

## CHRONIC TOXICITY SUMMARY

# N-HEXANE

(normal hexane)

CAS Registry Number: 110-54-3

### I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	<b>7000 mg/m<sup>3</sup></b> (2000 ppb)
<i>Critical effect(s)</i>	Neurotoxicity; electrophysiological alterations in humans
<i>Hazard index target(s)</i>	Nervous system

### II. Physical and Chemical Properties (HSDB, 1999)

<i>Description</i>	Colorless liquid, gas
<i>Molecular formula</i>	C <sub>6</sub> H <sub>14</sub>
<i>Molecular weight</i>	86.10
<i>Density</i>	0.660 g/cm <sup>3</sup> @ 20° C
<i>Boiling point</i>	68.95°C
<i>Melting point</i>	-95.3°C
<i>Vapor pressure</i>	150 torr @ 25° C
<i>Solubility</i>	Insoluble in water; soluble in most organic solvents; very soluble in alcohol
<i>Conversion factor</i>	1 ppm = 3.52 mg/m <sup>3</sup> @ 25° C

### III. Major Uses or Sources

n-Hexane is used in the extraction of vegetable oil from seeds such as safflower, soybean, cotton, and flax (HSDB, 1995). It is also used as a alcohol denaturant and as a paint diluent. The textile, furniture and leather industries use n-hexane as a cleaning agent. Many petroleum and gasoline products contain n-hexane. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 999,225 pounds of hexane (CARB, 1999).

### IV. Effects of Human Exposure

In an offset printing factory with 56 workers, symptomatic peripheral neuropathy was noted in 20 of 56 (36%) workers, while another 26 (46%) had evidence of subclinical neuropathy (Chang *et al.*, 1993). Reduced sensory action potentials; reduced motor action potentials; decreased motor nerve conduction velocity; and increased distal latency were found in most workers. Giant axonal swellings with accumulation of 10 nm neurofilaments, myelin sheath attenuation, and widening of nodal gaps were noted upon sural nerve biopsy of a severe case. Optic neuropathy and CNS impairment were not usually found. Personal air samples had 80 to 210 ppm hexane (mean = 132 ppm), 20 to 680 ppm isopropanol (mean = 235 ppm), and 20 to 84 ppm (mean = 50 ppm) toluene. The workers worked 12 hours per day for 6 days per week. The mean duration of employment was 2.6 years, with a range of 1 month to 30 years.

An epidemiologic study was performed on workers employed in a factory producing tungsten carbide alloys and exposed for an average of 6.2 years to solvent vapors consisting of an 8-hour time weighted average of 58 ppm ( $\pm 41$  ppm) n-hexane and 39 ppm ( $\pm 30$  ppm) acetone (Sanagi *et al.*, 1980). Neurological examinations performed on both control and exposed workers examined cranial nerves, motor and sensory nerves, reflexes, coordination and gait. Neurophysiological and nerve stimulation studies were also performed. While no overt neurological abnormalities were noted, the mean motor nerve conduction velocity and residual latency of the exposed group were significantly decreased as compared to unexposed workers. The effects observed are consistent with other reports of n-hexane-induced peripheral neuropathy. The study reports a LOAEL of 58 ppm n-hexane.

Polyneuropathy with subsequent development of muscular atrophy and paresthesia in the distal extremities was observed in workers exposed to between 500 and 1000 ppm n-hexane in a pharmaceutical plant (Yamada, 1967).

A group of 15 industrial workers exposed to n-hexane in vegetable oil extracting and adhesive bandage manufacturing processes was examined for signs of neurotoxicity and ophthalmological changes (Raitta *et al.*, 1978; Seppalainen *et al.*, 1979). The workers (11 males and 4 females) had been exposed to hexane for 5 to 21 years (mean of 12 years). Ten healthy workers served as controls. Exposures were found to be variable; concentrations as high as 3000 ppm were found on some occasions, although exposure concentrations were usually well below 500 ppm. The authors concluded that the high short-term exposures, occurring occasionally for 1 to 2 hours at a time, could have been major factors in the effects observed. Visual evoked potentials (VEPs) were generally reduced among the exposed subjects and latencies tended to be increased (Seppalainen *et al.*, 1979). Visual acuity, visual fields, intraocular pressure, and biomicroscopical findings were normal. Macular changes were noted in 11 and impaired color discrimination was found in 12 of the 15 subjects, largely in the blue-yellow spectrum (Raitta *et al.*, 1978).

