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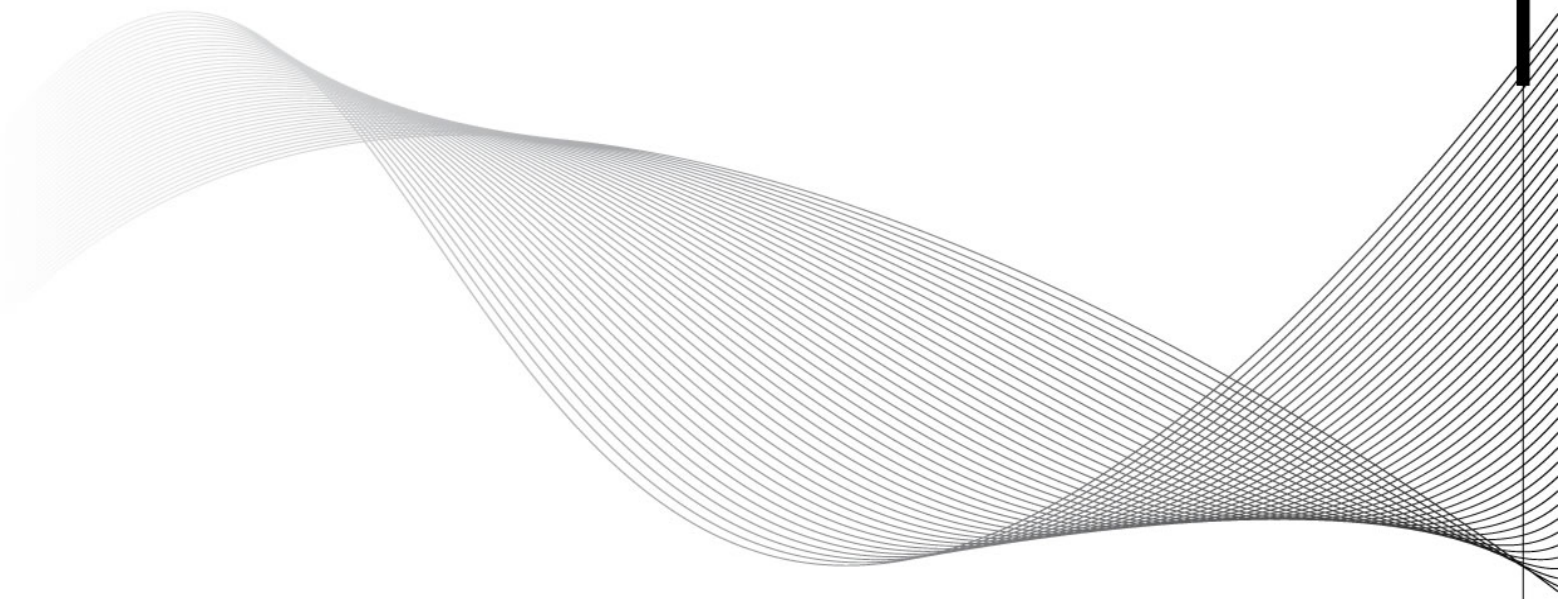

Recommendation from the Scientific Expert Group on Occupational Exposure Limits for n-hexane

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8 hour TWA	:	20 ppm (72 mg/m^3)
STEL (15 mins)	:	-
Additional classification	:	-

Substance:

n-Hexane CH_3-CH_2-CH_2-CH_2-CH_2-CH_3

Synonyms	:	Hexane
EINECS N°	:	203-777-6
EEC N°	:	601-037-00-0
EU Classification	:	F; R11 Xn; R48/20
CAS N°	:	110-54-5
MWt	:	86.1

Conversion factor (20°C, 101 kPa) : 3.58 mg/m^3 = 1 ppm

1. Occurrence/use

n-Hexane is a colourless liquid with a MPt of -95°C, a BPt of 68.7°C and a vapour pressure of 20 kPa at 25°C. It has a vapour density of 3 times that of air and is explosive in the range 1.25 - 6.9 % in air.

n-Hexane is released into the environment as a product from oil refining or cracking of aliphatic hydrocarbons. It is present in petrol at a maximum of 2%. Traces may also be present in natural gas. Commercial hexane contains 40-50% n-hexane in addition to other C6 hydrocarbons including benzene. Commercial hexane is used as an extractant for production of vegetable oils, as a solvent and reaction medium in industrial processes and as a solvent in adhesives. Pure n-hexane is only available commercially for specialised purposes, such as a laboratory reagent. Occupational exposure to hexane is mainly related to use of adhesives, often as small activities with no records of exposure levels.

