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N-hexane neuropathy in offset printers

C M Chang, C W Yu, K Y Fong, S Y Leung, T W Tsin, Y L Yu, T F Cheung, S Y Chan

Abstract

In an offset printing factory with 56 workers, 20 (36%) developed symptomatic peripheral neuropathy due to exposure to n-hexane. Another 26 workers (46%) were found to have subclinical neuropathy. The initial change in the nerve conduction study was reduced amplitude of the sensory action potentials, followed by reduced amplitude of the motor action potentials, reduction in motor conduction velocities and increase in distal latencies. These changes indicate primary axonal degeneration with secondary demyelination. Sural nerve biopsy in a severe case showed giant axonal swellings due to accumulation of 10nm neurofilaments, myelin sheath attentuation and widening of nodal gaps. The development of neuropathy bore no direct relationship to the duration of exposure, hence factors such as individual susceptibility may be important. Optic neuropathy and CNS involvement were uncommon and autonomic neuropathy was not encountered.

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N-hexane, present in many commonly used organic solvents, is known to cause peripheral neuropathy.[1] Outbreaks have been reported in laminating,[2 3] pharmaceutical,[4] sandal and shoe making,[5–9] furniture production[10] and adhesive bandage manufacturing[11] industries.

In the printing industry, n-hexane is used to remove residual colouring agents on the roller and has caused two outbreaks of neuropathy in the past.[12 13] We report our investigation on the clinical, electrophysiological and pathological features of n-hexane neuropathy in a printing factory.

Materials and methods

Following the diagnosis of peripheral neuropathy in the index case, the factory was inspected by a team of occupational health experts. Samples of commonly used chemicals and solvents were obtained. Under normal operating conditions, air samples were collected on two different days, each over 60 to 90 minutes (about four to six job cycles) by standand charcoal tube method with low flow sampling pumps. All liquid and air samples were analysed by high performance gas chromatography. The Time Weighed Average (TWA) air concentration of organic vapours were computed from the amount determined by gas chromatography and the calculated volume of the air sampled. All staff members of the offset printing department were seen by an occupational health physician and then by a neurologist. Standard questionnaires were administered, general and neurological examinations were performed, full blood counts, ESR, renal and liver function tests, and blood glucose were checked in all. Serum lead level and red blood cell delta aminolaevulinic acid (d-ALA) dehydratase activity were measured in the first three affected workers only. Standard nerve conduction study of the right upper and lower limbs and pattern reversal visual evoked potential study (VEP) were performed in all. The results were compared with 20 age and sex matched normal controls. Statistical analysis was carried out on a standard personal computer, using the Statistical Package for Social Sciences. Dunnett's t test was employed after analysis of variance. A p-value of $<0{\cdot}05$ was considered significant.

Results

The factory was situated on a multi-storey building with a floor area of 2000 m^2 and a floor height of 4 m. There were 17 offset printing machines placed on two floors.

There were no MSDS sheets on substances available in the factory, as the law did not require it. Cleaning solvents, such as, petroleum spirit and white gasoline were stored in large containers. They were used for manual cleaning of ink stains and dirts on rubber roller blankets, ink rollers, ink containers and zinc plates. The word n-hexane, a symbol for harmful substance, and a brief description on general precautions were printed on the container labels but the percentage of n-hexane was not specified. Analysis by gas chromatography revealed that they contained 14–20% n-hexane. These solvents and the emusifying oil, kerosene, diesel and solvent blend also contained a variable percentage of toluene but no methyl n-butyl ketone (MBK) or methyl ethyl ketone (MEK). The moistening solutions contained only trace amounts of phosphate at 42 ppm. The printing inks contained $0{\cdot}6–8{\cdot}2\ \mu g/g$ lead, $<0{\cdot}05–0{\cdot}95\ \mu g/g$ mercury and no volatile organic compound.