Fifteen (25%) of 59 press proofing workers had polyneuropathy (Wang *et al.*, 1986). All of the patients with polyneuropathy were regularly exposed to n-hexane, and there was a significant association between n-hexane concentration and prevalence of polyneuropathy. The ambient concentration of n-hexane of 190 ppm was found in one factory in which all six workers developed polyneuropathy. Workers exposed to less than 100 ppm n-hexane who frequently worked overtime demonstrated significant decreases in motor nerve conduction velocities in median, ulnar, and peroneal nerves. Twelve of 13 workers who regularly slept in the factory had polyneuropathy compared to three (7%) of 46 employees who did not sleep in the factory.

Ninety-three of 1662 Japanese workers were found to have polyneuropathy (Yamamura, 1969; Sobue *et al.*, 1978). All of the workers developing polyneuropathy were employed in pasting with rubber cement containing 70% or more hexane and small amounts of toluene. The worksites were poorly ventilated and concentrations in workrooms were measured at between 500 and 2500 ppm hexane. One patient developed numbness and weakness of the legs after 6 months of exposure to hexane-based solvents. This patient was hospitalized for over a year until the muscle weakness and atrophy improved enough to discharge the patient.

Urinary 2,5-hexanedione concentrations were significantly higher in 35 male workers exposed to n-hexane than in an unexposed group (Karakaya *et al.*, 1996). Significant decreases in serum IgG, IgM and IgA levels were also found, and a significant correlation was noted between urinary 2,5-hexanedione concentrations and serum Ig level of the exposed group.

An association between n-hexane and parkinsonism has been proposed based on two case reports (Pezzoli *et al.*, 1989; 1995). Regional striatal abnormalities of the nigrostriatal dopaminergic system and of glucose metabolism, observed with positron emission tomography studies, were considered distinct from those seen in idiopathic Parkinson's disease.

Co-exposure to acetone increased the urinary concentrations of free and total 2,5-hexanedione (2,5-HD) in a study of 87 hexane-exposed workers (Cardona *et al.*, 1996). Increased urinary 2,5-HD is noted also with coexposure to hexane and methyl ethyl ketone (Ichihara *et al.*, 1998).

## V. Effects of Animal Exposure

Groups of 12 Sprague-Dawley (SD) rats inhaled n-hexane (0, 6, 26, or 129 ppm) for 6 hours/day, 5 days/week for 26 weeks (Bio/dynamics, 1978). A second experiment from the same report involved inhalation exposures of SD rats for 26 weeks to 0, 5, 27, or 126 ppm hexane for 21 hours/day, 7 days/week. There were no consistent dose-related differences between exposed and control animals, although small numbers of animals were involved and examinations were limited to physical observation, body weight, hematological parameters, clinical chemistry, and necropsy of spontaneous deaths. The highest concentration (126 ppm for 21 hours/day, 7 days/week) was a NOAEL and represents a time-weighted average exposure of 110.2 ppm over the duration of the experiment.

F-344 rats and B6C3F1 mice (50/sex/concentration/species) inhaled commercial hexane solvent (0, 900, 3000, or 9000 ppm) for 6 h/day, 5 days/week over 2 years (Daughtrey *et al.*, 1999). No significant differences in mortality were noted between hexane-exposed and control groups. Small statistically significant reductions in body weight gain were noted in male and female rats inhaling 3000 ppm or more and in female mice inhaling 9000 ppm. Epithelial cell hyperplasia was increased in the nasoturbinate and larynx of exposed rats.

Fischer 344 rats (5/sex/dose) inhaled >99.5% pure n-hexane (0, 3000, 6500, or 10,000 ppm) for 6 hours/day, 5 days/week over 13 weeks (Cavender *et al.*, 1984). No statistically significant differences were noted in food consumption, ophthalmologic examination, neurological function, or hematological or serum chemistry parameters in either males or females. Female body weights and clinical observations were unaltered by hexane treatment. The mean body weight gain of male rats in the 10,000-ppm group was significantly decreased compared with controls at 4 weeks of exposure and thereafter. Axonopathy was noted in the tibial nerve of four of five male rats exposed to 10,000 ppm and in one of five male rats exposed to 6500 ppm. Axonopathy in the medulla was noted in one male rat exposed to 10,000-ppm. Males inhaling 10,000 ppm had slightly but significantly lower brain weights. No other adverse histopathological effects were reported. This study identifies a NOAEL for neurotoxicity of 3000 ppm, with an average experimental exposure of 540 ppm.