The production rate of n-hexane (as a component of various hydrocarbon mixtures) in the EC is estimated to be in the region of 100,000 tonnes per annum.

2. Health Significance

In experimental animals, n-hexane is absorbed rapidly through the lungs and is widely distributed (Dahl *et al.*, 1988). Particularly high levels have been found in peripheral nerves (Baker and Rickert, 1981). Dermal absorption is limited (Tsuruta, 1982), but may be enhanced by other solvents.

In man, n-hexane is absorbed slowly via the lung and very slowly though the skin. 2,5-Hexanedione was the main metabolite found in human blood and urine of workers exposed to n-hexane (Mutti *et al.*, 1984). Measurements of post-shift levels of 2,5-hexanedione in urine have shown a positive correlation with both the n-hexane TWA concentration in air and the end of shift blood levels of n-hexane, and indicate that n-hexane may accumulate in the human body (Mutti *et al.*, 1984; Perbellini and Bartolucci, 1985; Imbriani *et al.*, 1984). 2,5-Hexanedione has been proposed as the metabolite responsible for toxic effects in the testes and nervous system (Chapin *et al.*, 1983; Graham *et al.*, 1982).

n-Hexane has low acute toxicity, with an LC50 (1 hour) of 77,000 ppm (276 g/m^3) in rats (Pryor *et al.*, 1982). The critical effects of n-hexane appear to be testicular toxicity and neurotoxicity (both to the central and peripheral nervous systems). Exposure of rats to 5000 ppm (17900 mg/m^3) produced testicular effects which were reversible after a single exposure but irreversible after 2 weeks' exposure, 16h/d, 6d/w (De Martino *et al.*, 1987). Signs of testicular damage were clear before neuropathic symptoms developed in the animals.

The neurotoxicity is characterised clinically by hind limb weakness, progressing to paralysis. Rats exposed to 500 ppm (1790 mg/m^3) n-hexane (99%) 22h/d, 7d/w exhibited axonal swelling in the tibial nerve after 2 months leading to pronounced degeneration and loss of axons in the tibial and sciatic nerves and lumbar cord after 6 months' exposure (API, 1983a,b). No effects were seen at an exposure level of 125 ppm (448 mg/m^3). In addition to the effects on the PNS, recent publications have shown that n-hexane has an effect on the CNS in experimental animals (Pezzoli *et al.*, 1990). The biochemical mechanism of

action of the metabolite 2,5-hexanedione is similar for the CNS and PNS (Backstrom *et al.*, 1990, 1992).

Effects on pup weight gain and on the CNS have been reported at 1500 ppm (5370 mg/m^3) n-hexane, which also caused maternal toxicity (Stotlemburg-Didinger *et al.*, 1984, abstract). Exposure of rats to commercial hexane for two generations resulted in reduced body weight gains at 9000 ppm (32220 mg/m^3), but no adverse effects on reproduction(Daughtrey *et al.,* 1994). No effects were seen in rats exposed to 900 or 3000 ppm (3222 or 10740 mg/m^3) commercial hexane.

Chromosomal damage has been reported in Chinese hamster fibroblasts without metabolic activation *in vitro* (Ishidate and Sofuni, 1984) and in bone marrow cells of mice exposed to n-hexane (uv grade), 6h/d for 5 days (Hazleton Labs, 1981). There was no evidence for mutations in other *in vitro* tests. The relevance of the reported clastogenic effects to carcinogenicity are not clear at present, and these have therefore not been taken into account for setting the limit.

