Appendix B
Section J

n-HEXANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

The solvent n-hexane was frequently employed as a vehicle for glues and cements. Its use is now limited to analytical procedures and in oil extraction from seeds. Workers exposed to n-hexane have been found to have symptoms of peripheral neuropathy. Neuropathy was also noted in experimental animals exposed to this substance. These animal studies indicated that it impaired neural transmission both centrally and peripherally. A health-based maximum contaminant level (MCL) of 33 ug/L has been developed for n-hexane to protect against neuropathy.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical properties

Chemical name	n-Hexane
CAS #	110-54-3
Chemical formula	C_6H_{14}
Chemical structure	$CH_3-CH_2-CH_2-CH_2-CH_2-CH_3$
Molecular weight	86.17
Physical state	colorless liquid at room temperature
Melting point	-95 ^{o}C
Boiling point	69 ^{o}C
Vapor pressure	100 mm Hg at 15.8 ^{o}C
Specific gravity, density	0.66 at 20 ^{o}C
Water-odor threshold	0.0064 mg/L
Air-odor threshold	230-875 mg/m^3
Conversion factor	1 ppm = 3.52 mg/m^3 284 ppm = 1 mg/L
Solubility	75.5 mg/L in salt water at 20 ^{o}C (Amoore and Hautala, 1983) 13 mg/L in distilled water at 20 ^{o}C

Production and Use

Commercial hexane is a mixture of hexane isomers with small amounts of cyclopentane, cyclohexane, pentane and heptane isomers (ACGIH, 1983). It may contain as little as 20% or as much as 80% normal hexane (n-hexane).

n-Hexane has been used primarily as a solvent in glues. It is used to determine the refractive index of minerals and as a substitute for mercury in thermometers (U.S.EPA, 1985). n-Hexane is also used to extract oil from various seeds, particularly soybean and cotton seeds (U.S.EPA, 1985).

Guidelines, Regulations, and Standards

The National Institute of Occupational Safety and Health (NIOSH) has recommended a time-weighted-average (TWA) of 350 mg/m^3 limit with a ceiling of 1800 mg/m^3 for 15 minutes for alkanes (NIOSH, 1977).

In 1983, the American Conference of Government Industrial Hygienists (ACGIH) recommended a threshold limit value for n-hexane of 50 ppm (180 mg/m^3) (ACGIH, 1983-1984).

The U.S.EPA advises 4000 ug/L as a longer-term exposure drinking water limit for a 10 kg child (U.S.EPA, 1985).

ENVIRONMENTAL EXPOSURE

n-Hexane, a major component of petroleum fuels, constitutes approximately 1% of all emitted hydrocarbons from diesel and gasoline exhaust. Leaks and spills of petroleum fuels appear to be the most significant potential source of n-hexane contamination of ground water. In aqueous media, n-hexane can be degradaded by flora in ground water and by photo-oxidation (NIOSH, 1977).

n-Hexane is not being currently monitored under the New Jersey Assembly Bill A-280 program because suitable analytical techniques have not been developed.

METABOLISM AND PHARMACOKINETICS

Absorption, Distribution, and Excretion

n-Hexane is slowly absorbed by inhalation, oral, and dermal routes.

In one investigation, male rats were exposed by inhalation to 500, 1000, 3000 or 10,000 ppm of [^{14}C]n-hexane for 6 hours. Exposure was followed by a 72-hour nonexposure period. It was found that 12, 24, 38 or 68% respectively of the acquired body burden of was expired as n-hexane and that 35, 40, 31 and 18% was recovered in urine respectively with incremental n-hexane concentration. Radioactivity remaining in the tissues and carcass after 72 hours represented 6.1, 8.8, 7.4 and 5.4% of the body burden (Bus et al., 1983).

