Somatosensory evoked potentials in workers exposed to toluene and styrene

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Abstract

Somatosensory evoked potentials (SEPs) were used to evaluate possible subclinical impairment of the nervous system due to occupational exposure to toluene and styrene. A group of 36 rotogravure printers with severe exposure to toluene, 20 workers with severe exposure to styrene in a glass laminate manufacturing plant, and a comparison group of healthy subjects were studied. The severity of exposure was documented by measurements of toluene and styrene concentrations in breathing zone air, by hippuric acid concentration in urine in the group exposed to toluene, and by urinary mandelic acid concentration in the group exposed to styrene. Somatosensory evoked potentials were measured by stimulation of the median nerve at the wrist and the tibial nerve at the ankle. Peripheral conduction velocities (CVs) in both extremities and central conduction time (CCT) after tibial nerve stimulation were significantly decreased in both exposed groups. Significantly prolonged latencies of peripheral and cortical SEPs to median nerve stimulation as well as cortical SEPs to tibial nerve stimulation were found in workers exposed to styrene. Some abnormalities in SEPs at peripheral or spinal and cortical levels were found in eight workers exposed to toluene and six workers exposed to styrene. Of these, in three workers exposed to toluene and two to styrene increased CCT and delayed latencies of cortical responses at normal conduction values in the periphery were found. A trend for increased frequency of abnormal SEPs with duration of exposure to toluene and styrene and alcohol abuse was found.

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Abnormalities in SEPs in the exposed groups are most probably of multifactorial origin. Central SEP abnormalities in both exposed groups could indicate early signs of subclinical dysfunction at spinal and cortical levels and could be due to toluene or styrene exposure probably potentiated by alcohol consumption in the group exposed to toluene.

The development of neurophysiological and neurochemical tests enables detection of neurotoxic effects at early stages and at low levels of exposure to different chemicals. Consequently chronic and less readily noticed adverse effects caused by long-term exposure have become of primary interest in occupational medicine especially where improvements of working conditions have led to decreased prevalence of acute and severe intoxication.

Toluene and styrene are well known neurotoxic organic solvents widely used in industrial and occupational settings. Their adverse acute and chronic effects on the morphology and function of the nervous system have been documented in several experimental and clinical studies.[1-7] Various psychological and neurophysiological tests including electroencephalography, electromyography, and evoked potentials have been used for detection of possible impairment of the nervous system. Sensory evoked potentials, one of the non-invasive neurophysiological methods, enables the evaluation of functional integrity of all sensory pathways[8-9] and it reflects activity at the level of neural generators from the peripheral end organ to the higher integrative centres of the brain. Several authors[10-15] recommend the use of this method in neurotoxicology for detection of possible subclinical lesions of the nervous system. Various reports have described changes in visual evoked potential and brainstem auditory evoked potential due to acute and chronic exposure to organic solvents in experimental[16-18] as well as in clinical[19-20] studies.

In our study we used somatosensory evoked potentials (SEPs) for detection of possible subclinical impairment at the somatosensory pathway.

This method enables a more exact localisation of expected dysfunction at peripheral, subcortical, and cortical levels.

Materials and methods

STUDY POPULATIONS

Group 1: exposed to toluene
Thirty six male rotogravure printers exposed to toluene in a polygraphic plant in Prague were enrolled. Their age ranged from 19 to 68 (mean 39 (SD12)) years. Most (75%) were exposed to toluene for more than five years, with a maximum of 41 years (mean 12 years).

The extent of exposure was documented by (1) measurement of toluene concentration in the worker's breathing zone air. The mean value for the period 1977–87 was about 2000 mg/m³ (threshold limit value 200 mg/m³ with a peak of 1000 mg/m³); (2) by hippuric acid concentration in urine measured in samples collected at the end of each shift. This test represents a biological marker for toluene. The mean yearly value for the decade was about 45 mmol/l after correction for 1020 g/l standard density of urine. The normal limit is 14 mmol/l.

Group 2: exposed to styrene
A group of 20 workers exposed to styrene in a factory making glass laminates was studied. This group consisted of five men aged 24 to 48 (mean 38(SD9)) years and 15 women aged 31 to 51 (mean 45 (SD6)) years. Most (85%) were exposed to styrene for more than five years with a maximum of 22 years (mean 11 years). The exposure was documented by measurement of styrene concentration in the worker's breathing zone air and by mandelic acid concentration in urine as a biological marker for styrene. The mean year round value of styrene concentration in the air for the period 1980–9 ranged from 140 to 570 mg/m³ with a peak of 1250 mg/m³. The overall limit per eight hour shift is 200 mg/m³ with a maximal peak of 1000 mg/m³. Mandelic acid concentration in urine (samples taken at the end of the shift) ranged from 200 to 1400 μmol/mmol creatinine (biological limit is 246 μmol/mmol of creatinine).