Dilution ventilation was provided by air distribution ducts of air conditioning units. These were recycling units with limited fresh

University of Hong Kong, Hong Kong Department of Medicine
C M Chang
K Y Fong
Y L Yu
T F Cheung

Department of Pathology
SY Leung

Occupational Health Division, Labour Department, Hong Kong Government, Hong Kong
C W Yu
T W Tsin
S Y Chan

Correspondence to:
Dr Chang, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

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Table 1 Symptoms and signs in 20 patients with n-hexane neuropathy

	Number (%)	
	Upper Limbs	*Lower Limbs*
Numbness	8 (40)	14 (70)
Paraesthesiae	5 (25)	13 (65)
Pain	2 (10)	9 (45)
Cramp	1 (5)	8 (40)
Weakness	7 (35)	15 (75)
↓Pain	2 (10)	6 (30)
↓Light Touch	1 (5)	4 (20)
↓Vibration	1 (5)	5 (25)
↓Joint position	0 (0)	1 (5)
Proximal wasting	1 (5)	2 (10)
Distal wasting	2 (10)	4 (20)
Proximal weakness	1 (5)	3 (15)
Distal weakness	3 (15)	5 (25)
Hyporeflexia	9 (45)	9 (45)

air intakes from passive air inlets. Only two local exhausts and one window mounted fan were installed.

The offset machine workers worked 12 hours per day, 6 days per week. The mean duration of employment was 2·6 years (range 1 month to 12 years) in this printing factory and 6·4 years (range 1 month to 30 years) in the printing trade. Using cloths or sponges soaked with cleaning solvents, they cleaned the rubber roller blankets manually two to three times every hour, each time lasting two to five minutes.

The background TWA air concentrations were 30 to 110 ppm (mean 63 ppm) for n-hexane, 57 to 340 ppm (mean 130 ppm) for isopropyl alcohol (IPA) and 11 to 46 ppm (mean 26 ppm) for toluene. The TWA figures were higher in the personal air samples from the offset machine workers, 80 to 210 ppm (mean 132 ppm) for n-hexane, 20 to 680 ppm (mean 235 ppm) for IPA, and 20 to 84 ppm (mean 50 ppm) for toluene.

Five managerial staff were examined and found to be unaffected clinically or electrophysiologically. Fifty seven offset machine workers were investigated, but one worker with peripheral neuropathy was excluded because of alcoholism and diabetes mellitus. The remaining 56 workers were males with a mean age of 27 years (range 16 to 43); only one was aged over 40. Twenty five were smokers and 15 (27%) had mild alcohol consumption (one to two cans of beer daily). None of them had a history of alcoholism or diabetes mellitus. Fifty one workers (91%) wore gloves but none wore respirators at work.

Twenty workers (36%) had both clinical and electrophysiological evidence of peripheral neuropathy. Thirty six workers were asymptomatic and normal on examination but 26 (72%) had abnormalities in their NCS and hence subclinical neuropathy. There was no correlation between the development of neuropathy and the length of employment in printing. Nine workers (16%) developed neuropathy just a few months after exposure while five (9%) remained healthy four to eight years after exposure.

In the 20 patients with symptomatic peripheral neuropathy (table 1), the initial symptoms were most frequently numbness, followed by paraesthesiae, pain and weakness of the feet and distal part of the legs. Sensory disturbances usually preceded motor disturbances and lower limbs were affected earlier than upper limbs. However, in four workers who did not wear gloves, the earliest symptom was numbness in the hands and fingers. Symptoms developed retrogradely and ascended the limbs as the neuropathy progressed. Fourteen workers with mild neuropathy had only sensory disturbances while five with moderate and one with severe neuropathy had weakness and muscular atrophy in addition. The coasting phenomenon (initial deterioration of the neuropathy even after removal from exposure) was present in three workers.

