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Neurological and cognitive abnormalities associated with chronic petrol sniffing

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Summary

Substance abuse through the deliberate inhalation of petrol (petrol sniffing or gasoline sniffing) is prevalent in inner-urban and remote rural communities. Although acute toxic encephalopathy is a well-documented consequence of petrol sniffing, the neurological and cognitive effects of chronic petrol sniffing are unknown. A structured neurological examination and the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used to assess neurological and cognitive function in 33 current-sniffers (individuals who had sniffed petrol for >6 months), 30 ex-sniffers (individuals who had sniffed petrol in the past but had abstained for 6 months) and 34 matched non-sniffers (individuals who had never sniffed petrol). No subject was, or had been, encephalopathic from petrol sniffing and all were residing in their community. Blood lead and hydrocarbon levels and information about petrol sniffing behaviour were obtained from each subject. When compared with non-sniffers, current-sniffers showed higher rates of abnormal tandem gait, rapid alternating hand movements, finger to nose movements, postural tremor, bilateral palmomental reflexes and brisk deep reflexes. Cognitive deficits occurred in the areas of visual attention, visual recognition memory and visual paired associate learning. Ex-petrol sniffers showed higher rates of abnormal tandem gait and bilateral palmomental reflexes and cognitive deficits in the areas of visual recognition memory and pattern–location paired associate learning. Blood lead levels and length of time of petrol sniffing correlated significantly with the magnitude of neurological and cognitive deficits. Blood hydrocarbon levels were not related to neurocognitive deficits, although this may have been due to methodological difficulties in obtaining hydrocarbon levels. These results suggest that subtle neurological and cognitive abnormalities do occur in individuals who abuse petrol but who do not have acute toxic encephalopathy and that the severity of these abnormalities is reduced with abstinence.

Keywords: petrol; gasoline; sniffing; neurology; cognition

Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

Introduction

Substance abuse through the deliberate inhalation of petrol (petrol/gasoline sniffing) often occurs in inner-urban or remote rural communities (Sharp and Rosenburg, 1994; Tenenbein, 1997) and is also a relatively common practice among a number of tribal indigenous groups including Native Americans, Canadian Indians and Australian Aborigines (Keenlyside, 1984; Brady, 1992; Burns *et al*., 1995*a*). The acute effects of petrol sniffing occur rapidly (3–5 min) and can last for 5–6 h (Nurcombe *et al*., 1970; Poklis and Burkitt, 1977). These may include euphoria and relaxation, ataxia, diplopia and slurred speech. Intoxication may also be associated with visual hallucinations or distortions, psychosis or brief loss of consciousness (Poklis and Burkitt, 1977; Brust, 1993). More severe encephalopathy is also documented following extensive exposure to petrol with abnormalities including tremor, myoclonus, chorea, limb and gait ataxia, pyramidal signs, motor impairment, nystagmus seizures and coma (Seshia *et al*., 1978; Valpey *et al*., 1978; Goldings and Stewart, 1982; Edminster and Bayer, 1985; Brust, 1993; Goodheart and Dunne, 1994). CT or MRI of the brain in these patients may show abnormalities in the cerebellum, basal ganglia or brainstem (Kaelen *et al*., 1986; Roger *et al*., 1990). Petrol sniffers with acute toxic encephalopathy may also show significant deterioration of cognitive function

particularly in the areas of psychomotor control, attention, memory and learning (Boeckx *et al*., 1977; Robinson, 1978; Valpey *et al*., 1978; Goldings and Stewart, 1982).

In contrast to the acute effects, there is relatively little direct information about the long-term neurological and cognitive effects of chronic, recreational petrol sniffing among non-encephalopathic subjects who are still residing in their communities. In one study it was reported that there were increased rates of neurological signs in individuals who were referred to an out-patient clinic because of their chronic petrol sniffing but who were not encephalopathic (Seshia *et al*., 1978). In other community studies, poor school attendance and learning difficulties, low rates of employment and increased rates of crime and delinquency among petrol sniffers have been observed (Nurcombe *et al*., 1970; Kaufman, 1973; Eastwell, 1979; Coulehan *et al*., 1983; Brady, 1992; Burns *et al*., 1996). Taken together, these studies do provide some indirect evidence to suggest that there is neurological and cognitive impairment in petrol sniffers who are not encephalopathic. Therefore, the aims of this study were to investigate neurological and cognitive function in non-encephalopathic petrol sniffers who were residing in their community, and to examine the relationships between neurological and cognitive performance and measures of petrol sniffing behaviour. In addition, although it is generally stated that the acute cognitive and neurological deficits associated with volatile substance abuse are reversible with abstinence (Fortenberry, 1985; Brust, 1993; Sharp and Rosenburg, 1994) it is not known whether such reversibility also occurs in chronic petrol sniffers who have abstained. Therefore, in this study, we also sought to examine neurological and cognitive function in a group of individuals who had abused petrol chronically but who had been abstinent for $>$6 months.

Methods

Subjects

The study was carried out in two remote Aboriginal communities in Arnhem Land, an area of northern Australia where petrol sniffing has been prevalent among the indigenous people for some years (Brady, 1992). In these communities the method used to inhale petrol is to place ~200 ml of petrol in a 375 ml soft drink can which has had the top removed and to inhale the petrol directly from the can (Brady, 1992; Burns *et al*., 1995*a*). A total of 112 males aged between 13 and 32 years were recruited to the study with the assistance of local community health workers and paid indigenous research assistants recruited from within the same communities. After an initial explanation of the study, informed consent was obtained from each subject. Using a semi-structured interview (Burns *et al*., 1995*a*) all subjects were interviewed about petrol sniffing behaviour, history of alcohol and other drug use, and school attendance and employment, by one of the authors (C.B.B.) with the assistance of the research assistants from each subject's community. The validity of these self-reported histories was determined using a consensual methodology. Each subject's petrol sniffing history was compared with (i) local community health clinic records, (ii) the assessment of the subject's petrol sniffing history made by local community health workers and (iii) an assessment of current petrol sniffing behaviour made by research assistants recruited from the same language group (Matthews *et al*., 1988; Burns *et al*., 1995*b*). Data that were consistent from these three sources were inferred to be an accurate reflection of an individual's petrol sniffing history. From this consensual information, subjects were classified into one of three groups on the basis of their petrol sniffing history: (i) non-sniffers; individuals who had never sniffed petrol; (ii) current-sniffers; individuals who were currently and actively sniffing petrol and who had done so for a period of at least 6 months; and (iii) ex-sniffers; individuals who had previously sniffed petrol for a period of at least 6 months but who, at the time of the study, had not sniffed petrol for at least 6 months. All of the current-sniffers met the criteria for inhalant abuse from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, American Psychiatric Association, 1994). All of the subjects in the ex-sniffer group met the same criteria using a retrospective rating. Study exclusion criteria included a history of head injury with loss of consciousness, epilepsy, alcohol dependence or abuse, and psychiatric disorder. None of our subjects were excluded on these criteria. As previous studies have estimated that the acute effects of petrol sniffing can last for up to 6 h (Nurcombe *et al*., 1970; Poklis and Burkitt, 1977) subjects who had been petrol sniffing $<$12 h prior to testing were also excluded and retested at a later time (n = 1). Historical data for each subject were also assessed using the consensual methodology (Matthews *et al*., 1988). This led to exclusion of 16 subjects (11 current-sniffers and 5 ex-sniffers) because they had been admitted to hospital previously for acute toxic encephalopathy arising from petrol sniffing. The final study sample consisted of 34 non-sniffers, 33 current-sniffers and 30 ex-sniffers. Ethical approval of the project was obtained from the institutional ethics committees, an independent Aboriginal ethics committee and the town councils from the communities involved.

