Scand J Work Environ Health 1981;7(3):157-168
https://doi.org/10.5271/sjweh.3107
Issue date: Sep 1981

n-Hexane and its toxicologic effects – a review

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Key terms: conduction velocity; exposure; functional disturbance; maculopathy; motor conduction velocity; n-hexane; occupational exposure; occupational exposure limit; polyneuropathy; review; sensory conduction velocity; toxicology

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/20120580

Print ISSN: 0355-3140 Electronic ISSN: 1795-990X

have shown a marked decrease in the number of thick fibers (59, 63).

Muscle biopsies under a light microscope revealed significant muscle fiber atrophy, with clear central zones, so-called target fibers. The cells in cross-section were small with many edges (25, 29, 59, 66).

Electromyograms of peripheral nerves have shown a decreased nerve conduction rate in both motor and sensory nerves in both man and experimental animals. There was also an increased distal latency period (1, 14, 18, 28, 29, 45, 48, 49, 51, 63, 64, 66).

Electromyographic examinations have also revealed fibrillation potentials, positive "sharp-waves," and other changes in the electrical impulse potential which would point towards neurogenic damage (1, 18, 28, 29, 37, 45, 48, 59, 63, 66).

These morphological changes in the peripheral nervous system caused motor and sensory symptoms in workers, including sniffers, and experimental animals that had been exposed to n-hexane. Workers developed initial symptoms in the form of sensation disturbances and cold sensation in the legs after two to six months. In addition varying muscle weakness with a heavy sensation, easy fatiguability, pain, and spasms in the legs were also noted. Symptoms were distal and symmetric (1, 14, 18, 29, 31, 48, 66). The condition was progressive, and in severe cases flaccid paralysis of the legs and, in some cases, arms developed (51).

Sensory disturbances were in the glove-stocking distribution and were similarly progressive. The disturbances were comprised of mild to severe decreases in vibration, temperature, pain, position, pressure, and touch sensations (1, 14, 18, 29, 48, 51).

It is typical that glue sniffers develop symptoms two to three months after they shift to a glue product with a high content of n-hexane (1, 23, 55). The symptoms are the same as those previously described. However, the majority of symptoms are motor abnormalities involving the proximal muscle groups of the upper and lower extremities. In addition, quadriplegia can develop. A peculiar hyperhidrosis of the hands and feet has also been noted (3, 28, 38, 59, 63).

The functional disturbances caused by n-hexane commonly progress for two to three months after the cessation of exposure (51, 66). Recovery time varies, but in general it is long. With regard to both clinical and electrophysiological changes the majority of patients are well after about 1 a after the cessation of exposure (1, 3, 28, 38, 51, 63, 66). Some continue however to complain of pain, tiredness, and muscle weakness even after 2.5 a. In such cases both muscle atrophy and reflex disturbances have been noted clinically, and the physiological motor conduction velocity has continued to be depressed (1, 3, 38, 51, 63, 66).

Both workers and glue sniffers were exposed to products that contained between 50 and 99 % n-hexane. These products also contained toluene and other aliphatic hydrocarbons. There was, in addition, exposure to acetate and chlorinated hydrocarbons in a few cases.

Rat experiments have demonstrated a synergistic effect between methyl ethyl ketone and n-hexane. Methyl ethyl ketone alone did not produce the same functional or morphological changes in the peripheral nervous system (4, 6, 61).

Reproductive organs and birth

Rats were given a hydrocarbon blending containing approximately 40 % n-hexane (4,000 mg/kg) via nasogastric feeding. They received one feeding a day, 5 d a week, for a total of 90 d. Varying grades of atrophy in the germinal epithelium of testicular tissue were found. Fertility was examined in this study (35).

Rats were exposed to 1,000 ppm of 99 % n-hexane for 6 h a day. The rats were exposed on a different number of days and in different times of the gestation period. The only difference was that the babies of exposed mothers had a lower weight one week after giving birth. This difference was maintained for four to six weeks. The weight returned to normal after seven weeks. There were no differences in fetal resorption, birth weight, or other abnormalities (16).