A detailed history was obtained followed by neurological examination and testing of SEPs for each worker.

Group 3: the comparison group
The comparison consisted of 30 male (aged 16 to 64, mean 31 (SD11) years) and 40 female volunteers (aged 16 to 52, mean 32 (SD11) years) without known exposure to any neurotoxic agent. They had no history of or clinical findings of neurological disorders during examination.

MEASUREMENTS OF SOMATOSENSORY EVOKED POTENTIALS

A Neuromatic 2000 DISA was used for SEP examination. Electric stimuli (0·2 ms duration constant current square wave pulses, frequency 5 Hz) were delivered to the right median and tibial nerves at the wrist and at the ankle respectively, at an intensity producing a visible thumb or toe twitch. The stimulating electrode was positioned with the cathode placed proximally. The low frequency filter of the amplifier was set at 10 Hz and the high frequency filter at 5000 Hz. Evoked responses from 300 to 600 stimuli were averaged and each procedure was repeated. The analysis time was 20–50 ms in the right median nerve stimulation and 50–100 ms in tibial nerve stimulation.

The derivations used in the right median and tibial nerve stimulation were: Erb's point-Fz, C6-Fz, C3'-Fz, L1-Th12, and Cz'-Fz.

The following peak latencies, amplitudes, peripheral conduction time (PCT), and central conduction time (CCT) were calculated: N10, N13, N20 and late cortical components, N10–N13 (PCT), N10–N20, N13–N20 (CCT) for median nerve stimulation; N22, N33, P40 and late cortical components, N22–N33 and N22–P40 (CCT) for tibial nerve stimulation,[21] and amplitudes of primary cortical responses (N20 and P40).[22] The median nerve CV was calculated as the distance from the stimulating cathode to Erb's point over latency of N10.[23] The tibial nerve CV was calculated as the distance from L1 to the floor over latency of N22. Figure 1 shows samples of normal median and tibial nerve SEPs.

STATISTICAL ANALYSIS

The significance of differences of the mean values of study variables in the exposed and control groups were calculated with the Student's *t* test. Differences in latencies related to sex, age, height, and study group were assessed by multiple regression analysis. Where applicable the test for trend was used.[27]