Assessments

Blood tests

Blood samples were taken from each subject for analysis of the content of lead and the hydrocarbons toluene, *n*-hexane and benzene. The methods for taking blood and for analysis of blood levels of lead and hydrocarbons have been described in detail previously (Burns *et al*., 1994).

Neurological examination

The neurological examination was conducted by a physician using the Ataxia Scoring and Staging System (Pourcher and

Barbeau, 1980). This system rated the presence and severity of ataxia, pyramidal and deep tendon reflexes on a scale of absent, mild, moderate or severe. The physician who performed the examination was blind to each subject's petrol sniffing status.

Neuropsychological testing

The neuropsychological testing was carried out by a neuropsychologist blind to subjects' petrol sniffing history with a research assistant also present to help explain the testing procedure. Conventional neuropsychological tests of attention, memory and learning, such as those contained in the Wechsler Memory Scale or the revised Wechsler Adult Intelligence Scale were considered inappropriate since all of the subjects came from remote aboriginal communities in Arnhem Land, Australia where English was not the primary language. Therefore, the neuropsychological test battery consisted of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the covert orienting of visual attentional test. These tests were chosen on the basis of their (i) demonstrated validity for the assessment of attentional and memory processes, (ii) appropriateness for cross-cultural use in an indigenous group of people where English is not the primary language, (iii) acceptability among a cultural group with no exposure to psychological or educational testing, and (iv) ability to assess cognitive function in individuals who may show mild movement disorders (Fray and Robbins, 1996; Maruff *et al*., 1996). These tests have been extensively standardized in normal control subjects and validated for the detection of memory and attentional deficits in patients with movement disorders such as Parkinson's disease, motor neuron disease, Alzheimer's disease and Machado–Joseph disease (Sahakian *et al*., 1988; Sahgal *et al*., 1991; Owen *et al*., 1993, 1995; Chari *et al*., 1996; Fray and Robbins, 1996; Maruff *et al*., 1996) The methodological details of these tests have been extensively described in the literature and their administration in this study was according to standard protocols. The neuropsychological tests used were as follows.

Motor function. Subjects were required to use their dominant hand to touch the middle of a cross that was presented with random timing, and at random locations, on the computer screen. Twelve trials were administered following 12 practice trials. The accuracy and latency of hand movements to touch the computer screen were recorded.

Simple and choice reaction times. For the simple reaction time task, a single yellow stimulus appeared at random time intervals at a fixed location in the centre of the computer screen, marked by an open circle. Subjects were required to lift their dominant hand from a response pad and touch the yellow stimulus as quickly as possible when it appeared. The choice reaction time task was similar, except that the yellow stimulus could appear in one of five marked locations that were equidistant from the centre of the computer screen. The simple and choice reaction time tasks each consisted of 10 trials following 30 practice trials. Both the accuracy and latency of movements were recorded. The latency of responses consisted of two measures, the time taken to lift the dominant hand from the response pad (response time) and the time taken to move the hand from the response pad to the computer screen (movement time).

Visual search. A central box was displayed on the computer screen, surrounded by eight additional boxes. The target, a complex abstract pattern consisting of four different colours, then appeared in the central box and remained visible until the end of the trial. After a 2 s delay, an array of either two or eight similar abstract patterns, one of which was the initial target, appeared in the surrounding boxes. The target therefore appeared with either one or seven similar distractors. Subjects were required to identify which of the eight surrounding boxes contained the target pattern as quickly as possible by lifting their dominant hand from the response pad and touching the appropriate box. Response times, movement times and the number of correct hits were recorded.

Pattern recognition. Twelve abstract target patterns were presented sequentially for 2 s each in the centre of the computer screen. After a 3 s delay, two patterns were then presented simultaneously on the screen, one from the initial 12 targets and one novel but similar pattern. Subjects were required to touch the target pattern. Twelve pairs of stimuli, each containing a target and a distractor, were shown and the entire procedure was then repeated with a new set of 12 target patterns. The number of patterns recognized correctly was recorded.

Spatial recognition. A small target square was presented sequentially at five different locations on the computer screen, each for 2 s. Following a delay of 3 s, two squares were then presented simultaneously at separate locations on the screen. One of the locations had previously been included in the sequence of five target locations, the other location was novel. Subjects were required to touch the target square at the previously included location. Subjects were shown five pairs of stimuli, each of which contained a previously shown location and a distractor, and the entire procedure was then repeated four times each with new sets of five target locations. The number of locations recognized correctly was recorded.

Pattern–location paired associate learning. Eight boxes were presented at locations around the edge of the computer screen that were equidistant from the centre. At the beginning of a trial, each box opened for 2 s, in random order, to reveal that it contained either an abstract pattern or was empty. Each box closed after 2 s so that its contents

were no longer visible. Subjects were instructed to remember which boxes contained a pattern and what that pattern was. After all of the boxes had opened and closed, a single pattern was presented at the centre of the computer screen, which was identical to one of the patterns that the subject had just been shown. The subject was required to touch the box that contained the identical pattern. Another of the recently shown patterns was then presented in the centre of the computer screen, and again the subject was required to touch the box that had contained that pattern. This was repeated until all the pattern–location associations that made up the trial had been remembered correctly. If an error was made, the same set of pattern–location associations was shown to the subject again and the learning procedure was repeated. Subjects were required to learn sets of one, two, three, six or eight pattern–location associations to complete each test. Subjects were allowed up to 10 repeated trials to learn a single set of pattern–location associations. If the set of pattern–location associations was not learned within 10 trials the set was stopped. The number of trials and errors for each test was recorded.

The covert orienting of attention task. The design and administration of the covert orienting of visual attentional test used in the current study have been described extensively in previous publications (Maruff and Currie, 1995; Maruff *et al*., 1995). Briefly, the covert orienting of visual attentional test required subjects to keep their eyes fixed on a central point and respond, with a manual button press, to the appearance of a peripheral target in either the left or right visual field. At a predetermined time of either 150 ms or 550 ms before the target appeared (stimulus onset asynchrony), a spatial cue could indicate either the target location (valid cue) or the location opposite to the target (invalid cue). Subjects' eye movements were monitored by the experimenter and trials where eye movements occurred were excluded. Performance on the covert orienting of visual attentional test was measured by calculating each subject's mean reaction time to valid and invalid cues at both stimulus onset asynchronies. The mean reaction time to validly cued trials was subtracted from the mean reaction time to invalidly cued trials to give the the size of the invalid cue effect. The size of the invalid cue effect has been shown to be a valid measure of the speed with which attention can be directed across the visual field (Maruff and Currie, 1995; Maruff *et al*., 1995). Subjects were given 20 practice trials before the task began.

Drawing and copying. Subjects were instructed to trace over the top of a five-pointed star. They were then instructed to draw a house. If they could not draw a house they were shown a picture of a house and asked to copy it. The tracing was rated on a scale of 1 (severe tremor) to 4 (perfect trace). The drawings were rated on a scale of 1 (poor) to 4 (perfect).