In the electrophysiological evaluation (table 2), the control subjects and workers were males and their ages were comparable. In the asymptomatic healthy workers, the absolute values of the NCS were within normal ranges. However, the mean median nerve sensory action potential (SAP) was significantly reduced when compared with controls, while mean SAP amplitudes of the ulnar and

Table 2 Nerve Conduction Study

		Asymptomatic		
	Control n = 20	*Healthy worker n = 10*	*Subclinical n = 26*	*Symptomatic n = 20*
Age (years)	26·9 (4·4) (20–35)	25·8 (6·4) (16–37)	26·7 (7) (17–43)	28·2 (5·8) (16–38)
Amplitudes of SAP (uV)				
Median	37 (11) (20–65)	27 (6)* (20–40)	24 (8)* (11–41)	15 (5)* (5–24)
Ulnar	15 (4) (8–22)	14 (3) (10–18)	12 (5) (5–24)	7 (4)* (0–15)
Sural	24 (10) (12–45)	22 (6) (15–35)	18 (7)* (2–40)	11 (8)* (0–34)
Amplitudes of MAP (mV)				
Median	7 (2) (3–11)	8 (3) (4–13)	6·7 (2·4) (3·2–12·5)	4·6 (2·2)* (1·1–8)
Ulnar	5·7 (2·1) (2·8–10)	6·5 (1·9) (4–10)	4 (2·2)* (1–8)	3·6 (1·5)* (0·9–6)
Posterior tibial	6·6 (2) (3·5–11)	6·7 (2·3) (5–12)	5·3 (2·5) (2·2–15)	2·9 (1·7)* (1–7)
Common peroneal	4·4 (1·5) (2–7)	4·3 (1·4) (3–7)	3·6 (1·4) (1·5–7)	1·8 (1·4)* (0·25–6)
Distal Latency of SAP (ms)				
Median	2·3 (0·3) (1·9–2·8)	2·3 (0·1) (2·1–2·5)	2·6 (0·3)* (2·2–3·2)	2·9 (0·3)* (2·4–3·8)
Ulnar	2·1 (0·3) (1·7–2·8)	2·1 (0·1) (1·9–2·3)	2·3 (0·3) (1·9–3·1)	2·7 (0·4)* (2·0–3·5)
Sural	3·3 (0·3) (2·8–3·6)	3·1 (0·2) (2·8–3·3)	3·3 (0·3) (2·8–4·2)	3·7 (0·6)* (2·3–4·6)
Distal Latency of MAP (ms)				
Median	2·9 (0·4) (2·3–3·8)	3·0 (0·2) (2·7–3·3)	3·6 (0·5)* (2·8–4·8)	4·3 (1·2)* (2·6–7·2)
Ulnar	2·2 (0·3) (1·8–2·8)	2·3 (0·3) (2·1–2·8)	2·6 (0·5)* (2·0–3·9)	3·0 (0·7)* (2·2–4·5)
Posterior tibial	4·1 (0·6) (3·2–5·2)	3·9 (0·6) (3·1–4·8)	4·4 (0·6) (3·2–5·8)	5·6 (1·2)* (3·4–8·4)
Common peroneal	3·9 (0·5) (3·3–4·7)	3·5 (0·4) (3·0–4·2)	4·2 (0·7) (3·0–5·5)	5·4 (1·2)* (3·5–8·8)
Motor Conduction Velocity	(m/s)			
Median	59 (5·9) (48–68)	57 (5) (48–65)	55 (6·7)* (43–73)	46 (6·5)* (37–57)
Ulnar	61 (5·8) (44–69)	59 (6) (52–71)	55 (7·8)* (44–79)	48 (7·5)* (38–69)
Posterior tibial	50 (6·4) (41–66)	46 (3·4) (41–51)	45 (4·7)* (36–55)	38 (6·5)* (26–51)
Common peroneal	51 (4·5) (43–63)	46 (3·8) (40–53)	45 (5·1)* (36–56)	37 (7·1)* (26–54)

Mean (SD) (Range)
*$p < 0·05$ compared with control.

Table 3 Number (%) of workers with other abnormalities

	Symptomatic peripheral neuropathy n = 20	*Subclinical peripheral neuropathy n = 26*	*Asymptomatic healthy worker n = 10*
Systemic upset*	11 (55)	5 (19·2)	0 (0)
Subclinical optic neuropathy**	2 (10)	3 (11·5)	0 (0)
Autonomic neuropathy***	0 (0)	0 (0)	0 (0)
CNS symptoms****	5 (25)	0 (0)	0 (0)
CNS signs*****	2 (10)	0 (0)	0 (0)
Abnormal liver function test	0 (0)	1 (3·8)	1 (10)

*Weight loss >5 lb, anorexia.
**Delayed P100 latency in VEP.
***Postural hypotension, impotence, urinary difficulty, constipation, diarrhoea, anhidrosis, hyperhidrosis.
****Headache, deteriorating memory, drunken feeling, vertigo.
*****Hyperreflexia.

sural nerves and mean motor conduction velocities (MCV) also showed a decremental trend.

