British Journal of Industrial Medicine 1990;47:480–484

Chronic neurobehavioural effects of toluene

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Abstract

Neurobehavioural tests were undertaken by 30 female workers exposed to toluene and matched controls with low occupational exposure to toluene. The environmental air levels (TWA) of toluene was 88 ppm for the exposed workers and 13 ppm for the controls. The toluene in blood concentrations for the exposed workers was 1·25 mg/l and for the controls 0·16 mg/l. Statistically significant differences between workers exposed to toluene and controls in neurobehavioural tests measuring manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory (digit span) were observed. Further, the performance at each of these tests was related to time weighted average exposure concentrations of air toluene. The workers exposed to toluene had no clinical symptoms or signs. The question arises as to whether these impairments in neurobehavioural tests are reversible or whether they could be a forerunner of more severe damage.

Exposure to toluene may damage the central nervous system (CNS). Cerebral and cerebellar atrophy[1–3] have been well documented in solvent abusers exposed to high levels of toluene. In the occupational setting levels of exposure are generally lower and clinical neurobehavioural deficits are often absent[4–6]; this is so even among workers with reported serious impairment in neurobehavioural performance tests.[7] Epidemiological studies on neurobehavioural performance among workers exposed to toluene have been inconsistent,[8–11] partly because industrial solvents are often mixtures and the interaction of the various components of the solvents probably influences the outcome. Further, social habits, such as alcohol consumption, cigarette smoking, taking of drugs, and concentrations and duration of exposure[12] may confound the picture.

One limitation of previous cross sectional studies to assess the neurotoxic effects of solvents has been that they often lack both environmental and biological levels for solvents exposed.[12]

The present study was undertaken to assess the neurobehavioural performance of a group of female assembly workers exposed to a single solvent—toluene. The environmental and biological monitoring of toluene was also examined in the study.

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Material and methods

STUDY POPULATION

A cross sectional study on 30 female workers exposed to toluene was undertaken. They were engaged in electronic assembly work and the toluene was emitted from the resinous glue used to cement component parts. The workroom was equipped with a total recirculation air conditioning system. The factory operated a single shift from Monday to Friday.

A control group of 30 workers matched for age, sex, and ethnicity was selected from a different section of the factory in which toluene containing glue was not used. It was subsequently found that these controls were exposed to low levels of toluene because of cross contamination of work areas.

All the workers (exposed and control) were teetotallers, non-smokers, and were not taking any regular medication, nor did they take any medication on the day they were tested for their neurobehavioural performance. Medical assessments were undertaken to rule out conditions such as a history of central or peripheral nervous system illness or psychiatric disorders that might affect neurobehavioural performance not related to the exposure to toluene. Neurobehavioural tests were conducted on Wednesdays and Thursdays from 0900 to 1100 in the department of community, occupational, and family medicine before the workers reported for work.

EXPOSURE TO TOLUENE

Exposure to toluene of the two groups was monitored with diffusive personal sampling tubes packed with tenax GC (DCA™, Dosimeter Corp, USA). The workers studied were exposed to relatively steady concentrations of toluene during the workshift. Finger prick blood was used to estimate the blood toluene concentrations. Details of the environmental and biological monitoring of toluene exposure have been described previously.[13]

NEUROBEHAVIOURAL TEST BATTERY

The neurobehavioural assessment of workers exposed to toluene and controls was conducted with a battery of eight tests.

Benton visual retention test (BVRT)—The test consists of 10 drawings with geometric figures. Each drawing is shown for 10 seconds and the subject must reproduce it immediately after its removal. Both the number of errors (more than one error can be made for each item) and the number of entirely correct reproductions are scored. A higher correct score means a better performance.

Visual reproduction (VR)—The test consists of three pictures, each shown for 10 seconds. The subject must draw it immediately after its removal. Scoring is done according to Wechsler's method.[14] Perfect score is 14 points. The higher the score the better the performance.