Results

HISTORY AND CLINICAL NEUROLOGICAL EXAMINATION

In the workers exposed to toluene and styrene neurasthenic symptoms (for example, sleep disturbances, fatigue, occasional headache) occurred in 35% and 30% respectively. Mental disorders (forgetfulness, lability of mood, irritability) were reported in 5% and 10%. Back pain was reported by 60% of the groups exposed to styrene, consisting predominantly of women, whereas only 20% of such discomfort occurred in the group exposed to toluene. This significant difference may be attributed to a different work load. In the group exposed
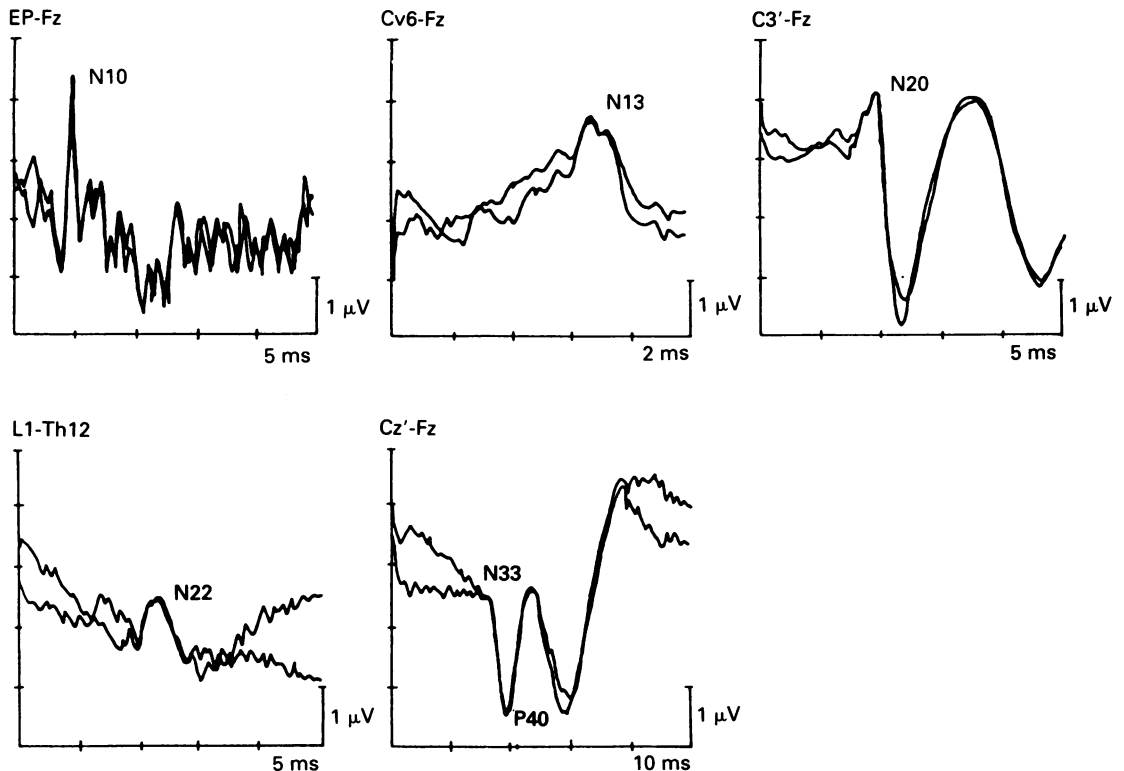
Figure 1 *Normal SEP curves in a healthy subject. Peripheral (EP-Fz), cervical (Cv6-Fz), and cortical (C3'-Fz) SEPs after stimulation of the median nerve at the wrist, and spinal (L1-Th12) and cortical (Cz'-Fz) SEPs after stimulation of the tibial nerve were recorded. The major components are marked (28 year old woman, 180 cm height).*

to styrene elbow pain was reported in 10% and paresthaesia of the second and third fingers of the right hand in 25% whereas no such complaints occurred in the other exposed group.

Findings of neurovegetative lability (finger and eyelid tremors, increased dermographism, hyper-reflexia, hyperhidrosis) were found in 50% of both exposed groups. Bilaterally decreased Achilles tendon reflexes were found in 20% of the group exposed to toluene and 10% of group exposed to styrene. Slight carpal tunnel signs were found in 15% of workers exposed to styrene. Subjective symptoms were not reported by 50% of workers exposed to toluene and 25% of workers exposed to styrene.

Drinking habits for all groups were categorised by the reported alcohol intake (table 1). Excessive daily intake of alcohol did not occur in any person of the comparison group. Thirteen workers exposed to toluene reported a daily alcohol intake exceeding 50 mg.

ASSESSMENT OF SEP FINDINGS
Differences in latencies for sex, age, height, and left and right site were computed for the comparison

group. For all components of latencies correlation with height was found to be highly significant after adjustment for other variables. Sex and site related differences were significant in most cases. Consequently the comparison group was subdivided into men and women and the SEP responses from the right side were used as standards. There were no height related changes for conduction times. For standard evaluation of differences in latencies the height was used. There were statistically significant differences in length of arms and legs between exposed and comparison groups. Therefore extrapolation from latency of N10 and N22 was used for computation of conduction velocity. For interpretation of the results of this study, the SEP response was considered abnormal if at least one of the following variables exceeded its 95% reference range: wave latencies (peripheral N10 and spinal N22, cervical N13, cortical N20, N33, and P40 waves), conduction times (PCT, CCT), and conduction velocities. The amplitudes of normal cortical SEP components showed considerable variability; consequently the amplitude was not used for interpretation of an abnormal response.[25] We divided the abnormal SEP findings into three categories: the

Table 1   Daily alcohol intake in the comparison group and in workers exposed to toluene or styrene

Daily alcohol intake (mg)	Comparison group		Exposed to toluene		Exposed to styrene	
	No	(%)	No	(%)	No	(%)
< 20 mg	64	(92)	14	(39)	16	(80)
20–50 mg	5*	(7)	9	(25)	2†	(10)
> 50 mg	1	(1)	13	(26)	2	(10)

Note: *Two women; †one woman

"peripheral" type consisting mainly of decreased peripheral CV with corresponding prolongation of peripheral N10 and spinal N22 as well as decrease in their amplitude. The "central" type was characterised mostly of delayed CCT, prolongation of cortical latencies, and decrease of their amplitude with normal responses at the periphery. The third type was a combination of both peripheral and central types.

