Polyneuropathy Induced by n-Hexane Intoxication in Taiwan

Chin-Chang Huang

Abstract- n-Hexane and methyl n-butyl ketone share a common metabolite, 2,5-hexanedione, a potent neurotoxin. Neurotoxic effects to both peripheral and central nervous systems may occur after occupational exposure or recreational abuse of n-hexane. Initial clinical manifestations include numbness and tingling sensation in the toes and fingers, followed by progressive weakness and areflexia, particularly in the distal limbs.

Chronic low-dose n-hexane exposure, often observed in industrial workers, apparently causes axonal loss with sensory impairment. Subacute high-dose n-hexane exposure, often observed in glue-sniffers, can cause axonal swelling and secondary demyelination with muscle wasting and weakness.

Electrophysiological studies demonstrate prominent prolongation of distal latencies, slowing of nerve conduction velocities, and conduction block with temporal dispersion particularly in severely intoxicated patients. Pathological hallmarks include giant axonal swelling with secondary demyelination and relative loss of large myelinated fibers. Giant axons are accumulated by 10nm neurofilaments. The clinical course tends to be biphasic with "coasting" for 2-3 months, followed by a slow recovery for about 1-2 years after cessation of exposure to n-hexane. Prognosis is usually favorable. Severely affected patients may develop sequelae of muscle wasting, foot drop, and spasticity. Increased awareness of the n-hexane neurotoxicity in industrial workers and glue sniffers as well as use of safe solvents and adequate ventilation systems are important for preventing n-hexane toxicity.

Key Words: n-Hexane, Methyl-n-butyl-ketone, γ-Diketone, Polyneuropathy, Electrophysiology, Giant axon, Demyelination

Acta Neurol Taiwan 2008;17:3-10

INTRODUCTION

The alkane n-Hexane, a 6-carbon aliphatic hydrocarbon (CnH2n+2), is a common component in lacquers, glues and glue thinner, and is widely used in numerous industrial processes[1,2]. The chemical is a colourless volatile organic solvent at room temperature with a characteristic odour and is known to be a potent neurotoxin. Approximately 80-90% of n-hexane can be absorbed by inhalation and then is distributed to lipid-rich tissues and organs such as the brain, peripheral nerves, liver, spleen, kidneys and adrenal glands. The

From the Department of Neurology, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taiwan.
Received November 8, 2007.
Revised and Accepted November 12, 2007.
Reprint requests and correspondence to: Chin-Chang Huang, MD. Department of Neurology, Chang Gung Memorial Hospital, No. 199, Tung Hwa North Road, Taipei, Taiwan.
E-mail: cch0537@adm.cgmh.org.tw

alkane n-hexane and methyl n-butyl ketone (MnBK) are structurally similar and can be metabolized to the active neurotoxin γ-diketone, 2,5-hexanedione (2,5-HD), although only a small fraction of n-hexane can be metabolized to 2,5-HD[3-6]. Whereas MnBK is moderately water soluble and has an acetone-like odour, 2,5-HD is compeletely miscible with water. The MnBK can be absorbed by inhalation as well as via dermal and oral routes while 2,5-HD is absorbed following dermal application in experimental animals. The urinary concentration of 2,5-HD is apparently comparable to that of airborne n-hexane[6]. Urinary 2,5-HD assays are complex but reliable biomarkers.

INDUSTRIAL USE AND SAFETY LEVELS

Industrial application of n-hexane include production of glues, cements, inks and adhesives, painting and coating products, laminating plastics, lacquers, press proofing chemicals and cleaning agents. The chemical is also used for manufacturing and processing leather and furniture, as well as vulcanization of rubber and in dilution and extraction solvents in chemical laboratories[6-8]. n-Hexane is also used to extract vegetable oils for human consumption and as a benzene substitute in solvent applications[9]. MnBK is a widely used as monoketonic solvent, and small amounts of 2,5-HD are used as a precursor for various heterocylic systems in synthetic organic chemistry[6].