Data analysis

Demographic and biochemical indices of petrol sniffing were compared between groups using separate ANOVAs (analyses of variance). The frequency of abnormal neurological assessments in each of the petrol sniffer groups was compared with the non-sniffer group using Fisher's exact test. For each subject, a global neurological abnormality score was also computed by summing the number of abnormal neurological assessments. The global neurological abnormality score was calculated using only the assessments for which significant differences between current-sniffers and non-sniffers were found. Neuropsychological measures were compared between groups using ANOVA. Where ANOVA indicated that the omnibus F was significant, group differences were investigated using Newman–Keuls *post hoc* ($P < 0.05$) t tests. Where the difficulty level was manipulated within the same task (simple and choice reaction time, visual search from two and eight items), task difficulty was treated as a repeated variable in the ANOVA. Before analysis, the distributions of data for each performance measure were inspected for normality and heterogeneity of variance. Where data did not meet the assumptions for ANOVA the distributions of scores were transformed. The distributions of raw data for blood lead levels and reaction time data were skewed significantly in the positive direction. Logarithmic base 10 (log) transformation returned these distributions to normal. In order to keep data for blood lead levels positive following transformation, a value of one was added to each subject's blood lead level prior to transformation. Performance accuracy measures were scored as percentage correct. The distributions of raw data for these measures were characterized by a significant negative skew and small numbers of outlying scores with low values. For each variable, an arcsin transformation returned these distributions to normal (Tabachnick and Fidel, 1996). The transformations necessary to return these distributions of scores to normal are consistent with those used in previous studies also using CANTAB to measure memory and attention (Owen *et al*., 1993, 1995; Maruff *et al*., 1996) or measuring blood lead levels (Burns *et al*., 1994). No transformations were performed for blood hydrocarbon data, as hydrocarbons were detected only in the current-sniffer group. Where variables did not meet the assumptions for ANOVA after transformation, or where the data was categorical, the untransformed scores were submitted to Kruskal–Wallis non-parametric ANOVA, Mann–Whitney U or χ^2 contingency analysis to compare groups. Finally, the relationships between behavioural and biochemical measures of petrol sniffing and performance on the neuropsychological tests and the neurological abnormality score were investigated using Pearson's product moment correlation or Spearman's ρ correlation. In order to protect against Type I error, the level of significance for comparisons within each of the domains assessed (behavioural, biochemical, neurological and neuropsychological) was set at 0.01.

Table 1 *Demographic variables in control and petrol sniffer groups*

	Non-sniffers (n = 34)		Ex-sniffers (n = 30)		Current-sniffers (n = 33)	Statistic	P-value
Demographic							
Age (years)	20.2 ± 3.9		21.5 ± 5.4		20.6 ± 4.9	0.83*	NS
Age range (years)	(14–32)		(13–31)		(15–35)		
Education (years)	10.3 ± 1.5	=	9.5 ± 2.3	=	8.9 ± 2.6	1.5†	NS
Percentage of group at work/school	74.3	>	48.5	>	25.6	18.4‡	0.0001
Regular alcohol users (%)	14.7		13.3		9.1	0.3‡	NS
Regular cannabis users (%)	15.1		10.0		12.1	0.4‡	NS
Behavioural							
Age petrol sniffing begun (years)	–		13.4 ± 2.9		12.7 ± 3.2	0.86*	NS
Number of 375-ml cans per week	–		4.5 ± 3.4		3.8 ± 2.6	0.93*	NS
Time sniffing (years)	–		6.2 ± 4.6		7.5 ± 4.7	1.09*	NS
Abstinence time (years)	–		2.4 ± 2.8				
Biochemical							
Blood lead level (μmol/l)	0.27 ± 0.15		1.08 ± 0.61		1.58 ± 0.72		
Blood lead level (log μmol/l)	0.10 ± 0.05	<	0.30 ± 0.13	<	0.40 ± 0.13	78.12*	<0.0001
Subjects with detectable toluene (n)	0		0		17		
Blood toluene level (μg/ml)	–		–		0.25 ± 0.19		
Subjects with detectable benzene (n)	0		0		10		
Blood benzene level (μg/ml)	–		–		0.068 ± 0.42		
Subjects with detectable *n*-hexane (n)	0		0		0		

Unless otherwise stated, data are shown as group means (± SD). NS = not significant. For statistic column: *ANOVA or t test; †Kruskal–Wallis ANOVA; ‡χ^2 test.

Results

Demographic, behavioural and biochemical measures

There were no significant differences between the subject groups for age and education or self-rated alcohol or cannabis use levels (Table 1). There were no significant differences between the current-sniffer group and ex-sniffer group for the age at which petrol sniffing began or the average volume of petrol sniffed per week. A significantly greater percentage of the non-sniffer group was in full time school or employment than the ex-sniffer and current-sniffer groups. On average, the current-sniffer group had sniffed petrol for ~1 year longer than the ex-sniffer group. Blood lead levels were significantly higher in the ex-sniffer group than in the non-sniffer group, and blood lead levels were significantly higher in the current-sniffer group than in ex-sniffer group. The hydrocarbons toluene and benzene were detected only in subjects in the current-sniffer group and *n*-hexane was not detected in any subjects. In the current-sniffer group, all subjects who had detectable levels of benzene in their blood also had detectable levels of toluene. There were no significant correlations between blood hydrocarbon levels and any measure of petrol sniffing behaviour. When the current-sniffer group was categorized according to whether toluene was detected or not, there was no difference between the hydrocarbon present and hydrocarbon absent subgroups on any of the demographic, behavioural or blood lead level measures (Table 4). There was a significant correlation between the blood lead level and the length of time petrol sniffing (r = 0.47, P = 0.005) but there were no significant correlations between the blood lead level and any of the other petrol sniffing behaviour measures. There were no significant correlations between blood hydrocarbon levels and the behavioural measures of petrol sniffing. For the ex-sniffer group (n = 30), blood lead level correlated significantly with length of time petrol sniffing (r = 0.37, P = 0.01) and with length of abstinence (r = –0.46, P = 0.003).

Neurological assessment

The frequency of abnormal neurological signs is shown in Table 2. Only those assessments where an abnormality was present in at least one subject from any group are shown. No abnormalities in peripheral sensory function, tone or muscle strength were present (data not shown). With the exception of nystagmus, cranial nerve signs were also normal in all subjects. Because the frequency of Ataxia Scoring and Staging System items with a severity of greater than one was very low (3%), neurological ratings were re-categorized according to whether abnormalities were present or absent. Compared with the non-sniffer group, abnormal neurological ratings which were more frequent in the current-sniffer group included a positive palmomental reflex, postural tremor, adiadyscokinesia (dominant and non-dominant hands), brisk deep reflexes, abnormal tandem gait and abnormal finger to nose movements (dominant and non-dominant hands) (Table 2). Where a positive palmomental reflex was found this occurred bilaterally in all cases. A subset of these abnormal neurological signs were also more frequent in the ex-sniffer group when compared with the non-sniffer group. These were a positive palmomental reflex and abnormal tandem gait. Accordingly, the neurological abnormality score

Table 2 *Numbers with each abnormal neurological sign in each group*

Neurological assessment	Non-sniffers (n = 34)	Ex-sniffers (n = 30)	Current-sniffers (n = 33)
Palmomental	2	14**	23***
Postural tremor	6	15	33***
Rapid alternating hand movements			
(non-dominant)	4	10	28***
(dominant)	1	7	22***
Deep reflexes	4	11	19**
Tandem gait	0	10**	15**
Finger to nose			
(non-dominant)	0	3	10**
(dominant)	0	3	9**
Standard gait	0	4	7
Heel to knee			
(non-dominant)	0	4	7
(dominant)	0	4	7
Nystagmus	6	5	11
Rapid finger tap			
(non-dominant)	0	3	6
(dominant)	0	3	6
Eye movements	0	1	2
Jaw jerk	0	3	2
Wrist flap	0	1	1
Glabellar tap	0	1	3
Spontaneous arm movements	1	1	1
Spontaneous trunk movements	0	1	3
Spontaneous facial movements	0	0	4
Spontaneous leg movements	0	0	0
Grasp	0	0	0
Pout	1	0	3

Fisher's exact test, comparison with non-sniffers: *$P < 0.01$, **$P < 0.001$, ***$P < 0.0001$.

was significantly different between groups [$F(2,96) = 22.182$, $P < 0.0001$; non-sniffer mean ($\pm$ SD) = 0.48 $\pm$ 1.1, ex-sniffer mean = 2.1 $\pm$ 2.4, current-sniffer mean = 3.7 $\pm$ 2.4].

Neuropsychological assessment

The group means and standard deviations for each of the neuropsychological measures are shown in Table 3.