The group exposed to toluene
Eight persons exposed to toluene had abnormal SEPs. Of these, three workers had an impairment of the peripheral NS ("peripheral" type) (CV for median nerve 55·4 m/s, CV for tibial nerve 44·4 m/s). Three workers had an impairment of the central segment ("central" type) (CCT for tibial nerve 15·3 m/s). Abnormalities of both peripheral and central SEP pathways were found in two workers (CV for median nerve 51·8 m/s, CV for tibial nerve 41·7 m/s, CCT for tibial nerve 15·0 ms). Table 2 shows the correlation of abnormal SEPs with duration of exposure to toluene. There was a significant trend of increasing frequency of abnormal SEPs with duration of exposure to toluene. A similar correlation was found with alcohol intake (table 3): again a significant trend was

found between alcohol intake and abnormal SEPs. Figure 2 shows an abnormal SEP finding. Tables 4 and 5 present comparisons of mean values of median and tibial nerve SEPs in the group of workers exposed to toluene, and in the comparison group. The results were similar after adjustment for the potential confounding variables sex, age, height, and differences among groups in multiple regression analysis. Decreased peripheral CVs for median and the tibial nerve stimulation were statistically significant. Delayed CCT for tibial nerve stimulation was also significant.

The group exposed to styrene
Six persons had abnormal SEPs. Of these, two had SEP abnormalities of the "peripheral" type (CV for median nerve 56·4 m/s, CV for tibial nerve 49·2 m/s), two had SEP abnormality of the "central" type (CCT for tibial nerve 20·4 m/s), and two subjects had an impairment in all SEP pathways (CV for median nerve 56·4 m/s, CV for tibial nerve 49·2 m/s, CCT for tibial nerve 14·8 m/s). The trend in correlation of SEP abnormalities with duration of exposure to styrene did not reach statistical significance (table 6). Increased alcohol intake in this group occurred in four persons only (see table 1); alcohol intake did not correlate with response to styrene. Figure 3 shows an example of abnormal SEP curves.

Tables 4 and 5 show the median and tibial nerve SEPs in the workers exposed to styrene and their comparison group. The major significant abnormalities were prolonged latencies of N10, P13, and cortical components of N20, P22, and P27 for median nerve stimulation and N33 and late cortical components for stimulation of the tibial nerve. Decreased peripheral CV for median and tibial nerve stimulation and delayed CCT for the tibial nerve stimulation were also significant.

EP-Fz   Cv6-Fz   C3'-Fz

N12·4   N21·4

                                N15·6

1 μV   1 μV   1 μV

5 ms   3 ms   5 ms
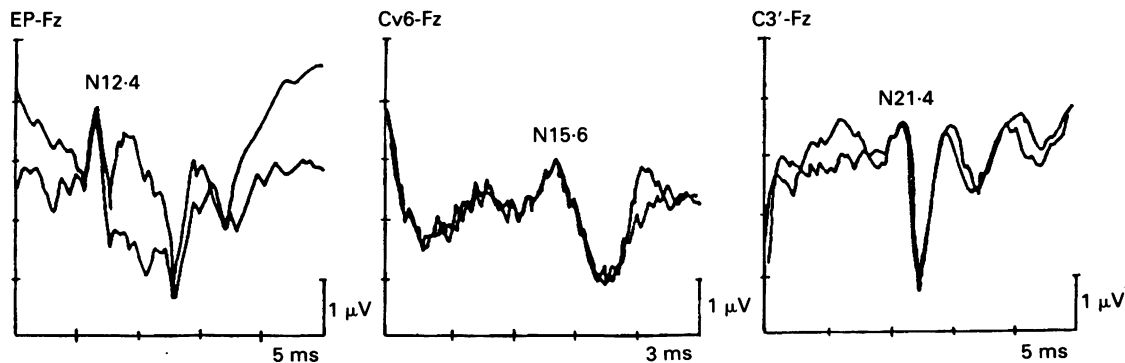
Figure 2   Abnormal SEP curves after median nerve stimulation showing an impairment of the peripheral part of the somatosensory pathway. Prolonged latency of N10 (12·4 ms) is followed by prolongation of cervical N13 (15·6 ms) and cortical N20 (21·4 ms) responses. Conduction times (N10–N13 and N13–N20 are in the normal range (35 year old male alcohol abuser, 180 cm height, exposed to toluene for four years).