Trail making tests (TMT)—The subject has to join 25 circles with a pencil. In the first part of the test the circles contain the numbers from 1 to 25 and the circles must be joined in the correct numerical sequence. In the second part 13 numbers (1–13) and 12 letters (A-L) are shown in the circles and the subject has to join alternate numbers and letters (1-A-2-B-). The time taken to complete each series is recorded.

Grooved peg board (GPB)—Apparatus supplied by Lafayette Instrument Company was used. The 25 key shaped pegs must be placed into holes with the flange of the key arranged in random order. The time to complete the task is measured with the subject using first the preferred and then the non-preferred hand. The time for completion is scored.

Digit span (DSp)—In the digit forward sequence test the examiner reads aloud number sequences that increase from three to nine digits and the subject must repeat each sequence exactly as he hears it. The digit backward sequence runs from two to eight digits and must be repeated in the reverse order. The score is the total number of digits in the longest correctly repeated sequences for the two sections.

Digit symbol (DSy)—Each special symbol is given a digit from one to nine shown on the top of the test sheet. In the written test the subject has to write the correct digits under the symbols given in random order as quickly as possible. The score is based on performance in 90 seconds. In the oral test the subject reads out the digits for the symbols given in the test. Thus the recorded score is positively correlated with performance.

Finger tapping (FT)—An instrument supplied by the Lafayette Instrument was used. The subject has to tap as quickly as possible with the index finger for 10 seconds. The performance is represented by the average number of taps scored in five trials.

Simple reaction time (SRT)—The test measured the mean reaction time of 16 responses to signals presented at random intervals of one to 10 seconds. The subject watches a panel with a blue, a yellow, and a red lamp and presses the corresponding buttons with their hands and right leg. When one of the lamps is lit the subject releases the corresponding button. The time between the lighting of the lamp and release of the button is measured and an error is recorded if the wrong button is released. Two scores are recorded, one for the reaction time and one for the number of errors made.

STATISTICAL ANALYSIS

Differences between the exposed workers and controls were tested with the Student's t test. The relation between neurobehavioural performance score and exposure levels was examined by analysis of covariance adjusting for years of education and years of exposure. Statistical analysis was run with software package by SAS Inc. PROC TTEST and PROC GLM were used.

Results

Table 1 indicates that workers exposed to toluene and their controls were well matched for ethnicity and age. Whereas the educational levels in both groups were under 12 years of education, the exposed group had a lower education level. In view of this, the analysis of the data for the neurobehavioural tests were statistically adjusted for years of education using the generalised linear model.

Table 2 shows the toluene concentrations in blood and the eight hour time weighted average (TWA) breathing zone toluene in air concentrations for the exposed workers and their controls respectively. The controls were also exposed to toluene but at much lower concentrations than the exposed workers, possibly due to cross contamination in the workplace. A linear correlation between the postshift toluene

Table 1 Characteristics of workers exposed to toluene and 30 controls (SD in parentheses)

	Ethnic group					
	C	*M*	*I*	*Mean age (y)*	*Years worked*	*Mean years of education*
Exposed	11	7	12	25·6 (5·64)	5·7 (3·2)	5·9 (2·8)
Controls	11	7	12	25·1 (6·15)	2·5 (2·7)	8·0 (2·5)

C = Chinese.
M = Malay.
I = Indian.

Table 2 Blood toluene concentrations of exposed workers, controls, and TWA toluene in air

	Toluene in blood (mg/l)	*TWA toluene in air (ppm)*
Exposed (30)	1·25 ± 0·37	88 ± 3·0
Controls (30)	0·16 ± 0·06	13 ± 4·0

Toluene in blood was linearly correlated to the TWA toluene concentration in air. The regression equation is Y = 0·086 + 0·013X and R = 0·90.

concentrations in blood and TWA exposure was observed.[13]

Table 3 shows the results of a battery of neurobehavioural tests undergone by the workers exposed to toluene and their controls. The difference in the simple reaction time and finger tapping scores between exposed workers and controls were not statistically significant. The rest of the neurobehavioural tests showed that the test performance results were poorer among the workers exposed to toluene and the differences of test scores between the exposed workers and their controls were statistically significant.