The safety level of n-hexane, including the threshold limit value (TLV)-time weighted average, is 50ppm (180mg/m^3) in the air according to the American Conference of Governmental Industrial Hygienists (ACGIH)[10]. The TLV for MnBK is 5ppm (20 mg/m^3) in the air, and permissible exposure level (PEL) is 100ppm. The U.S. Occupational Safety and Health Administration (OSHA) PELs are 500ppm for n-hexane and 1ppm for MnBK[11].

OUTBREAK OF N-HEXANE POLYNEUROPATHY

An outbreak of n-hexane-induced polyneuropathy due to occupational exposure was first reported in 1964 in poorly ventilated polyethylene laminating plants[12]. Subsequently, this neurotoxic disease also occurred in pharmaceutical and vinyl sandal manufacturing plants, as well as in furniture, printing, and shoe manufacturing facilities between 1966 and 1980[13-25]. Awareness of this neurotoxic agent and implementation of preventive measures have increased in most industrialized countries, but occasional outbreaks continue[26-29].

Because of the euphoric effects of n-hexane, teenagers are easily addicted to glue-sniffing[28,29]. Therefore glue-sniffing neuropathy, also known as huffer neuropathy, after habitual inhalation of glue vapors became a familiar neurological disease in 1970-1985[30-37]. The most notorious outbreak of MnBK-induced polyneuropathy was reported in Ohio in 1973[38]. The MnBK has greater neurotoxic potential than n-hexane. Additionally, despite its lack of neurotoxic effect, another organic solvent, methyl-ethyl-ketone (MEK) is known to potentiate the neurotoxic effect[6-8].

N-HEXANE POLYNEUROPATHY IN TAIWAN

Two outbreaks of n-hexane induced polyneuropathy have occurred in Taiwan[26,39,40]. In December, 1983, a 16-year-old young boy working in a press-proofing plant visited the author in Chang Gung Memorial Hospital due to muscle weakness and distal limb numbness for approximately 1 year. Moderate muscle weakness and intrinsic muscle wasting was noted in both hands and feet, with a glove and stocking pattern of sensory impairment and generalized areflexia[39]. Nerve conduction studies revealed significantly reduced nerve conduction velocities and prolonged distal latencies in all the nerves, particularly in the lower extremities. Therefore, the diagnosis of polyneuropathy was established. The young victim of polyneuropathy led to an extensive investigation among 54 workers from 16 press proofing factories in Taipei[26]. Fifteen workers had overt polyneuropathy, and two exhibited subclinical polyneuropathy. Analysis of bulk samples of organic solvent used in the workplace revealed n-hexane concentrations of 10% to 65%. A statistically significant association was noted between n-

hexane concentration in the bulk samples and the prevalence of polyneuropathy.

Concentrations of n-hexane in the press-proofing factories exceeded 50ppm (TLV). The airborne concentration of n-hexane in the main factory in which all six workers developed polyneuropathy was 190 ppm[26,39]. Additionally, victims who frequently worked overtime or slept in the factory had a high incidence of marked plyneuropathy, both clinically and electrophysiologically. The data indicated that high concentrations of n-hexane in the bulk samples and the habit of sleeping in the factories between shifts are risk factors for n-hexane polyneuropathy[26].

Although the first outbreak of n-hexane polyneuropathy occurred in 1983, and steps have been taken to reduce the content of n-hexane in organic solvents, the hazards of n-hexane poisoning were not well recognized by workers or even physicians. Measures to prevent excessive exposure at the worksites were not universally implemented. The second outbreak of n-hexane intoxication occurred in a ball-manufacturing factory in 1986[27]. The seven female victims developed polyneuropathy while processing of nylon fiber winding and cement coatings in a poorly ventilated room. Because the factory air was polluted by dust, the seven female workers attempted to enclose the fiber winding room. Therefore, although the room was free of dust, the air in the room accumulated high levels of n-hexane. The n-hexane concentrations in the personal air samples in the cement coating room ranged from 86 to 109 ppm, although the content of n-hexane in the bulk sample was low (14.1%)[27]. The data indicate that a good ventilation system is far more important for preventing n-hexane polyneuropathy than n-hexane concentration in the bulk samples.