B6C3F<sub>1</sub> mice were exposed to 500, 1000, 4000, or 10,000 ppm n-hexane 6 hours per day, 5 days per week for 13 weeks or to 1000 ppm n-hexane for 22 hours per day, 5 days per week for 13 weeks (Dunnick *et al.*, 1989). Mild inflammatory, erosive and regenerative lesions in the olfactory and respiratory epithelium were observed in the nasal cavity of mice exposed to 1000 ppm n-hexane and higher. "Minimal lesions" were noted in those mice exposed to 500 or 1000 ppm n-hexane. Paranodal axonal swelling in the tibial nerve was observed in 6/8 mice exposed to 1000 ppm for 22 hours per day and in 6/8 mice exposed to 10,000 ppm for 6 hours per day. No such swelling was noted in neurohistological examination of the control animals; neurohistological examination was not performed in those animals exposed to 500 and 1000 ppm for 6 hours per day. A NOAEL for histological lesions of the nasal turbinates of 500 ppm n-hexane was identified. Because neurohistological examinations were not performed in animals exposed to 500 or 1000 ppm (the NOAEL and LOAEL, respectively), the interpretation of the results from this study are seriously limited.

Male SM-A strain mice (10/group) were exposed continuously to 0, 100, 250, 500, 1000, or 2000 ppm commercial grade hexane (65 to 70% n-hexane with the remainder being other hexane isomers) for 6 days/week for 1 year (Miyagaki, 1967). Electromyography, strength-duration curves, electrical reaction time, and flexor/extensor chronaxy ratio, gait posture and muscular atrophy were studied. Increased complexity of NMU (neuromuscular unit) voltages during electromyographic analysis was noted in 0/6 controls, 1/6 in the 100 ppm group, 3/6 in the 250 ppm group, 5/6 in the 500 ppm group, 3/3 in the 1000 ppm group, and 4/4 in the 2000 ppm group. A dose-related increase in incidence and severity of reduced interference voltages from muscles was noted in mice exposed to 250 ppm or more, but not in controls (0/6

examined) or in the 100 ppm group (0/6). Dose-related abnormal posture and muscle atrophy were noted at 250 ppm or more. This study identifies a NOAEL of 100 ppm for neurotoxicity (68 ppm when adjusted for 67.5% n-hexane).

Rats inhaling 400-600 ppm n-hexane developed peripheral neuropathy after forty-five days of exposure (Schaumburg and Spencer, 1976). Giant axonal swellings and fiber degeneration were observed in the central and peripheral nervous systems. The changes were most notable in tibial nerves and in the cerebellum, medulla and spinal cord.

A dose-dependent decrease in motor nerve conduction velocity and body weight gain was observed in rats exposed to 500, 1200, or 3000 ppm n-hexane for 12 hours per day, 7 days per week for 16 weeks (Huang *et al.*, 1989). The neurotoxicity was significant in the two highest exposure groups; peripheral nerve degeneration, characterized by paranodal swellings and demyelination and remyelination in the myelinated nerve fibers, was observed and was more advanced in the highest exposure group.

Available studies indicate that the neurotoxicity of n-hexane is potentiated by concurrent exposure to methyl ethyl ketone (Altenkirch *et al.*, 1982).

Acetone has also been shown to potentiate the neurotoxicity of hexane and 2,5-HD. Male rabbits administered acetone and 2,5-HD intravenously had decreased body clearance of 2,5-HD (Lagefoged and Perbellini, 1986). Male rats were treated for 6 weeks with 0.5% w/v 2,5-hexanedione alone or in combination with 0.50% w/v acetone in the drinking water (Lagefoged *et al.*, 1994). Acetone potentiated effects on open field ambulation, or rearing and on the rotarod test. Giant axonal swelling was greater in acetone administered animals. During a dose-free 10-week recovery period, the acetone-supplemented group had less improvement in neurological parameters. Male Wistar rats were administered 0.5% w/v 2,5-hexanedione alone or in combination with 0.50% w/v acetone in the drinking water for 7 weeks (Lam *et al.*, 1991). Effects on radial arm maze behavior, a "brain-swelling" reaction, and synaptosomal functions were noted with 2,5-HD and exacerbated with acetone coexposure. In another study of male rats using the same doses for 6 weeks, testis weight, testis tubuli diameter and fertility were reduced with 2,5-HD exposure and potentiated with acetone coexposure (Larsen *et al.*, 1991).

