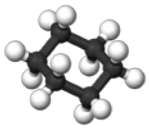
Cyclohexane (i.e. CyHx)

Revised: June 2, 2011

I. **IdentificationFW: Cyclx minutes review**

Chemical Name: Cyclohexane
Synonyms: Benzenehexahydride, Hexahydrobenzene; hexamethylene; hexanaphthalene
CAS Number: 110-82-7
Molecular Formula: C_6H_{12}
Structural Formula: see image at right



II. **Chemical and Physical Properties**

Physical State: liquid
Molecular Weight: 84.16 gm/mole
Conversion Factors: 1 ppm = 3.5 mg/m3 and 1 mg/m3 = 0.29 ppm
Freezing Point: 6.47 °C
Boiling Point: 80.7 °C
Vapor Pressure: 97 mmHg at 25 °C
Saturation Concentration: 103,530 ppm
Odor Description and Threshold: pungent/solvent/oil, no accepted references, all references ranged from 0.52 to 784 ppm, AIHA Review Committee reviewed all studies and accepted only one with detection limit of 784 ppm.
Flammability Limits: lower, 1.2%; upper 8.4% by volume in air
Flash Point: 8 °C (closed cup)
Specific Gravity: 0.78 gm/ml
Solubility in Water: immiscible
Stability: stable
Reactivity and Incompatibilities: reacts only with very strong acids

III. **Uses and Volume**

CyHx is used as a nonpolar solvent for the chemical industry, and raw material for the industrial production nylon. CyHx replaced benzene as glue solvent in the shoe, printing and leather factories. It is produced large-scale by reacting benzene with hydrogen. CyHx has been listed as an ingredient in spray adhesive, lacquer thinner, speciality auto product, contact cleaner, degreaser, caulk, spray paint, lab standards, insecticides and plasticizers from 1 to 70 percent. It may be present in gasoline less than one percent.

De Rosa E et al 1985 surveyed 504 solvent handling situations in the shoe, printing and painting industries. CyHx was used in 46.6% of all exposure situations and third after toluene (79.2%) and n-hexane (52.8%). Within these industries the frequency of CyHx use was: shoe 93.7%, painting 3.2% and printing 6.3%. Also, the CyHx exposure concentrations measured in these industries was: shoe 3 – 362; painting 2 – 153, and printing 3 – 17 (ppm). The CyHx exposure concentration within the shoe industry was predominately less than 150 ppm. Within the shoe industry the greatest solvent combination was n-hexane and CyHx (72.3%).

IV. **Toxicology Data**

A. Acute Toxicity and Irritancy

1. Oral

Two single-dose studies were identified but were of questionable value because they were high, single dose studies. Both were oral dosages, one in rabbits (1943) and the other in rats (1971). The actual studies were not obtained, but the abstracts indicated relatively high dosages required to cause death, the endpoint of interest.

2. Eye

Lammers et al 2009 and others conducting human clinical studies did not find significant eye irritation.

3. Skin

a. Irritation

Iyadomi et al 1998 studied neuropeptides in hairless rats exposed to acetone, cyclohexane, toluene and m-xylene for 240 minutes. Order of inflammation induced (greatest-least): toluene, m-xylene, cyclohexane, acetone.
Concowe 2010 reported aliphatic and cyclicalkanes to be mildly irritating.

b. Sensitization

No literature found in Pubmed search.

c. Absorption

Concowe 2010 studied absorption in volunteers and modeled uptake. Saturated hydrocarbons not likely to absorb enough to cause systemic effects, but prolonged defatting can lead to increased dermal uptake.

4. Inhalation

Lammers et al 2009 exposed rats to 0, 400, 2300 and 8100 ppm, 8 hr/day for three consecutive days (randomized). Functions evaluated: neuromuscular, activity, excitation, hyper-excitation, sensorimotor, and learned performance. There was slight reduction in psychomotor speed at 8100 ppm (LOAEL), but minimal central nervous system effects. It should be noted these effects were not consistent between assessments (there were differences between the first and third exposure days). Overall conclusion: "…at 8100 ppm, CyHx may have affected gait, tremor, sensorimotor reactivity and psychomotor speed, but all of the changes were small and their relationship to treatment was uncertain."