Sustained attention

All subjects achieved the maximum score for accuracy on both the simple and choice reaction time tasks. Analysis of log response times with a group (control, current-sniffer and ex-sniffer) $\times$ task difficulty (simple reaction time versus choice reaction time) ANOVA indicated no significant effect for group ($F < 1$) or task difficulty [$F(1, 96) = 2.21$, $P > 0.05$] and no group $\times$ task difficulty interaction ($F < 1$; Fig. 1). Analysis of the log movement times yielded a similar pattern of results with no significant effect for group ($F < 1$) or task difficulty [$F(1,96) = 3.8$, $P > 0.05$] and no significant group $\times$ task difficulty interaction [$F(2,96) = 1.6$, $P > 0.05$].

Visual search

For the accuracy of responses on the visual search task, a group $\times$ task difficulty (arcsin percentage correct of visual search from two versus eight stimuli) ANOVA indicated a significant effect for group [$F(2,96) = 14.8$, $P < 0.0001$] and task difficulty [$F(1,109) = 82.6$, $P < 0.0001$], and a significant group $\times$ task difficulty interaction [$F(2,96) = 10.5$, $P < 0.0001$; Fig. 1]. Simple effects ANOVAs with Newman–Keuls *post hoc* tests ($P < 0.05$) were therefore calculated for each of the petrol sniffer groups at both levels of task difficulty. There were no significant group differences for visual search from two stimuli [$F(2,96) = 1.98$, $P > 0.05$], but significant group differences were found for the visual search from eight stimuli [$F(2,96) = 14.9$, $P < 0.0001$], with the accuracy of the current-sniffer group significantly lower than that of the non-sniffer and ex-sniffer groups. There was no difference in accuracy between the non-sniffer and ex-sniffer groups. For the log latency of responses on the visual search task, ANOVA indicated a significant effect for task difficulty [$F(1,96) = 478.1$, $P < 0.0001$], but no significant effect for group [$F(2,96) = 2.29$, $P = 0.06$] and no significant group $\times$ task difficulty interaction [$F(2,96) = 1.21$, $P = 0.12$]. For the log movement

Table 3 *Cognitive performance measures in control and petrol sniffer groups*

Neuropsychological measure	Non-sniffers (n = 34)		Ex-sniffers (n = 30)		Current-sniffers (n = 33)	P-value
Sustained attention						
SRT accuracy (%correct)	100		100		100	
CRT accuracy (%correct)	100		100		100	NS
SRT respond (log latency)	2.49 ± 0.08		2.53 ± 0.21		2.49 ± 0.41)	
CRT respond (log latency)	2.50 ± 0.17		2.54 ± 0.07		2.51 ± 0.41	NS
SRT move (log latency)	2.45 ± 0.17		2.46 ± 0.19		2.49 ± 0.47)	
CRT move (log latency)	2.49 ± 0.13		2.51 ± 0.15		2.49 ± 0.43	NS
Visual search accuracy (arcsin percentage correct)						
with 2 pairs	1.57 ± 0		1.54 ± 0.12		1.51 ± 0.17)	
with 8 pairs	1.41 ± 0.62	=	1.23 ± 0.62	>	1.07 ± 0.54	<0.0001
Visual search response (log latency)						
with 2 pairs	3.03 ± 0.6		3.11 ± 0.17		3.18 ± 0.17)	
with 8 pairs	3.60 ± 1.7		3.69 ± 0.21		3.58 ± 0.26	NS
Visual search movement (log latency)						
with 2 pairs	2.68 ± 0.11		2.81 ± 0.21		2.75 ± 0.19)	
with 8 pairs	2.81 ± 0.21		2.91 ± 0.30		2.91 ± 0.42	NS
Covert visual attention						
Invalid cue effect 150 (ms)	61.5 ± 42.2		82.3 ± 58.6		87.2 ± 27.6	NS
Invalid cue effect 550 (ms)	59.1 ± 60.9		66.7 ± 72.8		69.5 ± 60.9	NS
Drawing and copying scores (range)						
Draw a house	4 (4–4)		4 (3.5–4)		4 (1.5–4)	NS
Copy a house	3 (3–3)		3 (2.5–3)		3 (1.5–3)	NS
Trace a star	3 (3–3)		3 (2–3)		3 (1–3)	NS
Pattern recognition memory						
(arcsin percentage correct)	0.99 ± 0.38	>	0.77 ± 0.38	=	0.72 ± 0.34	<0.0001
(log correct latency)	3.31 ± 0.14		3.39 ± 0.17		3.44 ± 0.24	NS
Spatial recognition memory						
(arcsin percentage correct)	0.94 ± 0.26	>	0.73 ± 0.22	=	0.69 ± 0.20	<0.001
(log correct latency)	3.29 ± 0.14		3.27 ± 0.17		3.25 ± 0.24	NS
Pattern–location paired associate learning (percentage of group successful)						
with 1 pair	100		100		100	NS
with 2 pairs	100		100		88.8	NS
with 3 pairs	100		100		85.2	NS
with 6 pairs	91.6		78.6		51.8	<0.01
with 8 pairs	83.3		64.3		48.1	<0.01
Pattern–location paired associate learning						
(total trials)	15.8 ± 4.8	=	21.8 ± 9.9	<	29.2 ± 17.9	<0.001
(total errors)	24.3 ± 15.8	=	36.8 ± 14.3	<	65.1 ± 23.9	<0.001
(list memory)	16.8 ± 3.3	>	12.9 ± 3.9	>	11.9 ± 6.3	<0.001

Unless otherwise stated, data are shown as group means (± SD). SRT = simple reaction time (task); CRT = choice reaction time (task); NS = not significant.

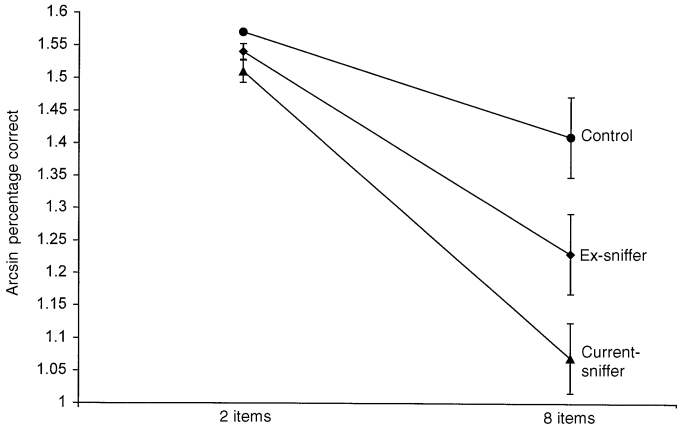

Fig. 1 Group mean (± SD) response accuracy for visual search with two and eight items.

times, ANOVA indicated a significant effect for task difficulty [$F(1,96) = 19.2$, $P < 0.0001$], but no significant effect for group [$F(2,96) = 2.4$, $P = 0.08$] and no significant group × task difficulty interaction ($F < 1$).

Covert orienting of visual attention

No significant group differences were found for the sizes of the invalid cue effects at either the 150 ms stimulus onset asynchrony [$F(2,96) = 1.23$, $P > 0.05$] or the 550 ms stimulus onset asynchrony [$F(2,96) = 2.11$, $P > 0.05$].

Pattern and spatial recognition memory

The arcsin percentage correct patterns recognized on the pattern recognition memory task was compared between

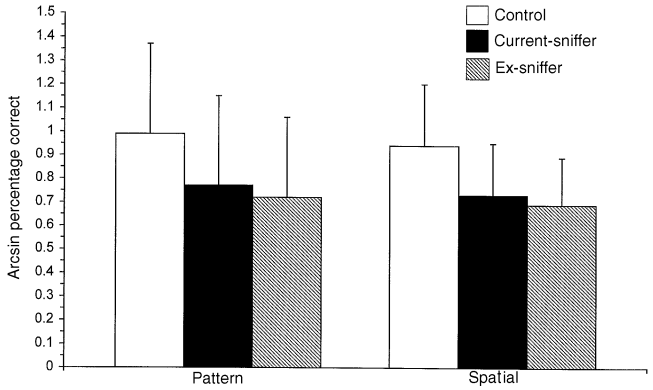

Fig. 2 Group mean (+ SD) accuracy for pattern and spatial recognition memory tests.