Pregnant rats were exposed to 200, 1000, or 5000 ppm n-hexane 20 hours per day on days 9-19 of gestation (Mast *et al.*, 1987). A statistically significant decrease in fetal body weight compared to controls was observed in male offspring following maternal exposure to 1000 and 5000 ppm n-hexane. Maternal toxicity, indicated by decreased body weight gain, was observed in all exposure groups.

Pregnant rats were exposed to hexane (0, 93.4, or 408.7 ppm) on days 6 through 15 of gestation (Litton Bionetics, 1979). There were no adverse effects noted in dams, and no hexane-induced teratogenicity, changes in sex ratio, embryotoxicity, or impaired fetal growth or development.

Male New Zealand rabbits exposed to 3000 ppm n-hexane for 8 hours per day, 5 days per week for 24 weeks developed exposure-related lesions of the respiratory tract with the terminal bronchioles exhibiting the most characteristic damage (Lungarella *et al.*, 1984). These changes were noted even after a 120-day recovery period. Clinical signs of ocular and upper respiratory tract irritation and respiratory difficulties (such as gasping, lung rales, mouth breathing) were observed throughout the study in exposed rabbits.

## Derivation of Chronic Reference Exposure Level

<i>Key study</i>	Miyagaki (1967)
<i>Study population</i>	Male mice
<i>Exposure method</i>	Discontinuous inhalation
<i>Critical effects</i>	Peripheral neuropathy (electromyographic alterations; dose-related abnormal posture and muscle atrophy)
<i>LOAEL</i>	250 ppm
<i>NOAEL</i>	100 ppm
<i>Exposure continuity</i>	24 hours/day, 6 days/week
<i>Exposure duration</i>	1 year
<i>Average experimental exposure</i>	57.9 ppm for LOAEL group (100 ppm x 0.675 x 6/7)
<i>Human equivalent concentration</i>	57.9 ppm (gas with systemic effects, based on RGDR = 1 using default assumption that $\lambda(a) = \lambda(h)$ )
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	3
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	30
<i>Inhalation reference exposure level</i>	2 ppm (2000 ppb; 7 mg/m <sup>3</sup> ; 7000 µg/m <sup>3</sup> )

Three studies, an experimental study with mice (Miyagaki, 1967) and two occupational studies (Sanagi *et al.*, 1980; Chang *et al.*, 1993), were considered by OEHHA to be most informative and relevant to the derivation of a chronic REL. This was because these studies (1) evaluated the most sensitive endpoint (peripheral neuropathy) and (2) involved exposures over a significant fraction of a lifetime. While significant limitations may be noted for each of these studies individually, viewed collectively they provide a consistent view of the chronic inhalation toxicity of hexane and yield a stronger basis for deriving a chronic inhalation REL.

While the animal study has the disadvantage of introducing the uncertainty of interspecies differences, the limitations of the human studies were considered to be more significant. Specifically, both human studies were considered likely to overestimate effects of inhalation exposures to hexane.

The Sanagi study, which U.S. EPA used as the basis of its RfC, may overestimate hexane effect because of a confounding coexposure to acetone, which is known to potentiate hexane neuropathy. The minimum effective acetone inhalation concentration for potentiating hexane neuropathy is unclear, as studies (Ladefoged *et al.*, 1994; Lam *et al.*, 1991; Larsen *et al.*, 1991) have used orally administered acetone. The minimum effective acetone inhalation dose for potentiation of carbon tetrachloride hepatotoxicity in male Sprague-Dawley rats was 2500 ppm over 4 hours (Charbonneau *et al.*, 1986). A dose of 0.5% acetone in human drinking water is comparable, assuming equal absorption, to an inhalation concentration of approximately 1400 ppm (0.5% w/v x 2 L/day ÷ 2 m<sup>3</sup>/day = 5 g/m<sup>3</sup>; 5 g/m<sup>3</sup> x 1000 mg/g ÷ 3.52 mg/m<sup>3</sup> per ppm = 1400 ppm). As the acetone potentiating effects were all noted at higher exposures than are being considered in occupational studies and are at much higher concentrations than the REL itself, the significance of these findings is uncertain.

