283–418.
3 Gamberale F. The use of behavioral performance tests in the assessment of solvent toxicity. *Scand J Work Environ Health* 1985;11suppl 1:65–74.
4 Anderson I. In: Cherry N, Waldron HA, eds. *The neuropsychological effects of solvent exposure, exposure chamber studies, Chapter 10. The proceedings of a symposium held at the London School of Hygiene and Tropical Medicine*, 5–6 April 1982.
5 Anderson I, Lundqvist GR, Molhave L, *et al.* Human response to controlled levels of toluene in six-hour exposures. *Scand J Work Environ Health* 1983;9:405–18.
6 Gamberale F, Hultengren M. Toluene exposure II. Psychological functions. *Work Environment Health* 1972;9:31–9.
7 Winneke G. The behavioral effects of exposure to some organic solvents: Psychological aspects. In: Junten J, ed. *Occupational neurology. Acta Neurol Scand* 1982;66suppl 92:117–29.
8 Iregren A, Akerstedt T, Olson BA, Gamberale F. Experimental exposures to toluene in combination with ethanol intake. *Scand J Work Environ Health* 1986;12:128–36.
9 Dionisi A. Effitti dell 'assunzione di piccole dosi di alcool sulla attivita di volo. *Minerva Med* 1981;72:2571–86. (Abstract in English.)
10 Klein RH, Jex HR. Effects of alcohol on a critical tracking task. *J Stud Alcohol* 1975;36:11–20.
11 Baker SJ, Charzan GJ, Park CN, Saunders JH. Behavioral effects of 0 and 0·05% blood alcohol in male volunteers. *Neurotoxicol Teratol* 1986;7:77–81.
12 Wilson JR, Erwin GV, McClearn GE, *et al.* Effects of Ethanol: II. Behavioral sensitivity and acute behavioral tolerance. *Alcoholism: Clinical and Experimental Research* 1984;8: 366–74.
13 Echeverria D, Fine L, Langolf G, Schork A, Sampaio C. Acute neuro-behavioral effects of toluene. *Br J Ind Med* 1989;46: 483–95.
14 Echeverria D, Fine L, Langolf G, Schork A, Sampaio C. The validity of a behavioral battery at 0, 33mg%, and 66mg% blood alcohol concentrations. *Ergonomics and Safety II*, 1990: 835–72.
15 Jones AW. Variation of the blood: breath alcohol ratios in vivo. *J Stud Alcohol* 1978;39:1931–9.
16 Maizlish NA, Langolf G, Whitehead LW, *et al.* Behavioral evaluation of workers exposed to mixtures of organic solvents. *Br J Ind Med* 1985;42:579–90.
17 Baker EL, Letz RE, Fidler AT. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: rationale, methodology, and pilot study results. *J Occup Med* 1985;27:206–12.
18 Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura DL, Lyndon ML. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: methodology and validation studies. *Neurobehavioural Toxicology* 1985;7:369–77.
19 Smith PJ, Langolf GD, Goldberg J. Effects of occupational exposure to mercury on short-term memory. *Br J Ind Med* 1983;40:413–9.
20 Jex HR, McDonnell JD, Phatak AV. A "critical" tracking task for manual control research. *IEEE Transactions on Human Factors in Electronics* 1966;7:138–45.
21 Salvendy G. Selection of industrial operators: the one-hole test. *International Journal of Production Research* 1975;13:303–21.
22 Pearson RG, Byars GE. *The development and validation of a checklist for measuring subjective fatigue.* Randolf Field, Texas: School of Aviation Medicine, 1956. (USAF Report No. 56–115.)
23 Winer RJ. *Statistical Principles in Experimental Design.* 2nd ed. New York: McGraw-Hill Book Company, 1962. (Chapter 6.)
24 Vonesh EF, Schork AM. Sample sizes in the multivariate analysis of repeated measurements. *Biometrics* 1986;42: 601–10.
25 Vonesh EF, Schork AM. *Sample sizes in the multivariate analysis of repeated measurements.* October, 1983. (Biostatistics technical report No 28.)
26 Sidell FR, Pliss JE. Ethyl alcohol: blood levels and performance decrements after oral administration to man. *Psychopharmacologia (Berlin)* 1971;19:246–61.
27 Stewart RD, Hake CL, Wu A, *et al. Effects of perchloroethylene/ drug interaction on behavior and neurological function.* Washington, DC: Dept of Health Education and Welfare, 1977 (DHEW (NIOSH) publ No 77–191).
28 Dick RB, Setzer JV, Wait R, *et al.* Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. *Int Arch Occup Environ Health* 1984;54:91–109.

29 Fergussen RC, Vernon RJ. Trichloroethylene in combination with CNS drugs. *Arch Environ Health* 1970;20:462–7.
30 Lindenschmidt R, Brown D, Cerimele B, Walle T, Forney RB. Combined effects of propranolol and ethanol on human psychomotor performance. *Toxicol Appl Pharmacol* 1983; 67:117–21.
31 Baker SJ, Charzan GJ, Park CN, Saunders JH. Validation of human behavioral tests using ethanol as a CNS depressant model. *Neurobehavioural Toxicology and Teratology* 1985;7: 257–61.
32 Schumacher JM. *The effects of aging in four behavioral tests.* Ann Arbor, Michigan: University of Michigan, July, 1981. (Unpublished Master's thesis.)
33 Greenberg BD, Moore PA, Letz R, Baker EL. Experimental nitrous oxide exposure as a model system for evaluating neurobehavioral tests. *Clinical Pharmacol Ther* 1985;38: 656–60.
34 Cherry N, Johnston JD, Venables H, Waldron HA. The effects of toluene and alcohol on psychomotor performance. *Ergonomics* 1983;26:1081–7.
35 Olson AB, Gamberale F, Iregren A. Coexposure to toluene and p-xylene in man: central nervous functions. *Br J Ind Med* 1985;42:117–22.
36 Lindstrom K. Psychological performances of workers exposed to various solvents. *Scand J Work Environ Health* 1978;4:19–45.
37 Elofsson SA, Gamberale F, Hindmarsh A, *et al.* Exposure to organic solvents: a cross-sectional epidemiological investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. *Scand J Work Environ Health* 1980;6:239–73.
38 Iregren A. Effects on psychological test performance of workers exposed to a single solvent (toluene): a comparison with effects of exposure to a mixture of organic solvents. *Neurobehavioural Toxicology and Teratology* 1982;4:695–701.
39 Kantowitz BH. Stages and channels in human information processing: A limited analysis of theory and methodology. *Journal of Mathematical Psychology* 1985;29:135–74.
40 Maylor EA, Rabbitt PMA, James GH, Kerr SA. Effects of alcohol and extended practice on divided-attention performance. *Perception & Psychophysics* 1990;48:445–52.
41 American Medical Association. *Alcohol and the impaired driver—a manual on the medicological aspects of chemical tests for intoxication.* Chicago, Il: Committee on Medicological Problems, 1968:27–59.

Accepted 18 March 1991

Correspondence and editorials

The *British Journal of Industrial Medicine* welcomes correspondence relating to any of the material appearing in the journal. Results from preliminary or small scale studies may also be published in the correspondence column if this seems appropriate. Letters should be not more than 500 words in length and contain a minimum of references. Table and figures should be kept to an absolute minimum. Letters are accepted on the understanding that they may be subject to editorial revision and shortening.

The journal now also publishes editorials which are normally specially commissioned. The Editor welcomes suggestions regarding suitable topics; those wishing to submit an editorial, however, should do so only after discussion with the Editor.