Table 2 Abnormal SEP findings in relation to duration of exposure to toluene

	Somatosensory evoked potentials			
Exposure (y)	Normal No	Abnormal No	(%)	
0–4	9	1	(10)	
5–14	11	3	(21)	t = 2·11*
15 and more	5	7	(58)	p < 0·01

*Test of trend was used

Table 3 Abnormal SEP findings in relation to daily intake of alcohol in the group exposed to toluene

	Somatosensory evoked potentials			
Daily alcohol intake (in mg)	Normal No	Abnormal No	(%)	
< 20 mg	12	2	(17)	
20–50 mg	7	2	(22)	t = 2·06*
> 50 mg	6	7	(54)	p < 0·01

*Test of trend was used

Discussion

An abnormal response of the nervous system to stimuli is non-specific for the aetiology of dysfunction. In our study abnormal SEPs were found in subjects exposed to severe exposure to toluene and styrene, mostly without any subjective complaints or objective neurological symptoms of impairment of the nervous system.

The median and tibial nerve SEPs in groups exposed to toluene or styrene showed a statistically significant decrease in peripheral CVs. Increased latencies of median SEP were found in workers exposed to styrene but not in workers exposed to toluene. These findings suggest impairment of the peripheral nervous system. Some authors consider such impairment to be due to chronic exposure to styrene.[26 27] Kovařík et al[28] found slight distal sensitive motor neuropathies by electromyography in 28·5% of workers exposed to styrene. They excluded any other professional or non-professional

causes of these electromyography findings. Cherry and Gautrin[29] reported a mild sensory nerve conduction deficit increasing from 23% to 71% depending on exposure of less than 50 ppm to more than 100 ppm styrene. By contrast, Triebig et al[30] found no significant differences in motor and sensory nerve conduction velocities between workers exposed to styrene and controls. Our group exposed to styrene consisted predominantly of women working daily with excessive strain on their right hand. The abnormal findings could be because women may be more sensitive to adverse effects of toxic substances or excessive strain on the hands combined with neurotoxic exposure could lead to compressive ischaemic neuropathy (for example, carpal tunnel syndrome). A direct neurotoxic effect of styrene on the peripheral nervous system is also possible.

The workers exposed to toluene had more SEPs with decreased peripheral CVs during stimulation of the tibial nerve. These findings, with slight clinical signs of impairment of the peripheral nervous system (hyporeflexia of Achilles tendon reflexes) suggest an incipient polyneuropathy associated with prolonged exposure to other neurotoxic substances, for example, alcohol. Increased alcohol consumption among workers exposed to organic solvents is well known.[3 31] A possible interaction of both neurotoxic substances in humans is supported by a study of metabolic interaction between toluene and ethanol in rabbits, which showed an inhibitory effect of ethanol on excretion of toluene.[32]

Significant prolongation of CCT occurred after stimulation of the tibial nerve in both exposed groups. There were no significant changes registered for CCT of median nerve SEPs. Similar changes in SEPs were reported in chronic alcoholic patients.[33] The SEP pathway consists of very long fibres from periphery through the dorsal columns and therefore it is considered to be more vulnerable to exposure to neurotoxic substances.[15 34 35] Chang[36] stated that both the absolute latencies and CCT in median nerve SEPs were delayed in cases of sub-

Table 4 Somatosensory evoked potentials (mean (SD)) to median nerve stimulation in men exposed to toluene, woman exposed to styrene, and their corresponding comparison groups