In the Chang study, the workers were probably intermittently exposed to higher inhalation exposures than were estimated from ambient air sampling, and significant dermal exposures were also likely. Furthermore, coexposure to high levels of isopropanol and toluene, may have confounded the results, although CNS effects were not noted and these substances are not known to induce or potentiate peripheral neuropathy.

As shown in Table 1, the human studies by Sanagi *et al.* (1980) and Chang *et al.* (1993) yield 7 to 10-fold lower RELs than the Miyagaki study. In view of the likely overprediction of hexane risks from these studies, due to co-exposure to other materials, which may potentiate the effects of hexane, these calculations may be viewed as generally supporting the 7000 µg/m<sup>3</sup> REL.

Table 1: Reference Exposure Levels (RELs) from Selected Human Studies

Study	Duration	Effect	LOAEL (ppm)	LOAEL (ppm) (TWA)	NOAEL (ppm)	NOAEL (ppm) (TWA)	total UF	REL (ppb)	REL ( $\mu\text{g}/\text{m}^3$ )
Sanagi <i>et al.</i> , 1980	6.2 years	decreased motor nerve conduction velocity; increased residual latency	58	20.7	Not observed		100 <sup>a</sup>	200	700
Chang <i>et al.</i> , 1993	mean 2.6 years: range 1 month to 12 years	Symptomatic peripheral neuropathy; decreased motor nerve conduction velocity; increased residual latency; axonal swelling of sural nerve	mean 132: range 80 - 210	83	Not observed		300 <sup>b</sup>	300	1000

<sup>a</sup> LOAEL uncertainty factor, 10; Intraspecies uncertainty factor, 10

<sup>b</sup> LOAEL uncertainty factor, 10; Subchronic uncertainty factor, 3; Intraspecies uncertainty factor, 10

The hexane exposure estimate was reduced for the Miyagaki data as the solvent used contained 67.5% n-hexane.

The average occupational exposure for the Chang study, which involved an unusual 72-hour work week, was calculated by assuming that 12 hours of occupational exposures at an inhalation rate of 20 L/min was followed by 4 hours of light work at 20 L/min and 8 hours of rest at 7.5 L/min. With these assumptions an estimated 63% of daily inhaled air occurred at the workplace.

The Chang study found that the severity of effects was not correlated with the length of exposure, suggesting that (1) susceptibility may differ markedly between individuals and/or (2) shorter exceedances of the time-weighted average concentration might be significant. Thus the subchronic uncertainty factor was reduced to 3-fold.

## VII. Data Strengths and Limitations for Development of the REL

There is a substantial database on the health effects of n-hexane in both humans and animals from which to derive a chronic reference exposure level. Some relevant studies are summarized in the table below.

<i>Study</i>	<i>Species</i>	<i>Exposure concentration</i>	<i>Exposure regimen</i>	<i>TWA from NOAEL<sup>a</sup></i>	<i>TWA from LOAEL<sup>a</sup></i>
Sanagi <i>et al.</i> (1980)	Humans	58 ppm (mean)	10 m <sup>3</sup> /d, 5 d/wk, 6.2 yr (mean)	None	20.7 ppm
Chang <i>et al.</i> (1993)	Humans	130 ppm (mean)	12 hr/d, 6 d/wk, 2.6 yr (mean)	None	83 ppm
Miyagaki (1967)	Male mice	0, 100, 250, 500, 1000, 2000 ppm	Continuous, 6 d/wk, 1 yr	57.9 ppm	121 ppm
Daughtrey <i>et al.</i> (1999)	F344 rats	0, 900, 3000, 9000 ppm	6 hr/d, 5 d/wk, 2 yr	None	161 ppm

Daughtrey <i>et al.</i> (1999)	B6C3F1 mice	0, 900, 3000, 9000 ppm	6 hr/d, 5 d/wk, 2 yr	None	161 ppm
Dunnick <i>et al.</i> (1989)	B6C3F1 mice	0, 500, 1000, 4000, 10,000 ppm	6 hr/d, 5 d/wk, 13 wk	89 ppm	179 ppm
Huang <i>et al.</i> (1989)	Wistar rats	0, 500, 1200, 3000 ppm	12 hr/d, 7 d/wk, 16 wk	None	250 ppm
Bio/dynamics (1978)	SD rats	0, 5, 27, 126 ppm	21 hr/d, 7 d/wk, 26 weeks	110 ppm	None
Cavender <i>et al.</i> (1984)	F344 rats	0, 3000, 6500, 10,000 ppm	6 hr/d, 5 d/wk, 13 wk	540 ppm	1160 ppm

<sup>a</sup> The experimental exposure was extrapolated to an equivalent (time-weighted average or TWA) continuous exposure.