A dose-effect relation was noted in six of the eight neurobehavioural performance tests: digit span, digit symbol, visual reproduction, Benton visual retention, grooved peg board, and trail making tests. The duration of exposure, however, was not statistically significant. Figure 1 illustrates the change in the digit span total score with the TWA toluene exposure level. Digit span score decreases with the increase of air toluene concentrations. The trail making test scores (part A), on the other hand, increase with the increase of air toluene exposure levels (fig 2). With the exception of simple reaction time and finger tapping tests, similar dose effect trends were observed in the other neurobehavioural test scores (fig 3–6).

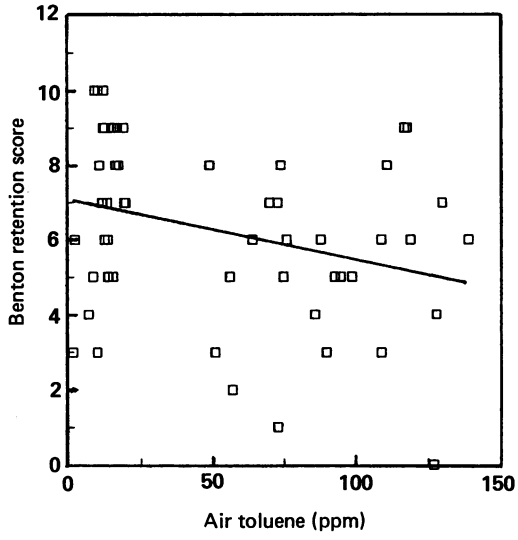

Figure 1 Relation between Benton visual retention scores and eight hour TWA personal toluene exposure concentrations.
Y = 7·11 − 0·0164X, R = −0·31, p = 0·03.

Discussion

Our study was conducted on workers who were teetotallers and non-smokers. They were not habitual drug takers. Statistically significant differences in neurobehavioural performance tests

Table 3 Effects of toluene on neurobehavioural performance

	T test (mean)			*Analysis† of covariance*
Type of test	*Exposed*	*Control*	*p*	*p*
Brenton retention	5·4	7·1	0·003	0·01
Visual reproduction	5·8	8·3	0·0004	0·02
Trail making:				
Part A	55·0	33·8	0·0008	0·003
Part B	157·0	104·0	0·009	0·007
Grooved pegboard:				
Dominant hand	65·6	57·1	0·0002	0·002
Non-dominant hand	72·0	64·7	0·002	0·03
Digit span:				
Forward	5·8	6·8	0·02	0·005
Backward	4·1	5·0	0·006	0·002
Total	9·9	11·8	0·007	0·002
Digit symbol:				
Written	34·9	45·9	0·0008	0·002
Oral	38·2	50·6	0·0004	0·0003
Finger tapping:				
Dominant hand	43·2	45·1	NS*	NS
Non-dominant hand	40·1	42·0	NS	NS
Simple reaction time:				
Total	79·0	74·7	NS	NS
Error	2·2	1·4	NS	NS

*Probability > 0·05.
†Statistically adjusted for years of education and years of exposure.

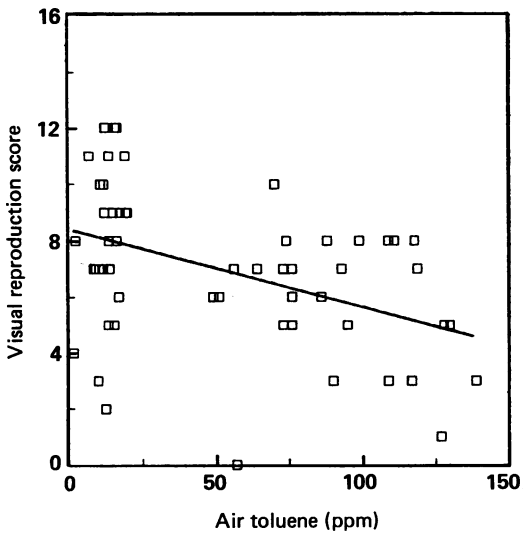

Figure 2 Relation between visual reproduction scores and eight hour TWA personal toluene exposure concentrations. $Y = 8{\cdot}58 - 0{\cdot}0291X, R = -0{\cdot}44, p = 0{\cdot}007$.