CLINICAL MANIFESTATIONS

Peripheral nervous system (PNS) effects

The clinical manifestation of n-hexane polyneuropathy is known as central-peripheral distal axonopathy or "dying-back neuropathy"[40]. The onset is usually subacute or chronic, and the course is progressive with initial symptoms of numbness and burning sensation in the toes and fingers, followed by distal limb muscle weakness[26,27,39-41]. The symptoms of polyneuropathy are usually symmetrical[42]. Sensory impairments include reduced sensation of temperature, pin-prick, light touch, and vibration as well as position senses in the distal limbs[38-41,43]. The muscle wasting usually occurs in the intrinsic hand and foot muscles, and muscle weakness often involves the extensor and flexor muscles of the legs and forearms. The extensor muscles are usually affected more severely than the flexor muscles in the forearms and legs[32,43-44].

In severely intoxicated patients, proximal muscles may become weak with Gower's phenomenon. Tendon reflexes are usually absent in ankle jerks and decreased in knee jerks and biceps[43,45]. Autonomic dysfunctions in glue sniffers often include nausea, vomiting, abdominal pain, impotence and skin changes such as coldness, sweating, and exfoliation[18]. Cranial neuropathy includes blurred vision, impaired color vision, retinal or macular changes, decreased corneal reflexes and facial numbness[18,43].

Central nervous system (CNS) effects

The neurotoxic effects of CNS after intoxication by n-hexane, MnBK, or 2,5-HD include headache, sleep disturbance, irritability, mental impairments and spastic gait[1,7,8]. Acute exposure to high n-hexane concentrations may induce narcosis, euphoria, hallucination, dizziness, giddiness, and headache[7,8]. Severely intoxicated patients may develop respiratory depression, convulsion, coma, and even death. The acute effects are more common in glue sniffers than in industrial workers[1,7].

Hyperreflexia with spasticity is usually observed in polyneuropathic patients several months after recovery of the peripheral neuropathy[7,8]. The sequelae of spasticity may persist for several years, even after cessation of n-hexane exposure. Extrapyramidal symptoms including rigidity, bradykinesia and tremor are not found. There are no cerebellar signs of nystagmus, tremor, ataxia, nor sphincter disturbance.

CLINICAL COURSE AND PROGNOSIS

Recovery from n-hexane polyneuropathy is slow and

usually begins after a period of deterioration known as "coasting". Deterioration of muscle strength and sensory deficit is common and become maximal within 2-3 months after terminating exposure[40,43-44]. The symptoms usually worsen for 2-5 months then slowly recover for 1-2 years. Except for severely intoxicated patients, the prognosis of n-hexane intoxication is usually favorable [39,44]. Many patients recover within 1-3 years. In severely intoxicated cases, drop foot, claw hand and spastic gait may persist[44]. Affected victims with sequelae are more likely to exhibit initial worsening[43].

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies of n-hexane polyneuropathy indicate primary axonal degeneration and focal demyelination[7,8,45]. Characteristic changes are marked slowing of nerve conduction velocity (NCV) (decrease >40%), focal conduction block (reduction >50%) with temporal dispersion of compound muscle action potentials, and marked prolongation of distal latencies (>50%), particularly in the lower extremities[38,45-52]. Sensory fiber involvement precedes that of the motor fibers. Electromyogram (EMG) changes of the distal lower limbs may occor earlier than those of the proximal limbs[46,47]. Spontaneous activities with fast firing, high-amplitude polyphasic motor unit potentials are common[52]. Long-term studies indicate that motor nerve function may improve, but the sensory nerves are more seriously affected and occasionally do not completely recover for as long as 10 years after exposure[52-54]. The findings of series NCV studies also reveal initial worsening followed by slow recovery[39,52-54]. In the distal limbs, the slowing is much more pronounced than that in the proximal limbs, which indicates a distal axonopathy.