The major strengths of the REL for hexane include: (1) the primary use of an animal study (Miyagaki, 1967) with controlled, nearly continuous chronic hexane exposures not confounded by coexposure to other solvents, which observed both a NOAEL and LOAEL; and (2) the results obtained from two different human studies (Sanagi, 1980; Chang *et al.*, 1993) which were viewed as being generally consistent with the animal study based REL.

There is uncertainty about interspecies as well as intraindividual differences in susceptibility to n-hexane peripheral neuropathy. In one study, controlled TWA exposures of 540 ppm (Cavender *et al.*, 1984) were not found to cause neuropathy in rats. Also human studies (especially that of Chang *et al.*, 1993) have shown that some individuals develop peripheral neuropathy within months, whereas others remain symptom-free despite years of employment at the same occupation at the same workplace.

OEHHA staff also estimated RELs from two other animal studies for comparison. In Bio/Dynamics (1978), 126 ppm for 21 hours/day, 7 days/week for 26 months was a NOAEL and represents a time-weighted average exposure of 110.2 ppm. Using an RGDR of 1 and a cumulative 30-fold uncertainty factor (3 for interspecies differences not accounted for by the RGDR method and 10-fold for intraspecies differences), a REL of 4 ppm (10,000 µg/m<sup>3</sup>) was derived. Cavender *et al.* (1984) identified a NOAEL for neurotoxicity of 3000 ppm, with an average experimental exposure of 540 ppm. A REL based on this study, using an RGDR of 1 and a 100-fold uncertainty factor (3 for subchronic (13 weeks) to chronic, 3 for interspecies, and 10 for intraspecies) would be 5.4 ppm (19,000 µg/m<sup>3</sup>).

## VIII. References

- Altenkirch H, Wagner HM, Stoltenburg G, and Spencer PS. 1982. Nervous system responses of rats to subchronic inhalation of N-hexane and N-hexane + methyl-ethyl-ketone mixtures. *J. Neurol. Sci.* 57:209-219.
- Bio Dynamics Inc. 1978. 26 Week Inhalation Toxicity Study of n-Hexane in the Rat. US EPA; Document #FYI-AX-1081-0137.
- Cardona A, Marhuenda D, Prieto MJ, Marti J, Periago JF, Sanchez JM. 1996. Behaviour of urinary 2,5-hexanedione in occupational co-exposure to n-hexane and acetone. *Int Arch Occup Environ Health* 68(2):88-93.
- Cavender FL, Casey HW, Salem H, Graham DG, Swenberg JA, Gralla EJ. 1984. A 13-week vapor inhalation study of n-hexane in rats with emphasis on neurotoxic effects. *Fundam. Appl. Toxicol.* 4(2 Pt 1):191-201.