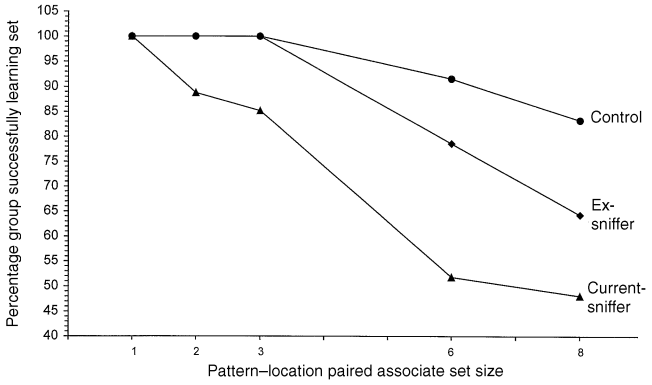

Fig. 3 Proportion of subjects successfully completing each level of the pattern–location paired associate learning test.

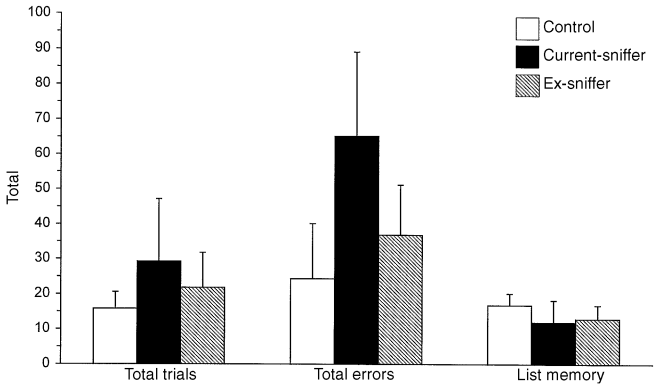

Fig. 4 Group mean (+ SD) performance across all trials of the pattern–location paired associate learning test.

groups using a one-way ANOVA. The group effect was significant [$F(2,96) = 14.5$, $P < 0.0001$; Fig. 2] and Newman–Keuls *post hoc* tests indicated that the accuracy of pattern recognition was equal in the current-sniffer and ex-sniffer groups, although both groups were significantly less accurate than the non-sniffer group. One-way ANOVA indicated that there was no significant difference between non-sniffer and petrol sniffer groups for the log latency to recognize the correct pattern [$F(2,96) = 3.61$, $P = 0.03$]. The arcsin percentage correct spatial locations recognized was compared between groups using one-way ANOVA. Once again, the group effect was significant [$F(2,96) = 18.12$, $P < 0.0001$]. Newman–Keuls *post hoc* tests indicated that the accuracy of spatial recognition was equal in the current-sniffer and ex-sniffer groups, although both groups were significantly less accurate than the non-sniffer group. Analysis of the log latency to recognize the correct spatial location using a one-way ANOVA indicated no significant group differences [$F(2,96) = 3.61$, $P = 0.06$].

Pattern–location paired associate learning

In the first analysis the relationship between the size of the pattern–location paired associate set and the subject group was investigated. Fisher's exact test was used to compare the percentage of current-sniffers and ex-sniffers who failed to learn a set of pattern–location associations with the percentage of non-sniffers who also failed to learn the same set size of pattern–location associations. There were no significant relationships between group membership and performance for the one [χ^2 (2) = 1.5, $P > 0.05$], two [χ^2 (2) = 3.1, $P > 0.05$] or three [χ^2 (2) = 4.6, $P > 0.05$] pattern–location paired associate sets. However, significant relationships between group membership and performance were found for the six [χ^2 (2) = 10.3, $P < 0.01$] and eight [χ^2 (2) = 10.34, $P < 0.01$] pattern–location paired associate sets (Fig. 3). Investigation of these relationships showed that compared with non-sniffers, significantly less subjects in the current-sniffer group (Fisher's exact test = 0.001) and in the ex-sniffer group (Fisher's exact test = 0.02) were able to learn the six pattern–location paired associate set within 10 trials. Similarly,when compared with non-sniffers, significantly fewer subjects in the current-sniffer group (Fisher's exact test = 0.001) and in the ex-sniffer group (Fisher's exact test = 0.003) were able to learn the eight pattern–location paired associate set within 10 trials. The second analysis used a series of one-way ANOVAs with Newman–Keuls *post hoc* tests ($P < 0.05$) to compare the three groups on four indices of learning and memory calculated across all trials and all sets on the pattern–location paired associate test: total trials to criterion; total errors committed; and total number of patterns correctly located after a single presentation (Fig. 4). There was a significant group difference for the total number of trials to criterion [$F(2,96) = 12.58$, $P < 0.0001$] with the current-sniffer group requiring more trials than the ex-sniffer group and non-sniffers to complete the test. However, there was no significant difference between the ex-sniffer and non-sniffer groups for the total trials to criterion. There was a significant group difference for the total number of errors committed [$F(2,96) = 4.5$, $P < 0.01$], with the current-sniffer group making more errors than the ex-sniffer and non-sniffer groups in completing the test. Once again, there was no difference between the ex-sniffer and non-sniffer groups for the total errors in completing the test. Finally there was a significant group difference for the list memory score [$F(2,96) =$

Table 4 *Demographic and cognitive measures in current petrol sniffers with and without detectable toluene*

Measure	No toluene detected (n = 16)	Toluene detected (n = 17)	t-value	P-value
Age (years)	21.8 ± 5.0	19.4 ± 4.8	<1	NS
Age petrol sniffing begun (years)	12.4 ± 2.9	13.3 ± 3.1	<1	NS
Number of 375 ml cans per week	3.1 ± 1.5	2.8 ± 2.0	<1	NS
Time sniffing (years)	6.9 ± 4.7	5.5 ± 2.8	<1	NS
Blood lead level (μmol/l)	1.61 ± 0.79	1.59 ± 0.65		
Log of blood lead level (log μmol/l)	0.39 ± 0.14	0.39 ± 0.12	<1	NS
Neurological abnormality score	3.2 ± 2.1	4.3 ± 2.6	<1	NS
Pattern plus spatial recognition (arcsin of percentage correct)	0.78 ± 0.19	0.73 ± 0.2	<1	NS
Visual search from eight stimuli (arcsin of percentage correct)	1.1 ± 0.26	1.1 ± 0.33	<1	NS
Paired associate learning (list memory)	12.6 ± 6.1	13.4 ± 6.3	<1	NS
Paired associate learning (total errors)	54.4 ± 45.3	58.1 ± 48.6	<1	NS

Data are shown as group means (± SD). NS = not significant.

12.5, $P < 0.001$], with the current-sniffer group locating significantly fewer patterns on the first attempt than the ex-sniffer group. The ex-sniffer group located significantly fewer patterns on the first attempt than the non-sniffer group (Fig. 4).

Drawing and copying

Kruskal–Wallis non-parametric ANOVA (KW) was used to compare scores for the three drawing and copying tests. No significant group differences were found for the house drawing (KW = 2.3, $P > 0.05$), star copying (KW = 1.9, $P > 0.05$) or star tracing (KW = 2.1, $P > 0.05$) tests.

The relationship between neurocognitive measures and petrol sniffing behaviour

The comparison of groups identified significant differences between the non-sniffer and current-sniffer groups on four neuropsychological measures: (i) visual search from eight items (arcsin percentage correct); (ii) pattern and spatial recognition (arcsin percentage correct) calculated by adding the number of correct trials on the pattern and spatial recognition tests and expressing this as a percentage of possible number correct for the both tests combined (maximum possible score = 44); (iii) paired associate list memory score; and (iv) paired associate learning total error score (Table 3). These four measures and the neurological abnormality score were used to investigate the relationships between neurocognitive function and the biochemical and behavioural measures of petrol sniffing.