Metabolism

Metabolites of n-hexane were identified in the urine of Charles River rats dosed orally with 570 mg/kg of this substance (DiVincenzo et al., 1980). Metabolites identified included 2-hexanol, methyl n-butyl ketone (MBK), 5-hydroxy-2-hexanone, 2,5-hexanediol and 2,5-hexanedione. Metabolites of hexane identified in the urine of shoe factory workers exposed to 10-140 ppm included: 2-hexanol, 2,5-hexanedione, 2,5-dimethylfuran and o-valerolactone (Perbillini et al., 1980).

Human Exposure and Body Burden

Human exposure to n-hexane has occurred principally from use of glues and cement containing this material. Occupational exposure may also occur by the inhalation of gasoline (ACGIH, 1980). Nonoccupational

exposure has occurred through the sniffing of n-hexane containing glues by children and adults.

HEALTH EFFECTS

Overview

n-Hexane is known to be neurotoxic in both animals and humans. Toxicity produces both central and peripheral effects, notably peripheral denervation neuropathy. There is no evidence that it is a carcinogen, although this aspect has not been researched in animals.

Human

An exposure of 5,000 ppm for 10 minutes has been reported to cause dizziness. Slight nausea, headache and eye and throat irritation were found at 1,400 to 1,500 ppm (ACGIH, 1980).

Employees working in a room with 650 to 1,300 ppm showed clinical signs of n-hexane toxicity after two to four months. Common symptoms were headache, burning sensation of the face, abdominal cramps, numbness, paresthesia and weakness of distal extremities. Physical examination revealed foot drop gait, bilateral wrist drop, and absence of Achilles tendon reflex. Biopsies of the anterior tibial muscle and sural nerves revealed small angulated fibers and other fibers with clear central zones (denervation type of injury). Motor endplates were also damaged. The symptoms diminished after the subjects left employment (Hershkowitz et al., 1971).

A major outbreak of n-hexane polyneuropathy occurred in Japan, in 1968 (Iida, 1982). Of 1662 workers exposed to n-hexane during the manufacture of sandals, 93 suffered from this impairment. The concentration of n-hexane in the work environment ranged from 500-2500 ppm, exceeding the allowable concentration limits in Japan at that time. In 82% of the cases, numbness in the distal portion of the extremities was found initially. A chief finding on neurological examination was sensorimotor involvement of the extremities characterized as sensorimotor polyneuropathy with amyotrophy or sensoripolyneuropathy.

A rescreening of workers from the same industry in 1981 showed 21 cases of mild polyneuropathy associated with n-hexane exposure, although the n-hexane air levels were below 50 ppm (Iida, 1982). This polyneuropathy occurred without observable denervation activity.

Animal

Acute. Male Sprague-Dawley rats that had received a single oral dose of 1290 mg/kg of n-hexane in corn oil (the control animals received

corn oil alone) showed no measurable effects either in organ weights or in glutamic pyruvic transferase and ornithine carbamyl transferase enzyme levels after 42 hours (Hewett et al., 1980).

Chronic. Charles River male rats were given oral doses of 570 mg/kg of n-hexane 5 days per week for 90 days (Krasavage et al., 1980) and 1,140 and 4,000 mg/kg for 120 days. The toxic endpoint for these studies was hind limb paralysis. Once this point occurred the animals were killed and autopsied. There were no clinical or histologic signs of toxicity at either the 1,140 or 570 mg/kg dose levels. At the 4,000 mg/kg level there were multifocal axonal swellings, adaxonal myelin infolding and paranodal myelin retraction.

A study of Wistar strain male rats exposed to 3,000 ppm (10.6 g/m^3) of n-pentane, n-hexane, or n-heptane for 12 hrs per day for 16 weeks showed that n-hexane severely disturbed the motor nerve conduction and transmission across the neuromuscular junction. Weight loss occurred at all dose levels (Takeuchi et al., 1980).