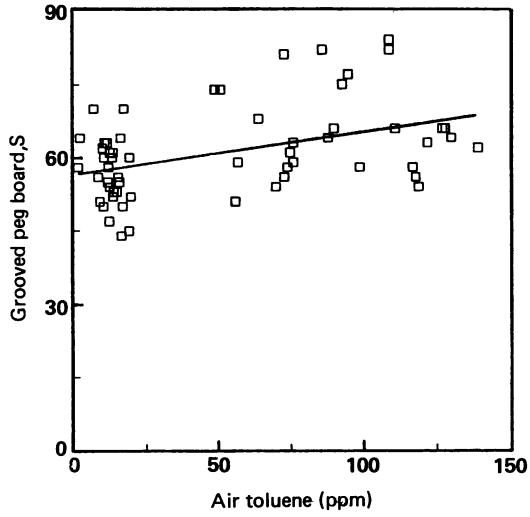

Figure 4 Relation between grooved peg board (dominant hand) scores and eight hour TWA personal toluene exposure concentrations. $Y = 56{\cdot}8 + 0{\cdot}0851X, R = 0{\cdot}41, p = 0{\cdot}009$.

were detected between the workers exposed to toluene and their controls. Motor speed (simple reaction time and finger tapping tests) was not affected by exposure to toluene. Manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory (digit span) were affected and a dose effect relation was observed between TWA exposure levels of toluene and performance.

Earlier studies found little or no neurological performance deficits in workers exposed to toluene. Among the 11 tests Iregren detected only one test, the simple reaction time (speed) ($p < 0{\cdot}001$), in workers exposed to toluene was significantly lower than their controls.[8] Differences in synonyms, block design, figure classification, digit symbol, identical numbers, mental arithmetic, memory (reproduction), hand dexterity, finger dexterity, and simple reaction time (decrement) test were not significant.

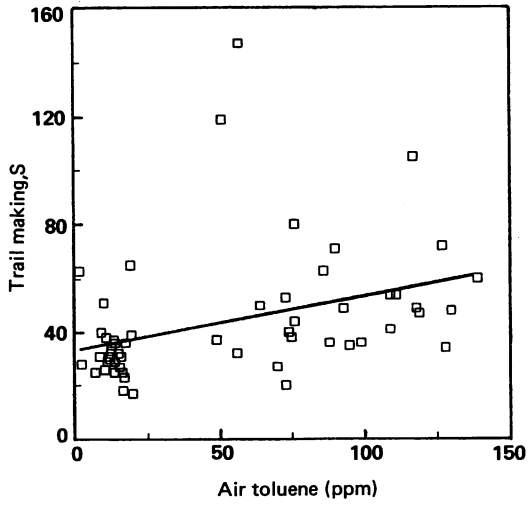

Figure 3 Relation between trail making (part A) scores and eight hour TWA personal toluene exposure concentrations. $Y = 34{\cdot}0 + 0{\cdot}199X, R = 0{\cdot}36, p = 0{\cdot}02$.