Christoph GR Drug Chem Tox 2000.

Adult male rats pressed a lever on a multiple fixed ratio-fixed interval (FR20-FI120 sec) schedule of food presentation, and after attaining a stable baseline subjects received an acute inhalation exposure to cyclohexane vapor (0 ppm, 500 ppm, 2000 ppm, or 7000 ppm) for 6 hr. During the operant session that began 30 min after termination of exposure, FR running rate for the 7000 ppm group decreased 11% relative to performance on the previous day. FR post-reinforcement pause duration and the rate and pattern of FT performance were unaffected. Cyclohexane exposures of 500 or 2000 ppm had no detectable effects. No enduring effects of cyclohexane occurred up to 2 weeks after exposure. An independent set of rats, trained under nominally identical conditions, received various doses (i.p.) of d-amphetamine (AMPH) or chlorpromazine (CPZ) at 1-2 week intervals. Effective doses of AMPH decreased FR running rate, decreased FR post-reinforcement pause duration and increased FI rate of response. AMPH also decreased the FI index of curvature, indicating a change from an accelerating rate during the FI to a more constant rate. Effective doses of CPZ decreased FR rate, increased FR pause duration, decreased FI rate, and decreased FI index of curvature. Thus, schedule-controlled operant procedures that were sensitive to the effects of psychoactive drugs were able to identify only a minor and transient effect of the highest concentration (7000 ppm) of cyclohexane vapor on operant performance.

Yasugi I Intl Arch Occup Environ Health 1994. 30-120 minutes, rabbits, cats, pigs, mice. NOAEL: 2,667 ppm

B. Genotoxicity

Mutat Res, 168: 69-240, 1986. Salmonella typhimurium, Histidine, Ames assay, results negative.
Mutat Res, 114: 283-385, 1983. Syrian hamster embryo (SA7/SHE) cells, viral enhanced, results negative.
Daughtrey WC, J Appl Toxicol, 1994; negative chrom abber in hamster cells.
Gupta KP, Cancer Lett, 1990; weak promoter skin tumor in mouse.

C. Metabolism and Pharmacokinetics

Hissink et al 2009 exposed three volunteers via inhalation to CyHx and measured blood and exhaled air during and following exposure of four hours. Within two hours blood levels reached 90% of four-hour level. Exhaled air concentrations dropped; 50% within first 20 minutes.

Perico A, Int Arch Occup Environ Health. 1999

This article reports the results obtained with the biological and environmental monitoring of occupational exposure to cyclohexane using 1,2-cyclohexanediol (1,2-DIOL) and 1,4-DIOL in urine. The kinetic profile of 1,2-DIOL in urine suggested by a physiologically based pharmacokinetic (PBPK) model was compared with the results obtained in workers. Individual exposure to cyclohexane was measured in 156 workers employed in shoe and leather factories. The biological monitoring of cyclohexane exposure was done by measurement of 1,2-DIOL and 1,4-DIOL in urine collected on different days of the working week. In all, 29 workers provided urine samples on Monday (before and after the work shift) and 47 workers provided biological samples on Thursday at the end of the shift and on Friday morning. Another 86 workers provided biological samples at the end of the work shift only on Monday or Thursday. Individual exposure to cyclohexane ranged from 7 to 617 mg/ m3 (geometric mean value 60 mg/m3). Urinary concentrations of 1,2-DIOL (geometric mean) were 3.1, 7.6, 13.2, and 6.3 mg/g creatinine on Monday (pre- and postshift), Thursday (postshift) and Friday (pre-shift), respectively. The corresponding values recorded for 1,4-DIOL were 2.8, 5.1, 7.8, and 3.7 mg/g creatinine. A fairly close, statistically significant correlation was found between environmental exposure to cyclohexane and postshift urinary 1,2-DIOL and 1,4-DIOL on Monday. Data collected on Thursday and Friday showed only a poor correlation to exposure with a wide scatter. Both metabolites have a urinary half-life of close to 18 h and accumulate during the working week. Comparison between data obtained from a PBPK model and those found in workers suggests that 1,2-DIOL and 1,4-DIOL are urinary metabolites suitable for the biological monitoring of industrial exposure to cyclohexane.