First, performance on the four cognitive measures and the neurological abnormality score was compared between the subgroups of current-sniffers in whom toluene was, or was not, detected. No significant differences between the toluene-detected and toluene-not-detected groups were found for any of these measures (Table 4). Furthermore, in the subjects with detectable levels of toluene, there were no correlations between blood toluene level and neurocognitive function. Correlations between neurocognitive function and indices of petrol sniffing behaviour were investigated separately for each group. For the current-sniffer group, blood lead level was correlated significantly with all of the cognitive measures and with the neurological abnormality score (Table 5). Significant correlations were also found between the length of time sniffing and the list memory and total error scores from the paired associate learning task and with the neurological abnormality score. No other demographic or petrol sniffing behaviour measure was correlated with neurocognitive function. As there was a highly significant correlation between blood lead level and length of time sniffing ($r = 0.47$, $P = 0.005$), partial correlations between length of time of petrol sniffing and neurocognitive performance were calculated with the variance due to blood lead level removed. Significant partial correlations were found between length of time petrol sniffing and paired associate learning list memory ($r = 0.41$, $P = 0.001$), paired associate learning total errors ($r = 0.37$, $P = 0.01$) and the neurological abnormality score ($r = 0.39$, $P = 0.002$).

For the ex-sniffer group, the correlational analysis indicated significant relationships between blood lead level and paired associate learning list memory, total error scores and the neurological abnormality score (Table 6). There was also a significant correlation between length of time of abstinence from petrol sniffing and paired associate list memory score. As blood lead level was also correlated with length of time of abstinence, a partial correlation between length of time of abstinence and paired associate learning list memory was calculated, with the variance due to log blood lead level removed. This partial correlation was not significant ($r = 0.21$, $P = 0.32$).

Discussion

The results of the study show that neurological and cognitive impairment occurs in community dwelling individuals who are actively sniffing petrol but who do not have acute toxic

Table 5 *Current-petrol sniffers: correlations between demographic, biochemical and neurocognitive measures*

Measure	Pattern–location paired associate learning		Visual search from eight items (accuracy)	Pattern/spatial recognition memory (total correct)	Neurological abnormality (total score)
	List memory	Total errors			
Age	−0.10	0.13	−0.15	0.23	−0.17
Education	0.16	−0.14	0.14	0.18	−0.16
Age began sniffing	0.29	0.22	0.19	0.05	0.25
Length of time sniffing	0.46**	−0.49**	−0.00	0.22	−0.52**
Volume of petrol per week	−0.25	0.31	0.23	−0.18	0.24
Blood lead level	−0.33*	0.39*	−0.37*	−0.44**	0.55**
Blood toluene level ($n = 22$)	0.17	0.14	0.01	0.22	0.23
Blood benzene level ($n = 12$)	0.09	0.21	0.15	0.17	0.11

*$P < 0.01$, **$P < 0.001$.

Table 6 *Ex-petrol sniffers: correlations between demographic, biochemical and neurocognitive measures*

Measure	Pattern–location paired associate learning		Visual search from eight items (accuracy)	Pattern/spatial recognition memory (total correct)	Neurological abnormality (total score)
	List memory	Total errors			
Age	0.06	0.08	−0.14	−0.19	−0.19
Education	0.11	0.03	0.13	0.07	0.18
Age began sniffing	0.12	0.20	−0.08	0.12	−0.13
Length of time sniffing	0.14	0.02	0.05	0.28	0.11
Volume of petrol per week	0.18	0.22	0.09	0.27	0.16
Blood lead level	−0.43**	0.39*	−0.17	−0.21	0.39*
Abstinence time	0.23	–0.18	−0.16	0.13	−0.29

*$P < 0.05$, **$P < 0.01$.

encephalopathy. The presence of abnormal ataxic, pyramidal and primitive release signs in the current-sniffers suggests that damage or disruption to cerebellar areas and to fronto-cerebellar connections does occur with chronic petrol sniffing. It also suggests that significant CNS damage may occur in individuals who abuse petrol before they become encephalopathic. There was no evidence of peripheral or sensory neuropathy in any of the current-sniffers. These same neurological abnormalities have been reported previously, in different combinations, among in-patients being treated for acute toxic encephalopathy arising from petrol sniffing (Seshia *et al*., 1978; Valpey *et al*., 1978; Kaelen *et al*., 1986; Rischbieth *et al*., 1987; Goodheart and Dunne, 1994). However, these patients may also show appendicular, truncal and gait ataxia, myoclonus, choreoathetosis and hyperreflexia as well as the presence of Babinski's sign, positive glabellar tap, pout and grasp reflexes (Robinson, 1978; Valpey *et al*., 1978; Goldings and Stewart, 1982; Edminster and Bayer, 1985; Kaelan *et al*., 1986; Goodheart and Dunne, 1994). The additional abnormal neurological signs observed in petrol sniffers with acute toxic encephalopathy may reflect a greater exposure to petrol sniffing or the acute neurotoxic effects of petrol. The current results suggest that abnormal neurological signs observed in acute toxic encephalopathy reflect, to some extent, more subtle CNS changes that arise from the long-term and chronic abuse of petrol.

On neuropsychological testing, current-sniffers showed impairments in visual attention, visual recognition memory and visual paired associate learning. Importantly, the speed of performance on all of the tests given was normal, as was the speed of covert attentional shifts and visuoconstructive abilities (drawing and copying tasks). This pattern of neuropsychological task performance suggests strongly that the cognitive deficits found in the current-sniffers did not arise from a general inability to perform the tasks, or from extraneous factors such as decreased motivation, lack of compliance, increased distractability or lower levels of premorbid cognitive function. These findings are consistent with previous studies, in which the presence of cognitive deficits in the areas of attention and memory in petrol sniffers admitted to hospital for treatment of acute toxic encephalopathy have also been reported (Valpey *et al*., 1978; Goldings and Stewart, 1982). However, in these studies, cognitive deficits included psychomotor slowing and were observed as part of a generalized and severe deterioration of cognitive function. The presence of more specific cognitive deficits in the current non-encephalopathic petrol sniffers suggests that some deterioration of cognitive function does precede encephalopathy.

A qualitatively similar but quantitatively less severe pattern of neurological and cognitive deficits was found in the individuals who had sniffed petrol in the past but who had since abstained. Only two abnormal neurological signs were more frequent in the ex-sniffers group than in control subjects

(tandem gait and the presence of a bilateral palmomental reflex). Similarly, cognitive impairment was found only on tests of visual recognition memory and pattern–location paired associate learning. Performance on all of the other tests was within normal limits. Taken together, this qualitatively similar but quantitatively less severe pattern of neurological and behavioural abnormalities suggests that some of the neurocognitive consequences of the long-term chronic abuse of petrol are ameliorated with abstinence, although prospective studies are necessary to test this hypothesis.