After comparing hind limb weakness from n-hexane, methyl n-butyl ketone, and 2,5-hexanedione, Krasavage et al. (1980) concluded that 2,5-hexanedione is probably the neurotoxic metabolite of both n-hexane and methyl-n-butyl ketone.

Altenkirch et al. (1982) reported that male Wistar rats continuously exposed to 500 ppm n-hexane (24 hr per day, 7 days per week) showed complete hindlimb paralysis after nine weeks. Rats exposed to 500 ppm for 8 hours per day for 40 weeks did not develop clinical or morphological signs of neuropathy.

Howd et al. (1983) compared responses of weanling and young adult rats exposed to 1000 ppm n-hexane by inhalation (24 hrs per day, 6 days per week) for 11 weeks. Within two weeks of exposure, significant decreases in body weight and grip strength were seen. The older rats exhibited an earlier and more severe sign of hind limb flaccid paralysis. However, both groups showed the same degree of impairment in tail nerve conduction time and brain stem auditory-evoked response. The brain stem auditory-evoked response and the compound action potential of the ventral caudal nerve indicate that hexane exposure caused latency of nerve conduction both centrally and peripherally.

In a followup study (Rebert and Sorenson, 1983), Fisher 344 rats were exposed to 500, 1000, and 1500 ppm for 5 days per week, 24 hours per day for 11 weeks. The action potential of the ventral caudal (tail) nerve, the brain stem auditory-evoked response, and cortical somatosensory- auditory- and visual-evoked responses were recorded. Fore- and hind-grip strengths were also measured. At 500 ppm there was a decrease in conduction time in the brain stem and auditory-evoked responses, and diminished body weight and grip strength. There was no

clear effect at 500 ppm on the other parameters. At the higher n-hexane exposure levels there was clear impairment of responses in all measurable parameters.

Reproductive, Embryotoxic, and Teratogenic

In one study, n-hexane was found not to be teratogenic to rats. Pregnant rats were exposed for 6 hours per day to 1000 ppm n-hexane on days 8-12, 12-16, or 8-16 of gestation. Postnatal growth of pups born to dams exposed to 1,000 ppm n-hexane 6 hour per day on day 8-16 of gestation was significantly depressed ($p \leq 0.05$) (Bus et al., 1979) but normal weight recovered in 7 weeks. No significant variations in fetal resorptions, body weights, visible anomalies, and incidence of soft tissue and skeletal anomalies were noted in any treatment groups.

Krasavage et al. (1980) reported that administration of 4,000 mg/kg for 120 days of n-hexane led to varying stages of testicular atrophy. 2,5-Hexanedione alone also induced testicular atrophy.

Mutagenicity

No studies have been found that evaluate n-hexane mutagenicity.

Carcinogenicity

No studies have been found that evaluate n-hexane induced carcinogenicity.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

None of the animal studies described here studied the effects of chronic exposure to n-hexane. Krasavage et al. (1980) was the only study which used oral dosing and might be considered to be the most appropriate for such an evaluation. Hind limb weakness was seen only at the 4,000 mg/kg per day oral dose, whereas neuropathy was seen at lower doses in animal inhalation studies. Krasavage et al. (1980) identified a NOAEL (no-observed-adverse-effect-level) and a LOAEL (lowest-observed-adverse-effect-level) of 814 mg/kg per day and 2,860 mg/kg per day, respectively. [NOAEL and LOAEL were obtained by multiplying the intermittent dose levels of 1,140 and 4,000 mg/kg per day, respectively, by 5/7 (5 days per week)].

The Rebert and Sorenson (1983) study showed increased latency in neural response time with a 500-ppm dose and could be considered the most appropriate animal study to derive an acceptable level although a NOAEL was not observed. Rebert and Sorenson (1983) identified a LOAEL

of 1,257 mg/m^3. [LOAEL was obtained by multiplying the intermittent exposure level of 500 ppm (1760 mg/m^3) by 5/7 (5 days per week)]. This LOAEL is equivalent to an oral concentration of 359 mg/kg per day. The equivalent value was obtained by multiplying the intermittent exposure level of 1260 mg/m^3 by the human inhalation rate 20 m^3 per day) and dividing by the estimated weight of the human (70 kg).]