Studies of somatosensory evoked potentials studies show prolonged central conduction times[37,55]. Brainstem auditary evoked potentials (BAEP) reveal prolongation of interpeak latencies of I-V as well. The data indicate that the spinal cord and the brainstem are also affected by chronic n-hexane intoxication[37]. The absolute and interpeak latencies of the pattern-reversal visual evoked potentials (pVEP) are also prolonged[55-57]. Furthermore, central conduction times calculated by transcranial magnetic stimulation and spinal nerve root stimulation indicate that the descending motor pathway is affected[51].

NEUROPATHOLOGICAL STUDIES

Sural nerve pathology

Biopsied sural nerve samples from the patients with n-hexane, MnBK, or 2,5-HD induced polyneuropathy show degeneration of both axon and myelin[7,8,45,58]. Subperineurial edema and fusiform axonal enlargement with myelin retraction in the Ranvier nodes can be demonstrated by teased fiber preparation[48,58]. Semithin sections may disclose huge axons of 25-35 u in diameter. Eelectronmicroscopic studies reveal a reduction of fiber density in the myelinated fibers and an increase in the collagen fibers in the endoneurium and perineurium[58]. Axonal degeneration with mitochondrial clustering and neurotubule derangement also occurs. Histogram of myelinated fibers discloses marked reduction of large myelinated fibers with a relative preservation of small myelinated fibers[45]. Giant axonal swelling is due to an accumulation of 10 nm neurofilaments and develops on the proximal sides of the Ranvier nodes[5-7,21,32,33].

Experimental studies

Exposure to n-hexane or its related neurotoxic substances causes distally accentuated axonal degeneration in the peripheral nerves as well as the central nervous system in experimental animals[1-5,7,8]. In the PNS, characteristic giant axonal swelling, myelin thining and axonal degeneration develop 4 days after 45 min. exposure of sciatic nerves to 2,5-HD[59]. Electrophysiological abnormalities may precede the histopathological damage. In the CNS, the sites most vulnerable to these neurotoxic substances are the rostral regions of the long ascending tracts, dorsal spinocerebellar tracts, gracile, and cuneate regions, mamillary body, the lateral geniculate nucleus, and the superior colliculus[41]. Dose-rate may determine the onset and progression of the neurotoxicity[8]. The relative neurotoxic potency of n-hexane, MnBK, 2,5-HD and other metabolites have been examined. The time to achieve severe hindlimb weakness decreases from n-

hexane, 2-hexanol, MnBK, 2,5-hexanediol and 2,5-HD [60]. Additionally, the eyes are also vulnerable to n-hexane exposure. Maculopathy and colour discrimination defects are common.

PATHOGENESIS OF N-HEXANE POLYNEUROPATHY

n-Hexane is metabolized by hepatic cytochrome P450 to a series of metabolites, including the so-called γ-diketone such as 2,5-heptanedione, 6,6-octanedione, and 2,5-HD[8]. Most metabolites are excreted in urine. The γ-diketone can react with ε-amine residues to form 2,5-dimethyl pyrroles, and covalent cross-liking of neurofilament protein[6,8]. Only γ-diketones have neurotoxic effects while α, β and δ-diketones have none[8]. Increasing evidence indicates that administration of 3,4-dimethyl substitution of 2,5-HD (3,4-DMHD) can accelerate pyrrole formation and impair axonal neurofilament transport[6,61]. The neurotoxic effects of 3,4-DMHD can shift giant axon swelling from distal to proximal internodes[8,62]. Therefore, 3,4-DMHD intoxication is assumed to link between the proximal 3,-3'-iminodipropionitrile (IDPN) intoxication and those of the distal neurofilament axonopathies[8,63].

Animal studies have documented a relationship between slowing of fast axonal transport and focal axonal swelling[64]. Axonal enzymes are conveyed from the perikaryon to the distal axon. Intoxication of IDPN is known to induce similar giant axonal swellings caused by selective blocking of neurofilamentous proteins traveling by long slow transport[62,63]. The IDPN intoxication impairs neurofilament transport along the length of the axon. The 2,5-HD may also impair enzyme activity along the length of the axon[65]. Diminished energy supplies cause local neurofilament accumulation and nerve degeneration.