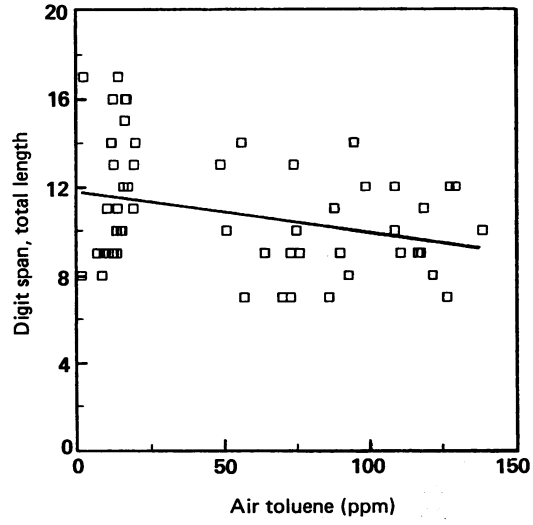

Figure 5 Relation between digit span (total) scores and eight hour TWA personal toluene exposure concentrations. $Y = 11{\cdot}8 - 0{\cdot}0184X, R = -0{\cdot}30, p = 0{\cdot}005$.

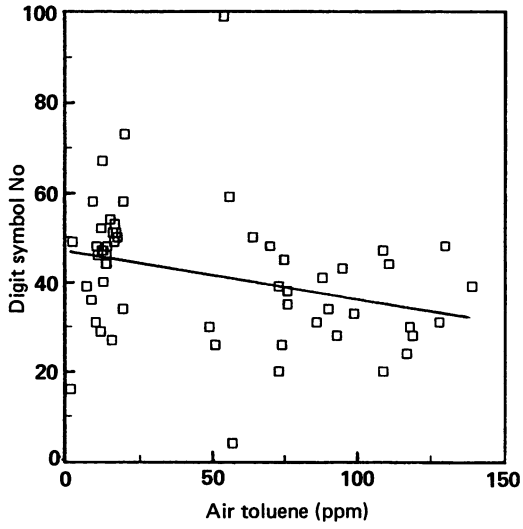

Figure 6 Relation between digit symbol (written) scores and eight hour TWA personal toluene exposure concentrations.
$Y = 46{\cdot}0 - 0{\cdot}109X, R = -0{\cdot}36, p = 0{\cdot}003$.

Cherry *et al* did not detect any statistically significant differences in neurobehavioural performance between workers exposed to toluene and their controls, even though the workers generally performed less well.[10] The tests used were dotting, trail making, visual search, digit symbol, block design, grooved peg board, simple reaction time, and memory and reading test.

Hanninen *et al* reported poorer performance of visual cognitive abilities ($p < 0{\cdot}01$) (embedded figures and block design) in rotogravure printers, after adjusting for variation in alcohol consumption.[11] Other neurobehavioural tests performed were synonyms, similarities, digit span, associative learning, block design, embedded figures, Benton visual retention, digit symbol, Santa-Ana, Flanagan coordination, and the Mira test.

Our results agree with those of a recent laboratory experimental study on the acute neurobehavioural effects of toluene. Paid healthy college students were exposed to three levels (0, 75, and 150 ppm) of toluene. Differences in digit span, symbol digit, one hole test, pattern memory, and pattern recognition scores were statistically significant between the test subjects and controls, whereas differences in simple reaction time and finger tapping were not.[15]

The duration of exposure was not significantly related to the performance in neurobehavioural tests. Earlier studies had indicated that neurobehavioural performance was less affected by the duration of exposure to toluene compared with current exposure concentrations.[4 8 10] In a comprehensive clinical study on a group of toluene abusers who showed clear cerebellar, cortical, and neuropsychological dysfunction, Fornazzari *et al* also found that the impairments were not well correlated with the duration of abuse.[16]

Conclusion

This study showed that the manual dexterity, verbal memory, and visual cognitive ability of the workers were affected by their exposure to toluene ranging from 49 to 130 ppm TWA. The question arises as to whether these impairments are reversible or a forerunner to more severe damage.

We thank Ms Nelly Chan, Mr George Chia, and Mr N Y Khoo for their technical help, Ms Norhayati Othman for typing this manuscript, and the National University of Singapore for financial support in the form of research grant, RB367/86.

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Accepted 4 December 1989