Although the study by Krasavage provides dose-response data which identifies a NOAEL and a LOAEL, the LOAEL identified by Rebert and Sorenson (1983) is lower than the NOAEL identified by Krasavage et al (1980). Therefore, the data presented by Rebert and Sorenson (1983) are most appropriate data for derivation of the MCL.

The study by Iida (1982) was judged inappropriate due to the lack of experimental details.

Calculation of the Health-Based Maximum Contaminant Level (MCL)

A LOAEL of 500 ppm from the Rebert and Sorenson study (1983) was used to derive the MCL.

Route-to-route extrapolation is appropriate to convert the inhalation dose to the oral dose for the rat. The U.S. EPA (1984) has outlined a method which incorporates an estimated respiratory rate for the rat and then extrapolates to an absorbed dose. The absorbed dose for the human is assumed to be the same as for the rat on a weight-to-weight basis.

Calculation of absorbed dose in rat. A respiratory rate for rats must be estimated on the basis of body weight (Anderson, et al., 1977).

For rats: $0.105\ (W_r/0.113)^{2/3}\ m^3/d$

$$R = 0.105\ \frac{0.210}{0.113}^{2/3}\ m^3/d$$

$$R = 0.130\ m^3/day$$

therefore:

$$ADr = \frac{(LOAEL)\ (d)\ (A)\ (R)}{Wr}$$

$$ADr = \frac{(1760)\ (5/7)\ (0.06)\ (.130)}{.210}$$

$$ADr = 46.7\ mg/kg/day$$

Calculation of Acceptable Daily Intake (ADI)

$$ADI = \frac{ADr}{10{,}000} = \frac{46.7}{10{,}000} \text{ mg/kg/day}$$

$$ADI = 0.00467 \text{ mg/kg/day}$$

Calculation of Health-Based Maximum Contaminant Level (MCL)

$$MCL = \frac{ADI\ (0.20)\ (70\ kg)}{(2\ L)}$$

$$MCL = \frac{0.00467\ mg/kg/day (0.20)\ (70\ kg)\ (1000\ ug/mg)}{2\ L}$$

$$MCL = 33 \text{ ug/L}$$

where

R = estimated respiratory rate in rat

W_r = average weight of rat from Rebert and Sorenson (1983) study

ADr = absorbed dose in the rat

d = number of days exposed per week

A = pulmonary absorption factor

LOAEL = lowest-observed-adverse-effect-level

70 kg = Assumed body weight of an adult Human

0.20 = Contribution from drinking water alone

2 L = Assumed volume of water consumed daily by an adult

1760 mg/m^3 = LOAEL

5/7 = Conversion of 5 day/week dosing schedule to 7 day/week

10,000 = Uncertainty factor appropriate for use with subchronic animal data, and to convert LOAEL to NOAEL (U.S. EPA, 1985)

70 kg = Assumed body weight of an adult

0.06 = Pulmonary absorption factor (EOHS, 1983)

Assumptions and Uncertainty

The calculation of the MCL was dependent upon inhalation rather than ingestion, the prefered mode. This was done because the ingestion study had a higher LOAEL than the inhalation study. A pulmonary-absorption factor of 0.06 was derived from the observation that the fraction of n-hexane absorbed from the lungs to the blood was of 5.6% to 15% (EOHS, 1983). Therefore, 0.06 was selected as the most conservative assumption concerning the extent of pulmonary absorption of n-hexane.

None of the studies available investigated chronic exposure to n-hexane.

Conclusions

A health-based MCL of 33 ug/L for n-hexane was derived. The calculation was based on neurotoxic effects observed in rats exposed to n-hexane by inhalation.

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