In the asymptomatic subclinical group, more marked reduction in mean SAP amplitudes and MCV was encountered. In addition, mild reduction in mean motor action potential (MAP) amplitudes and mild prolongation in mean distal latencies (DL) of SAP and MAP were also found.

In the symptomatic group, reduction in mean SAP, MAP amplitudes and MCV were marked while prolongation in mean DL of SAP and MAP were also obvious.

Other neurological and systemic abnormalities were listed in table 3. Most of these abnormalities occurred in workers with symptomatic neuropathy. Full blood picture, ESR blood glucose and renal function tests were normal in all 56 workers. Serum lead and red blood cell d-ALA dehydratase levels were normal in the three workers studied.

INDEX CASE

A 30 year old male printer from Mainland China came to Hong Kong in 1989. In August 1990, he was employed by the offset printing factory and his work involved regular cleaning of the rubber roller blanket with organic solvents. He did not wear protective gloves or a respirator at work. Six months later, he developed numbness and painful paraesthesiae in both legs, followed by weakness and muscle wasting. The upper limbs were also affected one month later. Despite stopping work, his symptoms deteriorated over the next two months. He did not consume alcohol or smoke and his past health was good. Some of his fellow workers experienced similar symptoms and the most severely affected one was wheel-chair bound and had returned to China.

On examination, he had a typical sensorimotor peripheral neuropathy, more severe in the lower than the upper limbs. There were severe distal and mild proximal wasting and weakness and glove and stocking sensory impairment to all modalities and hyporeflexia. The FBC, ESR, routine RFT, LFT, fasting blood glucose, serum and RBC vitamin B12 and folate levels, antinuclear and anti-DNA antibodies, serum complements, serum immunglobulin levels and immunoelectrophoresis, serum lead and other heavy metal screen, RBC d-ALA dehydratase activity, urinary lead and porphyrins were all normal or negative. Nerve conduction study showed very small median (10 uV), ulnar (1 uV) and sural (5 uV) SAP amplitudes, small and highly dispersed median (1·5 mV), ulnar (0·9 mV), posterior tibial (1 mV) and common peroneal (0·8 mV) MAPs. The DL of the MAP were mildly prolonged and the MCV were moderately reduced: median (38 m/s), ulnar (45 m/s), posterior tibial (28 m/s), common peroneal (26 m/s). Electromyography showed active denervation changes in distal muscles. Somatosensory, visual and brainstem auditory evoked potentials studies were normal. Sural nerve biopsy showed a normal number of myelinated and non-myelinated fibres, mild thickening of the perineurium and giant axonal swellings in many myelinated fibres. Electron micrograph showed that these swollen axons had considerably attenuated myelin sheaths (fig 1), accumulation of 10 nm neurofilaments in the axoplasm and loss of neurotubules (fig 2). Teased fibre examination (fig 3) demonstrated fusiform axonal swellings in the internodal region, some of which were 50 um in diameter. The myelin sheaths were considerably attenuated in the swollen areas and long segments of myelin degradation leaving a naked axon was present. In other areas, there was no axonal swelling but paranodal myelin attentuation resulting in a widened nodal gap. The result of the investigations in his factory were as shown above. With physiotherapy alone, recovery started to occur in the proximal limbs four months later. At the last follow up at 12 months, there was only mild distal weakness in the legs but he still had painful paresthaesiae in the feet and poor exercise endurance.