As all of the petrol sniffers in the current study had abused both leaded and unleaded petrol (Burns *et al*., 1994), they had been exposed to a complex mixture of volatile compounds which include the C4 to C12 aliphatic and aromatic hydrocarbons, naphthalenes, paraffins and alkenes and tetraethyl lead (Jensen, 1984; Grandjean and Lansdown, 1986; Brust, 1993; Sharp and Rosenburg, 1994; Tenenbein, 1997). To date, the neurotoxic effects of petrol sniffing have been attributed to both the aromatic hydrocarbons and to tetraethyl lead (Sharp and Rosenburg, 1994; Burns *et al*., 1996; Tenenbein, 1997), although the differential effects of the hydrocarbons and tetraethyl lead components of petrol on neurocognitive function have not been established. In Australia, leaded petrol contains tetraethyl lead currently added at concentrations between 0.4 and 0.8 g/l (Berry *et al*., 1993). Once absorbed into the body, tetraethyl lead is metabolized rapidly in the liver into triethyl lead, which is profoundly neurotoxic. Triethyl lead has a biological half-life of 3–5 days in blood. However, in lipid rich organs such as the brain, the half-life of triethyl lead has been estimated to be >500 days (Heard *et al*., 1979). Triethyl lead is broken down in the liver to alkyl lead, which is also neurotoxic. A small amount of alkyl lead is excreted in the urine and faeces, but most of it is stored in bone where it has a half-life of >10 years (Jensen, 1984; Grandjean and Lansdown, 1986). In animals, hyperexcitability, tremor and aggressive behaviour are produced by acute administration of tetraethyl lead, although the onset of these symptoms may take up to 2 days to manifest (Cremer, 1984). Case reports of adults with acute occupational exposure to tetraethyl lead emphasize the presence of psychotic and manic symptoms, insomnia and anorexia. However, reports of encephalopathy are rare (Ehle and McKee, 1990; Tenenbein, 1997). Subtle neurocognitive abnormalities have been observed in individuals with chronic low level occupational exposure to tetraethyl lead. These abnormalities have been found on tasks which assess the speed of manual and ocular motor responses, new learning and memory, manual dexterity and the complex cognitive performance required by tasks such as block design and digit symbol substitution tasks (Ehle and McKee, 1990; Schwartz *et al*., 1993).

Consistent with these observations, measurement of blood lead level gave the best indication of exposure to petrol sniffing, and it was correlated with the presence and severity of neurocognitive abnormalities in the current study. In the current-sniffer group, the length of time for which individuals had sniffed petrol was also associated with the severity of both neurological and cognitive abnormalities and this association remained significant when the effect of blood lead level was statistically removed. This suggests some independence between the effects on neurocognitive function of the duration of petrol sniffing and the amount of exposure to lead. However, it was not possible to determine the precise nature of this relationship from the current data. No other biochemical or behavioural measure of exposure to petrol sniffing was associated with neurocognitive function in either the current-sniffer or ex-sniffer groups. While the short-term effects of petrol sniffing have been attributed to the combined effects of hydrocarbons and tetraethyl lead, the long-term effects are considered to be mostly due to the neurotoxic effects of organic lead (Poklis and Burkitt, 1977; Seshia *et al*., 1978; Valpey *et al*., 1978; Goldings and Stewart, 1982; Keenlyside, 1984; Fortenberry, 1985; Grandjean and Landsdown, 1986; Goodheart and Dunne, 1994). In the current-sniffer group, blood lead levels were significantly greater than in the non-sniffer group (Table 1). The mean blood lead level in the non-sniffer group was below the recommended safe level (0.49 μmol/l, National Health and Medical Research Council, 1993) and no non-sniffer had a blood lead level above this limit. In contrast, the mean blood lead level in the current-sniffer group was more than three times the recommended ‘safe’ limit and every subject in this group showed a blood lead level greater than 1 μmol/l. Taken together these data suggest that the more severe neurocognitive deficits in current-sniffers were related to their increased body lead burden. The partial correlation found between neurocognitive deficits and the length of time for which individuals had sniffed petrol, when the effect of lead was removed statistically, suggests that blood lead levels taken at the time of testing do not account completely for the severity of neurocognitive abnormalities associated with chronic petrol sniffing. In addition, the extent to which blood lead levels reflect body lead burden in petrol sniffers has been questioned because of the rapid absorption of the organic lead into tissues, the poor understanding of the kinetics of both organic and inorganic lead and the fact that the blood lead level itself reflects a composite of inorganic and several species of organic lead (Tenenbein, 1997). We believe that in the current study, blood lead levels can be interpreted meaningfully, as the social circumstances, timing and geography of the petrol sniffing behaviour were homogeneous. Therefore, individuals’ blood lead levels should represent similar aspects of body lead burden and differences in blood lead levels provide an indirect and relative measure of exposure to leaded petrol and index of body lead burden.

Blood lead levels were significantly lower in the ex-sniffer group and they correlated negatively with length of time of abstinence from petrol sniffing. In addition, although neurocognitive abnormalities were less severe in the ex-sniffers, correlations between the blood lead level and list memory, associate learning total errors and the neurological abnormality score remained significant and of approximately

the same magnitude as those found in the current-sniffer group (Table 5). Thus, despite the decreases, blood lead level was still associated with the severity of neurocognitive abnormalities. This observation supports the validity of blood lead level as an indirect marker for body lead burden in the current study. It is also consistent with the hypothesis that exposure to tetraethyl lead does contribute to the neurocognitive abnormalities observed in current-sniffers and ex-sniffers. The decreased severity of neurocognitive abnormalities in the ex-sniffers is consistent with recent reviews of studies of volatile substance abuse which also conclude that improvement in neurocognitive function occurs with abstinence (Fortenberry, 1985; Brust, 1993; Sharp and Rosenburg, 1994). In the ex-sniffer group, the lower mean blood lead level and the significant correlation between length of abstinence and reduction in blood lead levels suggests that, when individuals cease to sniff petrol actively, blood lead levels decrease slowly over time. However, the correlation between the severity of neurocognitive abnormalities and blood lead levels suggests that despite the overall reduction in body lead burden cognitive deficits remain more severe in ex-sniffers with higher blood lead levels. The absence of a correlation between length of time of abstinence and cognitive deficits may also reflect the unreliability of petrol sniffing histories, despite the use of the consensual methodology (Matthews *et al*., 1988; Burns *et al*., 1995*b*). This unreliability may be related to the retrospective nature of the petrol sniffing history required from the ex-petrol sniffers and the other informants. A significant proportion of the ex-sniffer group (33%) had abstained from sniffing petrol for >1 year prior to the assessment. Therefore, although the data suggest that some of the neurocognitive abnormalities associated with petrol sniffing decrease in severity when individuals abstain from sniffing petrol, the time required for this improvement and the relationship to decreases in body lead burden must be addressed in prospective studies.

The hydrocarbons benzene, *n*-hexane and toluene are also contained in petrol. These hydrocarbons are lipophilic and rapidly absorbed across the pulmonary epithelium. Although up to 20% of the inhaled dose is excreted unchanged in exhaled air, most hydrocarbons are converted to hydrophilic metabolites before being excreted in the urine. The half-life of these compounds in the body range from 7.5 h for toluene to 9–24 h for benzene (Flanagan *et al*., 1990). In humans, the neurotoxicity of hydrocarbons has been established from observations of individuals who have received high levels of exposure through deliberate or inadvertent (usually occupational) inhalation (Brust, 1993; Sharp and Rosenburg, 1994). Acute exposure to high concentrations of organic solvents gives rise to a 'drunkenness' which is similar to that observed following the ingestion of alcohol (Sharp and Rosenburg, 1994). High level exposure can result in excitement, nausea, ataxia, hallucinations and encephalopathy as well as polyneuropathy. However, the appearance of specific symptoms may depend upon which of the aliphatic hydrocarbons are inhaled. For example, polyneuropathy has been found after exposure to *n*-hexane, but not after exposure to toluene. Previous studies have found that acute high level exposure to benzene, *n*-hexane or toluene, alone or in combination, is sufficient for encephalopathy to occur (Brust, 1993; Sharp and Rosenburg, 1994). Neurological signs and symptoms that occur with long-term chronic exposure to organic solvents include peripheral neuropathy, cerebellar ataxia, myopathy, parkinsonism and encephalopathy (Fornazzari *et al*., 1983; Hormes *et al*., 1986; Brust, 1993; Sharp and Rosenburg, 1994). Cognitive deficits reported following chronic exposure to hydrocarbons include apathy, poor concentration, memory loss, visual spatial dysfunction and decreased speed of processing complex linguistic material. Such deficits have been observed both in inhalant abusers (Hormes *et al*., 1986) and in individuals with long-term occupational exposure (World Health Organisation, 1985; Morrow *et al*., 1990; Schwartz *et al*., 1991; Morrow, 1994; Stollery, 1996).