Parameter	No	Comparisons	No	Exposed to toluene	No	Comparisons	No	Exposed to styrene
N10 (ms)	23	10·3 (0·7)	35	10·5 (0·8)	32	9·3 (0·4)	15	9·7 (0·5)*
N13 (ms)	23	14·0 (0·7)	35	14·1 (0·8)	30	12·5 (0·5)	15	13·0 (0·6)*
N20 (ms)	29	19·7 (0·9)	35	19·7 (0·8)	40	18·2 (0·7)	15	18·9 (1·0)*
P22 (ms)	28	23·2 (0·9)	35	23·4 (0·8)	40	21·3 (0·9)	12	21·8 (0·9)
P27 (ms)	22	28·2 (2·1)	27	28·3 (2·4)	30	25·9 (1·6)	9	28·0 (2·7)*
N35 (ms)	24	35·1 (2·3)	33	34·9 (2·0)	36	34·5 (4·0)	10	34·5 (4·0)
P45 (ms)	26	43·7 (2·2)	24	43·7 (2·6)	26	43·8 (2·9)	11	40·2 (4·4)*
Ampl. N20 (μV)	29	5·4 (3·3)	36	4·0 (2·2)	40	4·4 (2·4)	15	4·2 (3·0)
N10–N13 (ms)	23	3·6 (0·4)	35	3·6 (0·6)	26	3·2 (0·3)	15	3·3 (0·5)
N13–N20 (ms)	23	5·8 (0·6)	35	5·6 (0·6)	30	5·7 (0·5)	15	5·9 (1·0)
N10–N20 (ms)	23	9·2 (0·5)	35	9·4 (0·6)	30	8·9 (0·5)	15	9·2 (0·6)
Peripheral CV (m/s)	23	65·1 (3·1)	35	59·4 (4·6)**	28	63·1 (2·5)	15	58·7 (2·1)**

*p < 0·05; **p < 0·01.

Table 5 Somatosensory evoked potentials to tibial nerve stimulation in men exposed to toluene, women exposed to styrene, and their corresponding comparison groups

Parameter	No	Comparisons	No	Exposed to toluene	No	Comparisons	No	Exposed to styrene
N22 (ms)	24	23·1 (1·4)	19	23·8 (1·6)	40	21·7 (1·6)	15	22·2 (1·2)
N33 (ms)	28	34·5 (2·1)	34	36·0 (2·4)	40	32·6 (1·7)	15	35·0 (2·2)*
P40 (ms)	28	41·0 (2·1)	34	41·4 (2·6)	40	38·1 (2·7)	14	39·5 (2·2)
N50 (ms)	26	49·4 (2·3)	34	50·3 (2·9)	38	46·4 (3·3)	12	48·4 (3·4)
P70 (ms)	26	61·3 (2·7)	34	61·7 (3·4)	40	57·8 (3·6)	12	59·5 (2·7)
N80 (ms)	26	75·1 (6·3)	33	75·9 (4·4)	40	74·1 (6·1)	12	76·0 (3·5)
Ampl. N20 (μV)	25	2·2 (1·1)	34	2·1 (1·1)	40	2·2 (1·1)	12	1·7 (1·1)
N22–N33 (ms)	24	11·1 (1·2)	18	13·0 (1·9)*	39	10·8 (1·2)	13	12·8 (2·3)
N22–P40 (ms)	24	17·2 (1·7)	18	18·4 (2·0)	35	16·4 (2·0)	12	17·1 (2·5)
Peripheral CV (m/s)	24	49·5 (2·2)	19	47·0 (3·0)**	28	50·5 (2·4)	13	48·3 (2·9)**

$*p < 0.05; **p < 0.01.$

Table 6 Abnormal SEP findings in relation to duration of exposure to styrene

	Somatosensory evoked potentials			
	Normal	Abnormal		
Exposure (y)	No	No	(%)	
0–4	3	0	(0)	
5–14	7	5	(42)	t = 1·56*
> 15	2	3	(60)	NS

*Test of trend was used

clinical and n-hexane polyneuropathy. The same author interpreted the decreased CCT as electrophysiological evidence for a neurotoxic effect of n-hexane on the spinal cord or the brainstem. Kokubun et al[37] reported similar delayed CCT during stimulation of the tibial nerve in chronic alcoholic patients with or without polyneuropathy and

suggested that the impairment of posterior columns and brainstem could be due to ethanol myelopathy. Moller et al[38] reported abnormalities in the central auditory pathways in workers exposed long-term to styrene. In our study both exposed groups showed an impairment of spinal or subcortical somatosensory pathways. This could be related to a neurotoxic effect of organic solvent, or ethanol, or both on dorsal columns or brainstem.