D. Developmental / Reproductive Toxicity

Kreckman KH et al 2000 did two-year reproduction and developmental studies in rats and rabbits to whole-body inhalation doses of 0, 500, 2000 and 7000 ppm. The 7000 ppm P1 and F1 females and males had lower mean body weights. During exposure clinical observations of adults found females with transient diminished or absent response to alert (sedative effect) at 2000 and 7000 ppm. (female NOAEL 500 ppm) Also females at 7000 ppm showed increased fur staining and wetness related to salivation and grooming briefly when animals were removed from the exposure chamber. Rabbits exhibited no clinical symptoms at any exposure level. The 7000 ppm F1 and F2 mean pup weight was low from lactation day 7 to day 25. (repro NOAEL 2000 ppm). 7000 ppm rats had reduced maternal body weight gain and food consumption. Clinical evaluation found rats had transient diminished response to auditory stimulus while exposed. (NOAEL 500 ppm for maternal effects). The rabbits showed no signs of maternal effects at the highest exposure group, 7000 ppm. No developmental toxicity was found for any exposure group in either rats or rabbits. (NOAEL 7000 ppm developmental effects).

The US EPA IRIS inhalation reference concentration (2004) is based upon the above study. The endpoint of concern was the reduced pup weights in the F1 and F2 generations. The EPA applied at total uncertainty factor of 300 to land on a 6 mg/M3 RfD.

E. Subacute

Bernard AM et al 1989 performed a series of experiments injecting female rats via I.P. at different dosages and examining for evidence of nephrotoxicity. The first experiment involved injection of a single 1.5 gm/kg cyclohexane dose. The only significant effect observed was an increased urinary excretion of B2-microglobulin. The second experiment involved repeated injections of 1 gm/kg cyclohexane. This caused a 3.2 fold increase in B2-microglobulin, but not a statistically significant

effect due to scatter of results. The final experiment involved repeated injection of 0.375, 0.75 and 1.5 gm/kg cyclohexane once a day for ten days. The increase in B2-microgloblinuria was both time and dose-dependent. Examination of the renal function of these animals at the end of treatment disclosed no change in glomerular filtration rate, renal plasma flow or the relative kidney weight. The renal concentrating ability was significantly depressed in rats treated with 1.5 gm/kg cyclohexane but not at 0.75 gm/kg. The LOAEL for renal effects was 1.5 gm/kg, and the NOAEL was 0.75 gm/kg. The study reported rat weight ranging from 0.15 to 0.25 kg, and if the average is assumed to be 0.2 kg, then the dose of 0.75 gm/kg equals 150 mg cyclohexane. Literature reports female rats inhale 0.182 M3/day. Thus, to estimate an inhalation dose, one could assume 100% of the inhaled cyclohexane is absorbed. Thus, the NOAEL would be the injected dose divided by the inhalation rate per day or 150 mg / 0.182 M3/day or 825 mg/M3. This approximately equals 2,800 ppm. The LOAEL would be twice this value or 5,600 ppm.

Savolainen H. Toxicol Lett, 1980.

Intermittent daily inhalation exposure to 300, 1000 or 2000 ppm of cyclohexane vapour resulted in a dose-dependent solvent concentration in the perirenal fat in rats. The linear relationship changed between the first and second week of exposure as the body solvent burden decreased, despite the continued exposure: this was especially clear in the brain cyclohexane analyses. The salient feature in the brain was the reduction in the activity of azoreductase, while no change could be found in the RNA or glutathione content or in glutathione peroxidase activity. The azoreductase activity was somewhat below the control range after a 2-week withdrawal period, while no solvent could be found and other biochemical variables were within the control ranges.