The mechanisms of the continued progression despite cessation of exposure of neurotoxic agents remain unclear. However, storage of n-hexane or its metabolites within organs such as the nerve sheath and the rate of subsequent conversion to toxic metabolite such as 2,5-HD are plausible explanations.

TREATMENT AND PREVENTION

Patients with n-hexane intoxication have no known antidotes. Prevention of further excessive exposure to the n-hexane is the first step to prevent neuropathy. Increased awareness of these neurotoxic substances by industrial workers and glue sniffers, substitution of safer solvents in industrial processes, and lowering of the 8h-TLV time- weighted average may be helpful. Although an initial worsening of distal weakness may develop for several months, most patients can be assured of an eventual recovery. Supportive measures including physical and occupational therapy, may also be helpful.

REFERENCES

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 & Wilkins, 1980:456-75.
2. Schaumburg HH, Spencer PS. Degeneration in central and peripheral nervous systems produced by pure n-hexane: an experimental study. Brain 1976;99:183-92.
3. O'Donoghue JL, Krasavage WJ. Identification and characterization of methyl n-butyl ketone neurotoxicity in laboratory animals. In: Spencer PS, Schaumburg HH, eds. Experimental and Clinical Neurotoxicology. Baltimore: Williams & Wilkins, 1980:856-62.
4. Spencer PS, Schaumburg HH. Ultrastructural studies of the dying-back process. IV. Differential vulnerability of PNS and CNS fibers in experimental central-peripheral distal axonopathies. J Neuropathol Exp Neurol 1977;36:300-20.
5. 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 NY Acad Sci 1979;329:14-29.
6. DeCaprio AP. n-Hexane, metabolites and derivatives. In: Spencer PS, Schaumburg HH, eds. Experimental and Clinical Neurotoxicology. Baltimore: Williams & Wilkins, 2000:633-47.
7. Allen N. Solvents and other industrial organic compounds. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. Vol 36. Intoxication of the Nervous System,