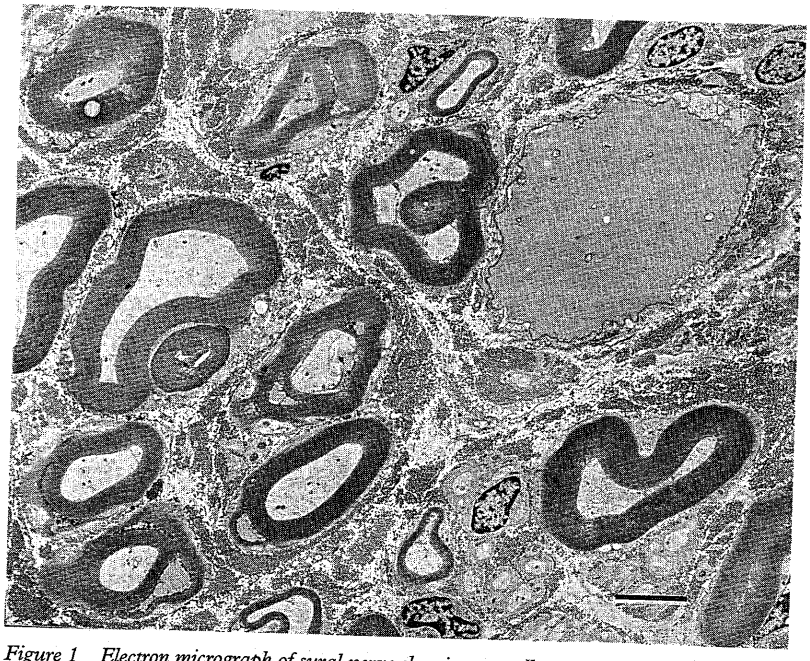

Figure 1 Electron micrograph of sural nerve showing a swollen axon with considerably attenuated myelin sheath. Bar = 1um 2800×.

Discussion

In our investigation, n-hexane was the only

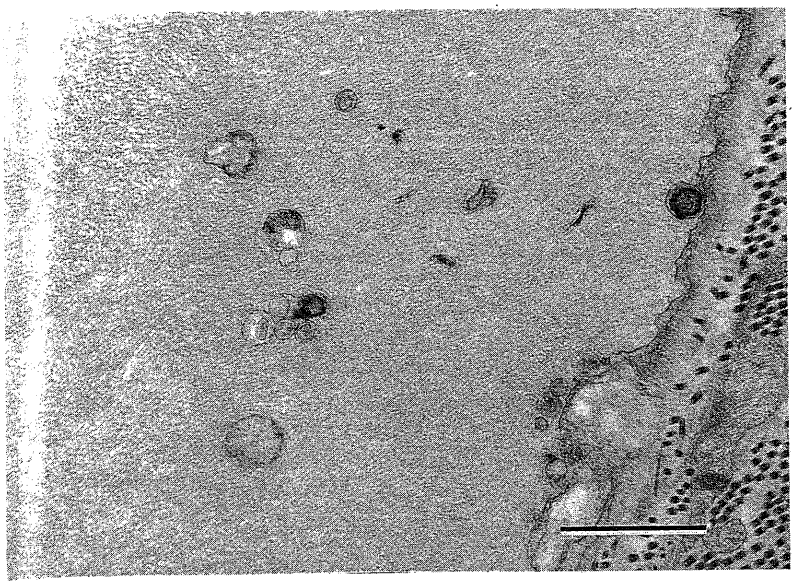

Figure 2 Higher power electron micrograph showing accumulation of 10 nm neurofilaments in the axoplasm. Bar = 1um 30,000×.

neurotoxic chemical present in the cleaning solvents in considerable quantity. Other neurotoxic substances such as methyl n-butyl ketone,[14] methyl ethyl ketone (not itself neurotoxic but can potentiate n-hexane or methyl n-butyl ketone induced neuropathy),[15] organophosphate,[16] lead or mercury were either absent or present in trace amount only. Moreover, the TWA air concentration of n-hexane was well above the recommended threshold limit value of 50 ppm, while the concentrations of other potential neurotoxic chemicals or gases were within internationally acceptable limits.[17] We concluded therefore that the neuropathy was due to n-hexane.