F. Subchronic Toxicity

Malley LA et al 2000: rats and mice exposed to CyHx by inhalation to 0, 500, 2000 or 7000 ppm 6 hrs/day, 5 days/week for 14 weeks. Subgroups were followed-up after a one-month recovery period. Functional observational battery (FOB) and motor activity (MA) behavioral test were conducted on rats prior to exposure and at weeks 4, 8, and 13 on non-exposure days. Clinical pathology evaluations were done after 7, 13 and 18 weeks. At weeks 14 and 18 tissues from rats and mice were histologically processed and evaluated by light microscopy. During exposure to 2000 or 7000 ppm rats and mice had diminished or no response to auditory alert. Immediately upon removed from exposure, 7000 group and 2000 females displayed a transient, compound-related increase in the incidence of wet and/or stained fur in the mouth, chin, and or perineum. During exposure to 7000 ppm, mice exhibited transient hyperactivity, circling, jumping/hopping, excessive grooming, kicking of rear legs, standing on front legs, and occasional flipping behavior. Immediately after exposure to 7000 ppm the mice exhibited transient hyperactivity, hyperactivity, ruffled fur (females only), gait abnormalities, spasms in both rear legs and excessive grooming (males only). These clinical signs were not present prior to the subsequent exposure. In rats, the NOAEL for acute, transient effects was 500 ppm based on a diminished/absent response to an auditory alerting stimulus at 2000 ppm and above. A few of the 2000 ppm mice appeared hyperactive during exposure in the latter portion of the study. There were no compound-related changes in mean body weights, body weight gains, food consumption, food efficiency or mortality; and there were no ophthalmological abnormalities in rats or mice. In mice, the NOAEL for acute, transient effects was 500 ppm based on behavioral changes during exposure at 2000 ppm and above.

There were no compound-related effects on 37 behavioral parameters assessed during the FOB or during motor activity tests in rats. The NOAEL for subchronic toxicity in rats was 7000 ppm based on the lack of adverse effects on body weight, clinical chemistry, tissue morphology, and neurobehavioral parameters.

Male and female mice exposed to 7000 ppm had slight increases in circulating erythrocyte mass (red blood cells, hemoglobin, hematocrit) and plasma protein concentration (male only). Male rats and fe/male mice exposed to 7000 ppm had significantly increased relative liver weights, and the 7000 ppm mice had significantly increased absolute liver weights at the end of the exposure period. At the end of the one-month recovery period, fe/male absolute and relative liver weights were similar to controls. However, relative liver weights of 7000 ppm male rats continued to be significantly higher at the end of the recovery period. Fe/male rats exposed to 7000 ppm had a significantly increased incidence of hepatic centrilobular hypertrophy at the end of the exposure period, which was not observed at the conclusion of the 1-month recovery period. No microscopic changes were observed in mice. The NOAEL for subchronic toxicity in mice is 2000 ppm based on hematological changes at 7000 ppm.

Perbellini, L. et al 1981 (abstract was English, article was Italian): Two sets of rats were given 200 mg/kg i.p. injections cyclohexanol (6 weeks) and cyclohexanone (13 weeks), expected metabolites of cyclohexane, twice daily for 5 days a week. Electrophysiological and neuropathological studies during and after the exposure failed to detect any damages to the peripheral nervous system. NOAEL 200 mg/kg (only dose).

Frontali N, Clin Toxicol, 1981

Rats were intermittently exposed (9 to 10 h/d, 5 to 6 d/week) to controlled concentrations of single analytical grad solvents in ambient air. After periods ranging from 7 to 30 weeks the animals were perfused with glutaraldehyde and samples of nerves were processed for light microscopy of sections and of teased fibers. Animals treated with n-hexane at 5000 ppm (14 weeks) or 2500 ppm (30 weeks) developed the typical giant axonal degeneration already described in rats treated continuously with 400 to 600 ppm of the same solvent for 7 weeks or more. No such alterations were found in rats subjected to the following intermittent respiratory treatments: n-hexane 500 ppm (30 weeks) or 1500 ppm (14 weeks), cyclohexane 1500 or 2500 (30 weeks), n-pentane 3000 ppm (30 weeks), n-heptane 1500 ppm (30 weeks), 2-methylpentane 1500 ppm (14 weeks), and 3-methylpentane 1500 ppm (14 weeks). The following metabolites were found in the urine of rats according to treatment (in parenthesis): 2-methyl-2-pentanol (2-methylpentane); 3-methyl-2-pentanol and 3-methyl-3-pentanol (3-methylpentane), 2-hexanol, 3-hexanol, gamma-valerolactone, 2,5-dimethylfuran, and 2,5-hexanedione (n-hexane). 2-Hexanol was found to be the main urinary metabolite of n-hexane, while 2,5-hexanedione was present only in a lesser proportion. This feature of rat metabolism suggests that in this species 2,5-