Hazemann et al[39] found similar SEP findings in workers exposed to a mixture of organic solvents (mean exposure duration was 12 years). Decreased peripheral nerve CV, slight increased latencies of late cortical components (N20, P22, N35) after stimulation to the median nerve, and late cortical components (P39, N50) after stimulation of the tibial nerve were obtained. The duration of exposure and its effect on SEP was not reported.
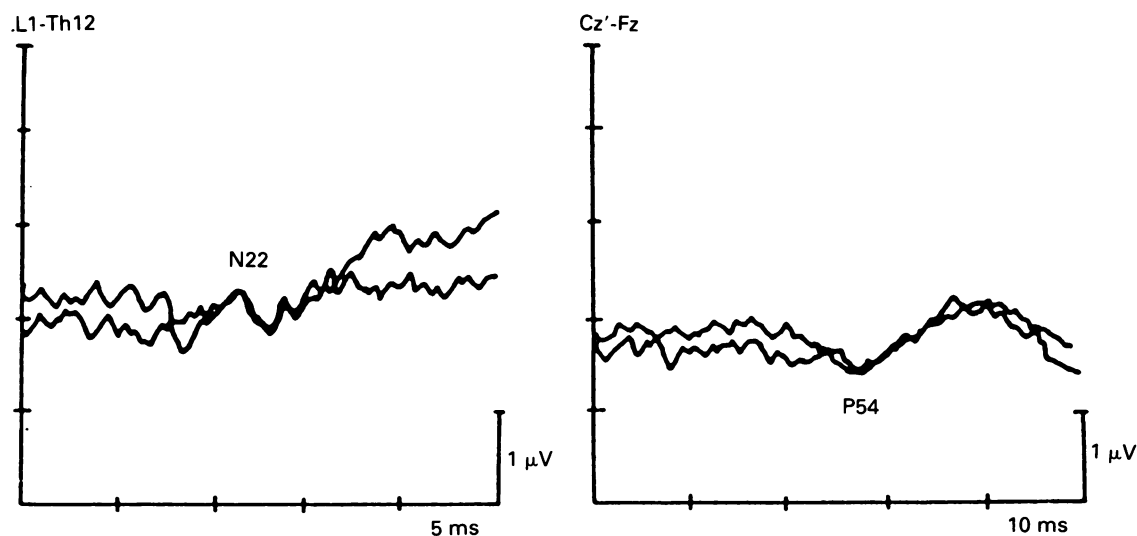

Figure 3 Abnormal SEP curves after tibial nerve stimulation showing an impairment of the central part of the somatosensory pathway. Spinal response N22 (22 ms) is in the normal range. Abnormal prolongation of latency of cortical response P40 (54 ms) with deformation of waveform and abnormal prolongation of central conduction times N22–P40 (32 ms) are presented (43 year old woman, 154 cm height, occasionally abusing alcohol, with a history of 14 years exposure to styrene).

Nevertheless we were able to show a significant correlation of the duration of exposure to the organic solvent or to alcohol intake with abnormal SEP findings.

Prolonged latencies and reduced amplitudes of cortical SEP responses have been reported by several authors. Langauer-Lewowicka et al[40] found prolonged latency and increased amplitude of N20 in workers exposed to carbon disulphide. On the other hand, Mutti et al[41] showed significantly prolonged latencies of N20 and N26 in 15 women exposed to n-hexane but the late phase (N41-N75) of cortical responses after stimulation of the median nerve led to decreased amplitudes. In our study there was a trend towards the prolongation of latencies of cortical SEP components but it did not reach statistical significance. The neurotoxic effect of styrene and toluene on the central nervous system is well known. The neurochemical and structural bases in humans are not known. Rosengren and Haglid[42] reported, from animal study, that exposure to styrene at moderate concentrations induced regional and long lasting astroglial reactions that served as an indicator of solvent induced brain damage. In rabbits a decrease in striatal concentration of dopamine due to exposure to styrene was shown.[43] A role for toluene in the induction of oxidative stress in the central nervous system was reported.[44] Rosenberg et al[45] showed diffuse changes in white matter of the central nervous system by magnetic resonance imaging in toluene abusers. Abnormal cortical SEP responses detected in our workers could be interpreted as early signs of toxic encephalopathy due to chronic exposure to neurotoxins (the organic solvent syndrome[46]).

The presented study shows evidence of functional impairment at all somatosensory pathways indicative of potential toxic polyneuropathy, myelopathy, or encephalopathy due to chronic exposure to neurotoxic agents (organic solvents, alcohol, a combination of both, predisposition, etc.). The SEP seems to be a useful method for screening and monitoring workers exposed to neurotoxic substances and should be included in the battery of electrophysiological tests to increase the sensitivity of detection of early dysfunction of the nervous system.[47]

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