As the respiratory tract is the main site of absorption for n-hexane[1] and since none of our workers wore respiratory protection, it is not surprising to find so many of them developing peripheral neuropathy. N-hexane may also be absorbed through intact skin,[18] and this may explain why upper extremity numbness was the initial symptom in four of the workers who worked without wearing gloves.

The symptomatology of our workers, including the coasting phenomenon, is typical of those described previously.[1] Compared with patients reported from Taiwan,[19] our workers' neuropathy was milder, even though the air concentrations of n-hexane were very similar in the two outbreaks. It is possible that our workers had a shorter duration of exposure as they did not eat or sleep in the factory as their Taiwanese counterparts. Also, skin absorption may be less because solvents with lower n-hexane content were used. It is very likely, however, that many would develop more severe neuropathy if this outbreak was not detected at an early stage.

Although the pathological evolution of n-hexane neuropathy has been well documented in experimental animals,[20] this has not been possible in human disease because nerve biopsies have only been performed in the more severely affected patients. Our NCS data, however, may be used to correlate with experimental pathology. The earliest change in NCS was reduction in the SAP amplitudes as evidenced by the asymptomatic ("healthy") workers. This electrophysiological change is consistent with the pathological finding of early distal axonal degeneration seen in experimental animals.[20] In the subclinical group, the NCS was characterised by further reduction in the SAP amplitudes, mild reduction of MAP amplitudes and MCV, and mild prolongation in DL of SAP and MAP. These findings may suggest a mild degree of demyelination, probably secondary to primary axonal degeneration.[20] Finally, in the symptomatic workers, all the above changes became much more obvious. In the most severely affected worker, there was evidence suggesting severe axonal degeneration (unrecordable SAP) and significant demyelination (MCV of 26 m/s in the lower limbs), which was confirmed by sural nerve biopsy. The absence of SAP is likely to be related to widespread multifocal giant axonal swellings,

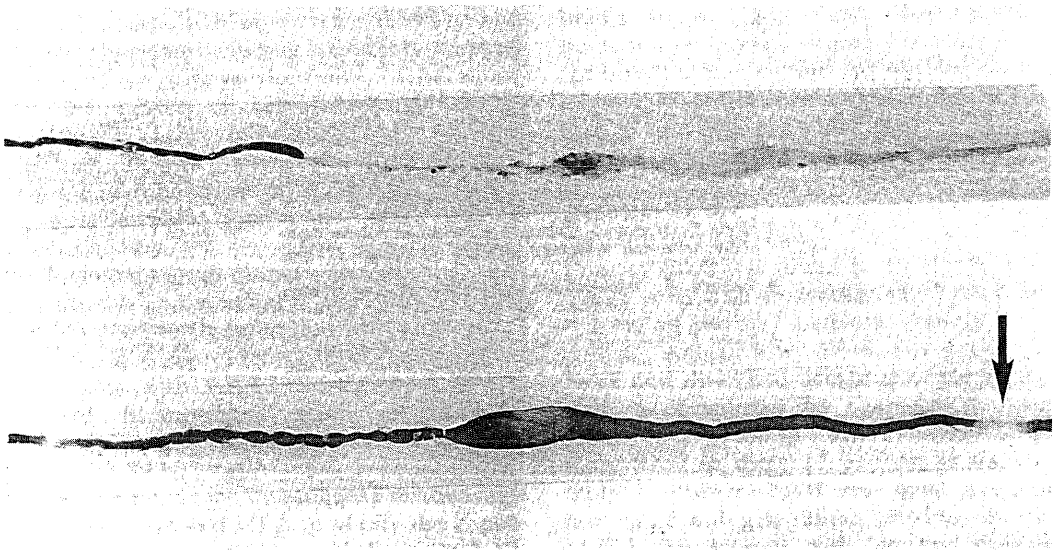

Figure 3 Two teased fibres with internodal axonal swellings, thinning of myelin sheath and widening of nodal gap in one (arrow) and myelin degradation leaving a naked axon in the other. Osmium tetroxide 100×.

while slowing of MCV is likely to be due to secondary myelin degeneration and widening of nodal gaps.[9 15 21]

As shown by other studies,[13 22] a direct relationship between the development of neuropathy and the duration of employment was not observed in this study. As n-hexane induces hepatic cytochrome p-450[23] and is metabolised to the neurotoxic 2,5-hexanedione (2,5-HD),[24] it is possible that individual difference in this specific metabolism may account for the difference in susceptibility. Analysis of serum 2,5-HD may shed light on this apparent differential susceptibility but the test was not available to us then.