Toluene, benzene and *n*-hexane were not detected in the blood of any subjects in the non-sniffer or ex-sniffer groups. Although the hydrocarbons, toluene and benzene were detected in the blood of current-sniffers, the rate of detection of hydrocarbons was lower than expected. Toluene was detected in only 17 of the 33 subjects, benzene was detected in only 12 and *n*-hexane was not detected at all. There was no correlation between blood hydrocarbon levels and neurocognitive indices. Even when the current-sniffer group was divided according to whether toluene was detected or not, and neurocognitive measures were compared between the two subgroups, no differences were observed. However, the absence of any associations between blood hydrocarbon levels and neurocognitive deficits in the current-sniffers and ex-sniffers should not be inferred to suggest that the neurocognitive deficits found were due only to the effects of tetraethyl lead. Three major factors have been shown to affect the analysis and interpretation of blood hydrocarbon levels in studies of volatile substance abuse. First, hydrocarbons are eliminated rapidly from the body. The half-life in blood of toluene is 1–2 h and that of benzene 15–20 h (Ramsey and Flanagan, 1982; Pekari *et al*., 1989; Flanagan *et al*., 1990; Streete *et al*., 1992). Therefore, in the current study, the requirement that subjects did not sniff petrol in the 12 h before testing, to minimize the acute behavioural effects of petrol sniffing, may have also resulted in the low blood hydrocarbon levels found in the current-sniffers. Secondly, hydrocarbons are highly volatile with a high potential for losses in storage (Pekari *et al*., 1989). Thirdly, although petrol mixtures contain high amounts of hydrocarbons, the component concentrations in the vapour may be low (Streete *et al*., 1992). Given these caveats, the absence of any associations between blood toluene and benzene levels and neurocognitive abnormalities may not accurately reflect the contribution of hydrocarbon exposure to the CNS dysfunction found in chronic petrol sniffers.

To date, there have been no studies of neurocognitive function in community dwelling, non-encephalopathic indi-

viduals who are actively sniffing petrol, or who have sniffed petrol in the past but have since abstained. However, the presence of neurocognitive abnormalities in the current-sniffer group is consistent with the previous study of neurological function in an out-patient group of chronic petrol sniffers. Using a group of subjects referred to a paediatric out-patient clinic for chronic petrol sniffing, Seshia *et al*. (1978) found that abnormal jaw jerk, intention tremor, stance, gait and deep reflexes occurred in individuals whose blood lead levels ranged from 3.29 to 4.67 μmol/l. No neurological abnormalities were observed in individuals with blood lead levels $<$3.29 μmol/l. These blood lead levels are considerably higher than in the current-sniffer groups. However, when compared with the current-sniffer group, the subjects in the Seshia *et al*. (1978) study were younger, had sniffed petrol for shorter periods of time, and had been referred to the out-patient clinic because of their petrol sniffing. Therefore, the blood lead levels detected in the Seshia *et al*. (1978) study may reflect the effects of a more acute and short-term exposure to lead through petrol sniffing. However, as has already been stated, the extent to which blood lead levels can be compared meaningfully between different studies of petrol sniffing is limited. The more important aspect of the Seshia *et al*. (1978) study was that none of their chronic petrol sniffers were encephalopathic at the time of testing. Therefore, the presence of abnormal neurological signs supports the data from the current study which indicate that significant CNS changes are detectable in individuals who abuse petrol chronically, but who do not have acute toxic encephalopathy. There is also a possibility that the effects of petrol sniffing on the CNS are different for subjects of different ages. Younger subjects may require a greater body lead burden before showing any neurocognitive deficits from petrol sniffing. In the current study, the ages of subjects varied considerably, although the groups were matched on age, and age did not correlate with the severity of any neurocognitive deficits. However, in order to investigate whether the effects of petrol sniffing on neurocognitive behaviour are modulated by age, it is necessary to control the duration of petrol sniffing. Unfortunately the number of current-sniffers in the current study was too small to afford such analyses. Studies of larger groups of subjects are required to determine whether age is a factor in the effects of petrol on the CNS and whether this is independent of the duration of petrol sniffing.

Neuroanatomical changes associated with the chronic abuse of petrol are understood poorly. Neuropathological investigations of individuals who have died with acute toxic encephalopathy arising from petrol sniffing show neuronal loss and gliosis in the cerebral cortex, hippocampus, cerebellum and brainstem. Specific neuropathological changes reported include chromatolysis of neurons in the reticular formation and cerebral cortex (with normal levels of thiamine and niacin), loss of Purkinje and granule cells in the cerebellum, and loss of neurons in the h3–5 sectors of Ammon's horn (Valpey *et al*., 1978; Kaelen *et al*., 1986). CT and MRI neuroimaging of individuals with petrol sniffing encephalopathy has found abnormalities in the cerebellum, basal ganglia and brainstem (Kaelen *et al*., 1986; Roger *et al*., 1990) although other reports have noted no abnormalities on CT (Goodheart and Dunne, 1994). EEG findings are generally non-specific or indicate a diffuse slowing (Seshia *et al*., 1978; Goldings and Stewart, 1982; Rischbieth *et al*., 1987; Roger *et al*., 1990; Goodheart and Dunne, 1994). In the current study, the findings of abnormal ataxic, pyramidal and primitive release signs suggest that damage or disruption of cerebellar areas and of frontocerebellar connections was present in the chronic petrol sniffers. The specific deficits in memory, learning and attention found in the current-sniffer group also suggest the involvement of cortical brain areas (Sahakian *et al*., 1988; Sahgal *et al*., 1991; Owen *et al*., 1995). However, as the petrol sniffers failed only on the difficult levels of the memory and attention tests, it is possible that petrol sniffing gives rise to a general decline in cognitive function that becomes evident on the more demanding tests. In future studies a broader range of neuropsychological tests need to be used, in order to identify whether specific cognitive functions are affected by petrol sniffing.

Although abnormalities of attention and memory have been reported previously in individuals who have abused both petrol and hydrocarbons (e.g. glue sniffers), these patients were tested as in-patients receiving treatment for toxic encephalopathy and therefore the deficits reflect both the acute and chronic effects of the volatile substances. The neurocognitive abnormalities found in the current sniffer group were unlikely to have arisen from the acute effects of petrol sniffing. First, great care was taken to ensure that no subject was assessed if they had been sniffing petrol immediately prior to testing. Secondly, there was no evidence of a generalized psychomotor slowing or disinhibition in the neuropsychological performance of the current-sniffer group, and no behavioural evidence of petrol 'drunkenness' in any of the subjects. Thirdly, the specific pattern of cognitive deficits found in the current-sniffer group was qualitatively similar, but quantitatively more severe, than those found in the group who had abstained from sniffing for $>$6 months. In conclusion, the results of the current study suggest that subtle neurocognitive abnormalities do occur in individuals who abuse petrol but who do not have acute toxic encephalopathy. These abnormalities most probably reflect the neurotoxic effects of tetraethyl lead and the hydrocarbons contained in petrol, although the differential effects of these substances could not be determined in the current study. Qualitatively similar, but quantitatively less severe, cognitive and neurological deficits were found in individuals who have abused petrol in the past but have since abstained. This suggests that the severity of the neurocognitive deficits associated with petrol sniffing is reduced with abstinence. The abnormalities found in the current study should provide a foundation for future studies investigating the nature and severity of neurocognitive abnormalities in volatile substance abuse and, perhaps more importantly, studies designed to

investigate whether neurocognitive function is fully restored with abstinence from volatile substance abuse.

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