hexanedione reaches an effective level at its site of action during intermittent respiratory treatment with n-hexane with difficulty and explains the high concentrations necessary to cause polyneuropathy in rats subjected to this treatment.

G. Chronic Toxicity and Carcinogenicity

Found no reported association between CyHx and initiating or promoting mutations or carcinogenicity.

Yasugi I, et al 1994 analyzed blood from nine exposed and nine non-exposed workers for a sister chromatid exchange study. The geometric mean exposure was 27 ppm and the peak was 274 ppm. At least twenty cells per person were examined with no significant differences between the two groups found.

H. Clinical Studies

Lammers YHCM et al 2009 exposed human volunteers to 86 and 860 mg/M3 (25 and 250 ppm) for four hours in two test sessions (double-blind, randomized). Attempts were made at measuring the same neurobehavioral effects in rats and humans. Functions evaluated: psychomotor performance, learning and memory, attention, mood and effect, and perceptual coding. Human blood samples were taken for comparison to the rat data. For these humans, there were no significant treatment-related CNS effects at the levels tested. In pre-exposure surveys, some subjects in the high exposure group reported headaches and dry throat prior to the second exposure (seven days later). Subjects reported their apparent ability to recognized which exposure group they had been assigned. There were no consistent reports of eye or respiratory irritation.

Hissink AM et al 2009 developed a physiologically based pharmacokinetic model for CyHx to compare internal doses in rats and humans. Model predictions were in close agreement with measured concentrations in blood, brain (rat only) and exhaled breath. Using Lammers et al 2009 rat acute CNS NOAEL/LOAEL's and assuming similar concentration-effect relationships in rats and humans, the Hissink predicted human-equivalent concentration for acute CNS effects are approximately 4,100 (NOAEL) and 13,700 (LOAEL) mg/M3.

V. **Human Use And Experience**

Yuasa J et al 1996 studied 18 workers exposed to predominately CyHx in a luggage factory. Nervous system effects were compared to matched controls, and the endpoints included conduction velocity, latency, amplitude and duration. Seven peripheral nerves were tested. Exposed workers where divided into two groups; high exposure (126-384 ppm, median 156, mean > 100 ppm) and lower (10-68 ppm, median 51). These were full-shift personal samples. The workers were tested twice, the second time being about one year after the first. There were no statistical differences between the three groups' peripheral nervous system parameters or between the first and second test period. The authors concluded no evidence of neurotoxic effects was found when almost the only occupational exposure was to cyclohexane for a relatively short time (one year) and at low concentrations (10 – 384 ppm).

Yasugi I et al 1994 studied 33 women spraying a solvent mixture of cyclohexane (76 to 83%), n-hexane (0.3 to 0.9%) and toluene (12 to 16%) as a glue solvent in a factory. Full-shift cyclohexane personal exposures had a geometric mean of 27 ppm and a peak level of 274 ppm. Exposed subjects were divided into two groups: 17 exposed up to 13 ppm and 16 exposed to 15 to 274 ppm and compared against 10 control subjects having no exposure. "Barely significant" differences were noted for leukocytopenia, but there were no other differences shown by hematology or serum biochemistry parameters in liver and kidney functions. Twelve subjective symptoms were compared, and there were no differences found. A similar analysis of 57 symptoms while not at work showed that non-exposed subjects complained of significantly more symptoms than the exposed subjects. However, no individual symptom was significantly different.