N-hexane may cause maculopathy or optic neuropathy, as seen in a few of our workers and in other studies.[5 11 19] There is growing concern whether it is also toxic to the CNS. We agree that symptoms such as headache, poor memory and a drunken feeling were non-specific and therefore may not necessarily reflect CNS toxicity. However, the unmasking of hyperreflexia and spasticity on recovery,[25] electroencephalography[26] and evoked potential abnormalities[27 28] and degeneration of CNS fibre tracts in experimental animals[20] are good evidence of CNS involvement. As in other outbreaks, autonomic neuropathy was not encountered.

The best way to avoid future outbreaks is to use cleaning solvent with very low n-hexane content, or better still, to find a non-toxic substitute for n-hexane. Short of this, safety regulations and guidelines in handling n-hexane must be strictly adhered to. Workers should be periodically screened for the development of toxicity. In this study, we have confirmed that standard NCS is reliable and sensitive.[29] Other potentially useful methods include multimodal evoked potential studies[30] and urinary 2,5-HD estimation.[31] The exact prognosis of our patients is not yet known because of the short duration of follow up, although some have already shown slow but definite improvement. Generally, an optimistic and encouraging attitude should be conveyed to the patients because the prognosis is favourable and good recovery can be expected within a few months to a few years.[5 6 19]

1 Spencer PS, Couri D, Schaumburg HH. n-Hexane and methyl n-Butyl Ketone. In: Spencer PS, Schaumburg HH, eds. *Experimental and clinical neurotoxicology*. Baltimore: Williams and Wilkins 1980:456–75.

2 Yamada S. An occurrence of polyneuritis by n-hexane in the polyethylene laminating plants. *Japanese Journal of Industrial Health* 1964;**6**:192.

3 Wada Y, Okanoto S, Takagi S. Intoxication polyneuropathy following n-hexane. *Clinical Neurology (Tokyo)* 1965;**5**:591.

4 Yamada S. Intoxication polyneuritis in the workers exposed to n-hexane. *Japanese Journal of Industrial Health* 1967;**9**:651–59.

5 Sobue I, Yamamura Y, Ando K, Iida M, Takayanagi T. n-Hexane polyneuropathy. Outbreak among vinyl sandal manufacturers. *Clinical Neurology (Tokyo)* 1968;**8**: 393–403.

6 Iida M, Yamamoto H, Sobue I. Prognosis of n-hexane polyneuropathy—follow up studies on mass outbreak in F district of Mie Prefecture. Igaku no Ayumi 1973;**84**:199–201.

7 Yamamura Y. N-Hexane polyneuropathy. *Fol Psychiat Neurol (Jpn)* 1969;**23**:45–57.

8 Inoue T. A health survey on vinyl sandal manufacturers with a high incidence of n-hexane intoxication. *Japanese Journal of Industrial Health* 1970;**12**:73–84.

9 Rizzuto N, Terzian H, Galiazzo-Rizzuto S. Toxic polyneuropathy in Italy due to leather cement poisoning in shoe industries. *J Neurol Sci* 1977;**31**:343–54.

10 Herskowitz A, Ishii N, Schaumburg H. n-Hexane neuropathy: a syndrome occurring as a result of industrial exposure. *N Eng J Med* 1971;**285**:82–5.

11 Seppalainen AM, Raitta C. Neurotoxic properties of n-Hexane among occupationally exposed workers. Proceedings of the Second Finnish-Estonian Symposium on early effects of toxic substances 1981: 180–87.