Part I. Amsterdam-New York-Oxford, Elsevier, North Holland Publishing Co, 1979:361-89.
8. Bruyn GW, Yaqub BA. Neurotoxic effects of n-hexane and methyl-n-butyl ketone. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. Vol. 64. Intoxication of the Nervous System, Part I. Amsterdam-Lausanne-New York-Oxford-Shannon-Tokyo, Elsevier. North Holland Publishing Co, 1994:81-94.
9. IPCS. Environmental Health Criteria 122: n-Hexane, World Health Organization, Geneva, 1991.
10. American Conference of Governmental Industrial Hygienist. TLVs and BEIs: threshold limit values for chemical substance and physical agents biological exposure index. Cincinnati, Ohio, ACGIH, 2005.
11. Occupational, Safety and Health Administration (OSHA). Occupational Safety and Health Standards for the construction Industry CFR. Code (29 CFR 1910, 1000) of Federal regulations. Washington D.C.: US Government, 2005.
12. Yamada S. An occurrenece of polyneuritis by n-hexane in the polyethylene laminating plants. Jpn J Ind Health 1964; 6:192-4.
13. Yamada S. Intoxication polyneuritis in the workers exposed to n-hexane. Jpn J Ind Health 1967;9:651-9.
14. Wada Y, Okamoto S. Intoxication polyneuropathy following exposure to n-hexane. Clin Neurol 1968;5:591-7.
15. Rizzuto N, Terzian H, Galiazzo-Rizzuto S. Toxic polyneuropathies in Italy due to leather cement poisoning in shoe industries. A light- and electron-microscopic study. J Neurol Sci 1977;31:343-54.
16. Cianchetti C, Abbritti G, Perticoni G, et al. Toxic polyneuropathy of shoe-industry workers. A study of 122 cases. J Neurol Neurosurg Psychiatry 1976;39:1151-61.
17. Herskowitz A, Ishii N, Schaumburg H. n-Hexane neuropathy. A syndrome occurring as a result of industrial exposure. N Engl J Med 1971;285:82-5.
18. Yamamura Y. n-Hexane polyneuropathy. Folia Psychiat Neurol (Jpn) 1969;23:45-57.
19. Abbritti G, Siracusa A, Cianchetti C, et al. Shoe-makers' polyneuropathy in Italy: the aetiological problem. Br J Ind Med 1976;33:92-9.
20. Buiatti E, Cecchini S, Ronchi O, et al. Relationship between clinical and electromyographic findings and exposure to solvents, in shoe and leather workers. Br J Ind Med 1978;35:168-73.
21. Davenport JG, Farrell DF, Sumi M. 'Giant axonal neuropathy' caused by industrial chemicals: neurofilamentous axonal masses in man. Neurology 1976;26:919-23.
22. Scelsi R, Poggi P, Fera L, et al. Toxic polyneuropathy due to n-hexane. J Neurol Sci 1980;47:7-19.
23. Allen N, Mendell JR, Billmaier DJ, et al. Toxic polyneuropathy due to methyl n-butyl ketone. An industrial outbreak. Arch Neurol 1975;32:209-18.
24. Paulson GW, Waylonis GW. Polyneuropathy due to n-hexane. Arch Intern Med 1976;136:880-2.
25. Sobue I, Yamamura Y, Ando J, et al. n-Hexane polyneuropathy. Outbreak among vinyl sandal manufacturers. Clin Neurol 1968;8:393-403.
26. Wang JD, Chang YC, Kao KP, et al. An outbreak of n-hexane induced polyneuropathy among press proofing workers in Taipei. Am J Ind Med 1986;10:111-8.
27. Huang CC, Shih TS, Cheng SY, et al. n-Hexane polyneuropathy in a ball-manufacturing factory. J Occup Med 1991;33:139-42.
28. Smith AG, Albers JW. n-Hexane neuropathy due to rubber cement sniffing. Muscle Nerve 1997;20:1445-50.
29. Chang CM, Yu CW, Fong KY, et al. n-Hexane neuropathy in offset printers. J Neurol Neurosurg Psychiatry 1993;56: 538-42.
30. Glaser HH, Massengale ON. Glue-sniffing in children. Deliberate inhalation of vaporized plastic cements. JAMA 1962;181:300-3.
31. Prockop LD, Alt M, Tison J. "Huffer's" neuropathy. JAMA 1974;229:1083-4.
32. Shirabe T, Tsuda T, Terao A, et al. Toxic polyneuropathy due to glue-sniffing. Report of two cases with a light and electronmicroscopic study of the peripheral nerves and muscles. J Neurol Sci 1974;21:101-13.
33. Oh SJ, Kim JM. Giant axonal swelling in "Huffer's" neuropathy. Arch Neurol 1976;33:583-6.
34. Altenkirch H, Mager J, Stoltenburg G, et al. Toxic polyneuropathies after sniffing a glue thinner. J Neurol 1977;214: 137-52.
35. Goto I, Matsumura M, Inoue N, et al. Toxic polyneuropathy due to glue sniffing. J Neurol Neurosurg Psychiatry 1974;37:848-53.
36. Spencer PS, Schaumburg HH, Raleigh RL, et al. Nervous