- Chang CM, Yu CW, Fong KY, Leung SY, Tsin TW, Yu YL, Cheung TF, Chan SY. 1993. N-hexane neuropathy in offset printers. *J. Neurol. Neurosurg. Psychiatry* 56(5):538-542.
- Charbonneau M, Brodeur J, du Souich P, Plaa GL. 1986. Correlation between acetone-potentiated CCl<sub>4</sub>-induced liver injury and blood concentrations after inhalation or oral administration. *Toxicol. Appl. Pharmacol.* 30;84(2):286-294.
- Daughtrey W, Newton P, Rhoden R, Kirwin C, Haddock L, Duffy J, Keenan T, Richter W, Nicolich M. 1999. Chronic inhalation carcinogenicity study of commercial hexane solvent in F-344 rats and B6C3F1 mice. *Toxicol. Sci.* 48(1):21-29.
- Dunnick JK, Graham DG, Yang RS, Haber SB, and Brown HR. 1989. Thirteen-week toxicity study of n-hexane in B6C3F1 mice after inhalation exposure. *Toxicology* 57(2):163-172.
- HSDB. 1999. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland. WWW database (<http://sis.nlm.nih.gov/sis1/>).
- Huang J, Kato K, Shibata E, Sugimura K, Hisanaga N, Ono Y, Takeuchi Y. 1989. Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. *Arch. Toxicol.* 63(5):381-385.
- Ichihara G, Saito I, Kamijima M, Yu X, Shibata E, Toida M, Takeuchi Y. 1998. Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to n-hexane and methyl ethyl ketone. *Int. Arch. Occup. Environ. Health* 71(2):100-104.
- Karakaya A, Yucesoy B, Burgaz S, Sabir HU, Karakaya AE. 1996. Some immunological parameters in workers occupationally exposed to n-hexane. *Hum. Exp. Toxicol.* 15(1):56-8.
- Ladefoged O, Perbellini L. 1986. Acetone-induced changes in the toxicokinetics of 2,5-hexanedione in rabbits. *Scand. J. Work Environ. Health* 12(6):627-629.
- Ladefoged O, Roswall K, Larsen JJ. 1994. Acetone potentiation and influence on the reversibility of 2,5-hexanedione-induced neurotoxicity studied with behavioural and morphometric methods in rats. *Pharmacol. Toxicol.* 74(4-5):294-299.
- Lam HR, Larsen JJ, Ladefoged O, Moller A, Strange P, Arlien-Soborg P. 1991. Effects of 2,5-hexanedione alone and in combination with acetone on radial arm maze behavior, the "brain-swelling" reaction and synaptosomal functions. *Neurotoxicol. Teratol.* 13(4):407-412.
- Larsen JJ, Lykkegaard M, Ladefoged O. 1991. Infertility in rats induced by 2,5-hexanedione in combination with acetone. *Pharmacol. Toxicol.* 69(1):43-46.
- Litton Bionetics Inc. 1979. Teratology Study in Rats. n-Hexane. US EPA; Document #FYI-AX-0183-0231.
- Lungarella G, Barni-Comparini I, and Fonzi L. 1984. Pulmonary changes induced in rabbits by long-term exposure to n-hexane. *Arch. Toxicol.* 55(4):224-228.
- Mast TJ, Decker JR, Clark ML, *et al.* 1987. Inhalation developmental toxicology studies: teratology study of n-hexane in rats: Final report. Iss. PNL-6453; Order No. DE88006812. p.208.
- Miyagaki H. 1967. Electrophysiological studies on the peripheral neurotoxicity of n-hexane. *Jap. J. Ind. Health* 9(12-23): 660-671
- Paulson GW, and Waylonis GW. 1976. Polyneuropathy due to n-hexane. *Arch. Int. Med.* 136:880-882. [cited in U.S. EPA, 1995].

- Pezzoli G, Barbieri S, Ferrante C, Zecchinelli A, Foa V. 1989. Parkinsonism due to n-hexane exposure. *Lancet* 2(8667):874.
- Pezzoli G, Antonini A, Barbieri S, Canesi M, Perbellini L, Zecchinelli A, Mariani CB, Bonetti A, Leenders KL. 1995. n-Hexane-induced parkinsonism: pathogenetic hypotheses. *Mov. Disord.* 10(3):279-82.
- Raitta C, Seppalainen AN, Huuskonen MS. 1978. N-hexane maculopathy in industrial workers. *Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol.* 209(2):99-110. Sanagi S, Seki Y, Sugimoto K, and Hirata M. 1980. Peripheral nervous system functions of workers exposed to n-hexane at a low level. *Int. Arch. Occup. Environ. Health* 47:69-79.
- Schaumburg HH, Spencer PS. 1976. Degeneration in central and peripheral nervous systems produced by pure n-hexane: an experimental study. *Brain* 99(2):183-192. Seppalainen AM, Raitta C, and Huuskonen MS. 1979. n-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroencephal. Clin. Neurophysiol.* 47:492-498.
- Sobue I, Iida M, Yamamura Y, and Takayanagui T. 1978. N-Hexane polyneuropathy. *Int. J. Neurol.* 11(4):317-330.
- U.S. EPA. 1999. U. S. Environmental Protection Agency. Integrated Risk Information System (IRIS). Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria Assessment Office.
- Wang J-D, Chang Y-C, Kao K-P, Huang C-C, Lin C-C, and Yeh W-Y. 1986. An outbreak of n-hexane induced polyneuropathy among press proofing workers in Taipei. *Am. J. Ind. Med.* 10(2):111-118.
- Yamada S. 1967. Intoxication polyneuritis in the workers exposed to n-hexane. *Jap. J. Ind. Health* 9:651-659 [cited in U.S. EPA, 1994].
- Yamamura Y. 1969. n-Hexane polyneuropathy. *Folia Psychiatr. Neurol. Jap.* 23(1):45-57.