12 Paulson GW, Waylonis GW. Polyneuropathy due to n-hexane. *Arch Intern Med* 1976;**136**:880–82.

13 Wang JD, Chang YC, Kao KP, Huang CC, Lin CC, Yeh WY. An outbreak of n-hexane induced polyneuropathy among press proofing workers in Taipei. *Am J Ind Med* 1986;**10**:111–18.

14 Allen N, Mendell JR, Billmaier DJ, Fontaine RE, O'Neill J. Toxic polyneuropathy due to methy n-butyl ketone. An industrial outbreak. *Arch Neurol* 1975;32:209–18.

15 Altenkirch H, Mager J, Stoltenburg G, Helmbrecht J. Toxic polyneuropathies after sniffing a glue thinner. *J Neurol* 1977;**214**:137–52.

16 Davis CS, Richardson RJ. Organophosphorous compounds. In: Spencer PS, Schaumburg HH, eds. Experimental and clinical neurotoxicology. Baltimore: Williams and Wilkins, 1980:527.

17 American conference of governmental industrial hygienists. *Threshold limit values for chemical substances and physical agents and biological exposure indices* 1991–1992: 23.

18 Nomiyama K, Yoshida T, Yanagisa WAH. Percutaneous absorption of n-hexane caused severe polyneuropathy. *Proceeding of the 46th annual meeting, Japan Association Industrial Health* 1973: 420.

19 Chang YC. Patients with n-hexane induced polyneuropathy: a clinical follow up. *Br J Ind Med* 1990;47:485–89.

20 Spencer PS, Schaumburg HH. Ultrastructural studies of the dyeing-back process, IV. Differential vulnerability of PNS and CNS fibres in experimental central-peripheral distal axonopathies. *J Neuropathol Exp Neurol* 1977;**36**: 300–20.

21 Korobkin R, Asbury AK, Sumner AJ, Nielsen SL. Glue-sniffing neuropathy. *Arch Neurol* 1975;**32**:158–62.

22 Abbritti G, Siracusa A, Cianchetti C, Coli CA, Curradi F, Perticoni GF, de Rosa F. Shoe-makers' polyneuropathy in Italy: the aetiological problem. *Br J Ind Med* 1976; **33**:92–9.

23 Scala RA. Recent developments in the toxicology of solvents. In: Collin AJ, Luxon SG, eds. *Safe use of solvents*. London: Academic Press, 1982: 75–104.

24 DiVincenzo GD, Hamilton ML, Kaplan C, Dedinas J. Characterization of the metabolites of methy n-butyl ketone. In: Spencer P, Schaumburg HH, eds. *Experimental and clinical neurotoxicology*. Baltimore: Williams and Wilkins, 1980: 846.

25 Schaumburg HH, Spencer PS. Clinical and experimental studies of distal axonopathy—a frequent form of brain and nerve damage produced by environmental chemical hazards. *Ann N Y Acad Sci* 1979;**329**:14–29.

26 Faggi L, Cosi V, Cavalleri S. Modificazioni Elettrocefalografiche in corso di polinevriti da collanti industriali. *Rivista di Neurobiologia* 1972;**18**:76–84.

27 Mutti A, Ferri F, Lommi G, Lotta S, Lucertini S, Franchini I. N-Hexane induced changes in nerve conduction velocities and somatosensory evoked potentials. *Int Arch Occup Environ Health* 1982;**51**:45–54.

28 Chang YC. Neurotoxic effects of n-hexane on the human central nervous system: evoked potential abnormalities in n-hexane polyneuropathy. *J Neurol Neurosurg Psychiatry* 1987;**50**:269–74.

29 Chang YC, Yip PK. N-Hexane induced electroneurographic changes and early detection of n-hexane intoxication. *Journal of the Formosan Medical Association* 1987; **86**:194–200.

30 Nolfe G, Palma V, Guadagnino M, Serra LL, Serra C. Evoked potentials in shoe-workers with minimal polyneuropathy. *Electromyogr Clin Neurophysiol* 1991;**31**: 157–62.

31 Governa M, Calisti R, Coppa G. Urinary excretion of 2,5-hexanedione and peripheral polyneuropathies in workers exposed to hexane. *J Toxicol Environ Health* 1987; **20**:219–28.