Other organs

Fifteen workers with more than 5 a of exposure to n-hexane vapor were examined

with reference to possible visual disturbances. Exposure was between 180 and 4,320 mg/m³ (50—1,200 ppm). There had also been short-term exposure of up to 10,800 mg/m³ (3,000 ppm) (50). Visual field testing and visual acuity was normal. There were, however, a few individual problems that could not be connected to the work. Twelve workers had abnormal color vision. However, only one had congenital deuteranopia (50). Eleven workers had mild pigment dystrophy with a dry appearing macula. Yellow spots were also absent in the fovea reflex. Perifoveal capillary proliferation was noted under fluorescein angiography (50).

In another study 8 of 93 sandal workers exposed to an n-hexane concentration of 1,800 mg/m³ had objective changes. Seven had narrowing of their visual fields, two had optic atrophy, and one had neuriits. The authors emphasized that all the changes were mild (66).

2,5-Hexanedione, a biotransformation product of hexane, caused degeneration of axons in the mamillary body and in the superior geniculate body of cats. There was no visual loss, abnormal pupil reflexes, or nystagmus (57).

Allergic and carcinogenic effects

The possible allergic effects on the skin and lungs have not been investigated, nor has any information appeared concerning a carcinogenic effect of hexane.

Indicators of exposure

Mice that had inhaled an n-hexane concentration of 28,800 mg/m³ (8,000 ppm) for 5 min have shown no notable disturbances, whereas 57,600 mg/m³ (16,000 ppm) produced mild anesthesia, and 115,200 mg/m³ (32,000 ppm) produced deep anesthesia. Respiratory arrest was caused by exposure to 230,400 mg/m³ (64,000 ppm) (11, 20).

Mice were exposed to n-hexane concentrations of 126,000—187,200 mg/m³ (35,000—52,000 ppm) for periods varying between 10—120 min. The mice laid on their sides after 9—90 min after exposure; 7 of the 17 mice were dead between 9—127 min after exposure (22).

Effects of long-term exposure

Data exist from workers with chronic exposure to pure n-hexane or to products that have a high n-hexane content. The mixed products also contain aliphatic hydrocarbons and toluene, or possibly other organic solvents. There are also data from glue sniffers who have had chronic exposure to glues containing both n-hexane and toluene.

Occupational exposure to n-hexane varies between 1,080 and 2,340 mg/m³ (300—600 ppm). Ceiling exposures of up to 9,000 mg/m³ (2,500 ppm) have been described. Most investigators have found concentrations between 1,440 mg/m³ (400 ppm) and 1,800 mg/m³ (500 ppm) for two to six months (1, 14, 18, 29, 45, 48, 66).

No investigations with negative results were found in the literature. The lowest doses after which man has shown functional disturbances is 194—720 mg/m³ (54—200 ppm). In this investigation one individual developed polyneuropathy after 1 a of exposure (62).

It has been impossible to define the exposure of glue sniffers, but many have used up to 0.5 l of glue per day (3). Progressive and symmetric distal paresthesia and muscle weakness have been noted. Morphological and electrophysiological changes have been found in the peripheral nerves and muscles.

Muscle weakness, atrophy, electrophysiological abnormalities in nerves and muscles, and histopathological changes have also been noted in animals. The same morphological changes in the CNS have also been demonstrated in research animals (57).

Exposure doses have ranged between 360 and 36,000 mg/m³ (100—10,000 ppm) for four to five months (37, 56, 58, 64). In one investigation five groups of mice were exposed to n-hexane for 12 months. The groups were exposed to the following n-hexane concentrations: 360, 900, 1,800, 3,600, 7,200 mg/m³ (100, 250, 500, 1,000, 2,000 ppm). Functional disturbances were found in all the groups, except that with the lowest exposure level (360 mg/m³, 100 ppm) (40).

In addition to muscular and neurological damage, nonspecific changes in the red

blood cells (51, 62, 66) and certain liver enzymes (7, 28, 45, 66) have been described.

When workers exposed to n-hexane vapor levels of 1,523 and 4,608 mg/m³ (423—1,280 ppm) for more than 5 a were examined, maculopathy comprised of changes in color vision, in retinal pigmentation, and in perifoveal capillaries was found (50).