system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch Neurol 1975;32:219-22.
37. Korobkin R, Asbury AK, Sumner AJ, et al. Glue-sniffing neuropathy. Arch Neurol 1975;32:158-62.
38. Billmaier D, Allen N, Craft B, et al. Peripheral neuropathy in a coated fabrics plant. J Occup Med 1974;16:665-71.
39. Huang CC, Chu NS. Evoked potentials in chronic n-hexane intoxication. Clin Electroencephalogr 1989;20:162-8.
40. Huang CC, Chu NS, Cheng SY, et al. Biphasic recovery in n-hexane polyneuropathy. A clinical and electrophysiological study. Acta Neurol Scand 1989;80:610-5.
41. Schaumburg HH, Spencer PS. Degeneration in central and peripheral nervous systems produced by pure n-hexane: an experimental study. Brain 1976;99:183-92.
42. Sanagi S, Seki Y, Sugimoto K, et al. Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int Arch Occup Environ Health 1980;47:69-79.
43. Schaumburg HH, Spencer PS. Toxic neuropathies. Neurology 1979;29:429-31.
44. Chang YC. Patients with n-hexane induced polyneuropathy: a clinical follow-up. Br J Ind Med 1990;47:485-9.
45. Huang CC, Chen SS, Lu CS. Diagnostic value of sural nerve biopsy and electrophysiological studies in n-hexane intoxication. Kaohsiung J Med Sci 1988;4:306-10.
46. Chang YC, Yip PK. n-Hexane electroneurographic changes and early detection of n-hexane intoxication. J Formos Med Assoc 1987;86:194-200.
47. Iida M, Yamamura Y, Sobue I. Electromyographic findings and conduction velocity on n-hexane polyneuropathy. Electromyography 1969;9:247-61.
48. Ishii N, Herskowitz A, Schaumburg HH. n-Hexane polyneuropathy: a clinical and experimental study. J Neuropathol Exp Neurol 1972;31:198-205.
49. Chang AP, England JD, Garcia CA, et al. Focal conduction block in n-hexane polyneuropathy. Muscle Nerve 1998;21: 964-9.
50. Kuwabara S, Nakajima M, Tsuboi Y, et al. Multifocal conduction block in n-hexane neuropathy. Muscle Nerve 1993; 16:1416-7.
51. Oge AE, Yazici J, Bayaciyan A, et al. Peripheral and central conduction in n-hexane polyneuropathy. Muscle Nerve 1994;17:1416-30.
52. Chang YC. An electrophysiological follow up of patients with n-hexane polyneuropathy. Br J Ind Med 1991;48:12-7.
53. Valentino M. Residual electroneurographic modifications in subjects with n-hexane induced polyneuropathy: a follow-up study. Med Lav 1996;87:289-96
54. Yoshida T, Yanagisawa H, Muneyuki T, et al. Electrophysiological studies of n-hexane polyneuropathy. Rinsho Shinkeigaku 1974;14:454-61.
55. 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.
56. Seppäläinen AM, Raitta C, Huuskonen MS. Nervous and visual effects of occupational n-hexane exposure. In: Lechner H, Aranibar A, eds. Electroencephalogr Clin Neurophysiol. Amsterdam: Excerpta Medica 1980;656-61.
57. Seppäläinen AM, Raitta C, Huuskonen MS. n-Hexane induced changes in visual evoked potentials and electroretinograms of industrial workers. Electroencephalogr Clin Neurophysiol 1979;47:492-8.
58. Shirabe T, Tsuda T, Terao A, et al. Toxic polyneuropathy due to glue-sniffing. Report of two cases with a light and electronmicroscopic study of the peripheral nerves and muscles. J Neurol Sci 1974;21:101-13.
59. Spencer PS, Schaumburg HH. Experiential neuropathy produced by 2,5-hexanedione - a major metabolite of the neurotoxic industrial solvent methyl n-butyl ketone. J Neurol Neurosurg Psychiatry 1975;38:771-5.
60. Graham DG, ST Clair MB, Amarnath V, et al. Molecular mechanisms of gamma-diketone neuropathy. Adv Exp Med Biol 1991:283;427-31.
61. Graham DG, Gottfried MR. Cross-species extrapolation in hydrocarbon neuropathy. Neurobehav Toxicol Teratol 1984;6:433-5.
62. Griffin JW, Fahnstock KE, Price DL, et al. Cytoskeletal disorganization induced by local application of 3-3'-iminodipropionitrile and 2, 5-hexanedione. Ann Neurol 1983; 14:55-61.
63. Chou SM, Hartmann HA. Electron microscopy of focal neuroaxonal lesions produced by 3-3'-iminodipropionitrile (IDPN) in rats, I. The advanced lesions. Acta Neuropathol 1965;4:590-603.
64. Mendell JR, Sahenk Z, Saida K, et al. Alterations of fast axoplasmic transport in experimental methyl n-butyl ketone

neuropathy. Brain Res 1977;133:107-18.
65. Griffin JW, Price DL, Spencer PS. Fast axonal transport through giant axonal swellings in hexacarbon neuropathy. J Neuropathol Exp Neurol 1977;36:603-10.