The carcinogenic potential of n-hexane has been inadequately investigated. There was no significant evidence of embryotoxicity or teratogenicity in rats exposed to 1000 ppm (3580 mg/m^3) (Bus *et al.*, 1979).

n-Hexane is a mild irritant when in contact with human skin for short periods. There are no reports of skin sensitisation.

There is a large number of studies linking occupational exposure to n-hexane to the incidence of peripheral neuropathy in humans. However, few of these report air concentrations, and where exposures are quoted it is not clear whether they refer to n-hexane or to commercial hexane. Also workers were exposed to mixtures of volatile solvents, and the proportions of n-hexane are not reported.

Several cross-sectional studies have reported mild sub clinical effects (i.e. electrophysiological changes in the peripheral nerves) in workers exposed within the range of 50 to 100 ppm (179 to 358 mg/m^3) n-hexane (NIOSH, 1981; 1983; Mutti *et al.*, 1982; Iida, 1982; Sanagi *et al.*, 1980). Transient paraesthesias were reported in two personnel at a hexane extraction facility (NIOSH, 1981). The maximum 8h-TWA hexane concentration at this site was 26 ppm (93 mg/m^3). However, leaks from some process equipment may have led to higher levels of acute exposure (NIOSH, 1983). Iida (1982) reported sensory neuropathy in Japanese sandal makers exposed to n-hexane at levels below 50 ppm (179 mg/m^3). Mild symptoms were also reported in a small group of workers in a factory producing tungsten carbide alloys where a mean 8h TWA of 58 ppm (208 mg/m^3) n-hexane was determined over a 2 year period (Sanagi *et al.*, 1980). Exposure to 190 ppm (680 mg/m^3) n-hexane for periods in excess of 8h/d was associated with the onset of clinically overt peripheral neuropathy (Wang *et al.*, 1986).

Aiello *et al.* (1980) reported electrophysiological changes in workers exposed to a mixture of ethyl acetate, cyclohexane, trichloroethane and n-hexane for 0.3 to 20 years in a shoe factory. The peak value for n-hexane was about 18 ppm (69 mg/m^3). The exposure levels were inadequately reported and it is possible that skin contact and oral ingestion occurred in addition to inhalation. This study was not taken into account for setting the

limit because of the inadequate reporting of atmospheric concentrations within mixtures of other solvents.

Most of these investigations do not allow thresholds to be established. However, Governa *et al.* (1987) studied electroneuromyographic changes in the peripheral muscles in workers exposed to n-hexane and determined levels of 2,5-hexanedione in urine. They concluded that, if the 2,5-hexanedione concentration in post-shift urine samples exceeded 7.5 mg/l, significant electroneuromyographic abnormalities occurred. According to the evaluation of the correlation of urinary 2,5-hexanedione and airborne n-hexane levels by ACGIH (1993), this corresponds to an 8h TWA of about 70 ppm (250 mg/m^3).

Recommendation

The study of Governa *et al*. (1987), establishing that electroneuromyographic abnormalities occur in workers with concentrations of 2,5-hexanedione in post-shift urine greater than 7.5 mg/l, corresponding to an 8-hour TWA of about 70 ppm (250 mg/m^3), together with the workplace observations cited above reporting electrophysiological changes at atmospheric concentrations in the region of 50 to 100 ppm (179 to 358 mg/m^3) n-hexane, were considered to be the best available basis for proposing an 8 hour TWA. The recent observations of CNS changes due to n-hexane in experimental animals and humans underline the importance of the neurotoxic effects of the metabolite 2,5-hexanedione for setting the limit value for n-hexane. It therefore seems that an atmospheric level of about 70 ppm (250 mg/m^3) is a LOAEL for effects on the PNS. An uncertainty factor of 2 was considered to be adequate for mild effects observed in workers. Taking into account the preferred value approach, an 8-hour TWA of 20 ppm (72 mg/m^3) is recommended.

No STEL or "skin" notation was considered to be necessary.

At the levels recommended, no measurement difficulties are foreseen.

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