Prolongation of the recovery time has been described for both workers and glue sniffers. Some individuals in both groups have had clinical or electrophysiological abnormalities 2 a after exposure (1, 3, 38, 51, 63, 66).

Discussion and evaluation

The specific toxic effects of n-hexane that have thus far been described in the literature have been limited to the neurological system. The observed changes in the blood cells and liver enzymes were nonspecific and could have been caused by other materials.

Workers (with several months' exposure) and young glue sniffers that had been exposed to products containing n-hexane developed a typical disease pattern, the so-called hexacarbon polyneuropathy. In these mixed exposures, n-hexane is generally found together with toluene. It is possible that hexacarbon polyneuropathly is caused by exposure to a combination of chemicals. Humans and experimental animals that had been exposed to pure toluene did not develop the characteristic functional disturbances. Experimental animals that had been exposed to pure n-hexane developed the same clinical, electrophysiological and histopatological changes that are found in humans (56).

An unexplained observation is that methyl ethyl ketone has a synergistic action in combination with n-hexane in humans and animals, while alone it is not neurotoxic (4, 5, 6).

Exposure to n-hexane (1,530—4,600 mg/m³, 423—1,280 ppm) for more than 5 a produced chronic damage in the form of maculopathy. The maculopathy was comprised of changes in color vision, retinal pigmentation, and perifoveal capillaries (39).

Mice exposed to 850 mg/m³ (250 ppm) for 1 a developed polyneuropathy. However, exposure to 360 mg/m³ (100 ppm) did not cause clinical, electrophysiological or histological changes (30).

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Appendix 1

Dose-effect and dose-response after occupational exposure to n-hexane

5,400 mg/m³ (1,500 ppm) short-term

Eye and throat irritation occurred, along with mild nausea and headache (11).

2,288—4,576 mg/m³ (650—1,300 ppm)

Three workers developed distal paresthesia and muscle weakness in all extremities after two to four months of exposure. Muscle atrophy, foot drop, reflex changes, and moderate abnormalities in touch sensations were described. An electrophysiological examination demonstrated decreased nerve conduction. There were histological indications of both a denervation of muscles and a degeneration of myelinized nerve fibers (29).

1,530—4,600 mg/m³ (423—1,280 ppm)

All of 15 workers with more than 5 a of exposure developed proliferation of perifoveal capillaries; 11 workers had abnormal color vision. Macular changes were also noted in 11 of the workers (50).

1,800 mg/m³ up to occasional exposures of 8,000 mg/m³ (500—2,500 ppm)

Ninety-three of 1,662 workers developed polyneuropathy after eight months of exposure. Distal paresthesia and muscle weakness were described. Muscle atrophy, absent reflexes and hyperesthesia in the glove-stocking distribution were described. The group of 93 workers with polyneuropathy could be subdivided into the following three groups on the basis of electrophysiological changes:

I. Sensory polyneuropathy (53 persons)
II. Sensory and motor polyneuropathy (32 persons)
III. Sensory and motor polyneuropathy with amyotrophy (8 persons)

The histological changes were muscle atrophy and nerve demyelinization. After 1.5 a, 15 % of the group continued to complain of muscle weakness, and clinical changes were still noted (66).

There are two other investigations that describe 11 and 3 cases, respectively, after 10 months' exposure. The symptoms and clinical and electrophysiological changes pointed towards n-hexane polyneuropathy (26, 65).

Received for publication: 30 March 1981

1,080—1,440 mg/m³ with occasional exposures up to 4,060 mg/m³ (300—400, 1,100 ppm)

Eight of 50 workers with long-term exposure developed a mild and predominantly motor polyneuropathy. Absent ankle reflexes and decreased vibration sensation was described. An electrophysiological examination revealed slowed nerve conduction with an indication of muscle denervation. The recovery time was six months (45).

In another investigation three cases with polyneuropathy were described after exposure to 1,080 mg/m³ (400 ppm) (17).

194—720 mg/m³ (54—200 ppm)

One worker developed severe proximate muscle symptoms after 12 months of exposure. Mild abnormalities in touch sensation and muscle weakness were present. Electrophysiological abnormalities comprised slowed nerve conduction with a small potential spike in the muscles of the arms and legs. After six months the nerve conduction was still abnormal (62).