VI. **Summary**

Numerous toxicology assessments have been done for cyclohexane. Acute inhalation investigations (Christoph 2000, Lammers 2009, Yasugi 1994) found NOALs for CNS, sensory/behavioral, psychomotor or subjective effects in humans at the highest dose of 250 ppm, rats at 2,000 ppm, mice at 2,667 ppm, cats at 2,667 ppm, pigs at 2,667 ppm, and rabbits at 2,667 ppm. Two IP studies, one subchronic (Perbellini 1981) and one sub acute (Bernard 1989), in rats found no effects levels for peripheral nervous system at the only dose of 58 ppm and nephrotoxicity at 2,800 ppm. A chronic inhalation investigation (Kreckmann 2000) in animals found transient diminished auditory response in female rats at 500 ppm, diminished weights in rats at 2,000 ppm, and no developmental or maternal behavioral effects at the highest dose of 7,000 ppm.

One human acute exposure modeling study (Hissink 2009) reported no CNS effects would be expected at 1,190 ppm based upon animal data and finding no human CNS effects at 250 ppm exposure. Two workplace investigations found no hematological, serum biochemistry (liver, kidney) subjective symptoms and only 'barely significant' leukocytopenia in highest exposure group (Yasugi 1994) of 27 ppm geometric mean and 274 ppm maximum and no peripheral nervous system effects (Yuasa 1996) with reported mean exposures greater than 100 ppm.

VII. **Recommended PEL**

The HEAC recommends the FAC consider a TWA PEL of 50 ppm. A value of 50 ppm as an 8-hour TWA is one-half the revised TLV of 100 ppm and a six-fold reduction from the current PEL of 300 ppm. One-half the TLV is suggested with a view toward prevention of adverse CNS, PNS, leukocytopenia, and kidney effects in workers and possibly reproductive health effects in workers' offspring. This recommended PEL is based upon the non-human NOAELs with transient effect ranging from 500 (females; male NOAEL at 2,000) to 7,000 ppm with other studies at 2,667 (three), 2,000, and 2,800. And this recommended PEL is based upon the human/rat pharmacokinetics modeling estimated NOAEL of 1,190 ppm and one human workplace investigation found 'barely significant' leukocytopenia seen in humans with mean exposures at 27 ppm and highest exposures up to 274 ppm.

Other Information:

- Cal/OSHA PEL 300 ppm.
- ACGIH TLV (2002), 100 ppm.
- NTP: no cancer or reproductive citations.
- EPA IRIS: 6 mg/M3 for decreased rat birth weights, basis BMCL (1-sd) of 1822 mg/m3 and uncertainty factor of 300.

VIII **References**

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17. Yuasa J, Investigation on Neurotoxicity of Occupational Exposure to Cyclohexane : a Neurophysilogical Study. Occupational and Environmental Medicine, 53, 1996.

Table 1: Summary of NOEL/LOEL Values

Type	Animal	Endpoint(s)	Reference	LOEL (ppm)	NOEL (ppm)
Workplace	Human	Hematological, serum biochemistry (liver, kidney) and subjective symptoms, found only 'barely significant' leukocytopenia in highest exposure group.	Yasugi, 1994	TWA GM 27, max 274	---
Workplace	Human	Peripheral nervous system effects	Yuasa 1996		Mean >100 ppm
Modeling	Human	Acute CNS	Hissink 2009	3,970	1,190
Acute inhal	Humans	CNS and human subjective	Lammers 2009	Highest dose	250
Acute inhal	Rats	Central Nervous System	Lammers 2009	Highest dose	2,500
Acute inhal	Rats	Sensory / behavioral	Christoph 2000	7,000	2,000
Acute inhal	Rabbits, Cats, Pigs, Mice		Yasugi 1994	Highest dose	2,667
Acute inhal	Rats	Sensory / behavioral, slight reduction in psychomotor speed, minimal CNS effects	Lammers 2009	8,100	2,300
subchronic IP	Rats	Peripheral Nervous System	Perbellini 1981	Only dose	58
subchronic inhal	Rats, Mice	Subchronic Hematological changes, hepatic changes	Malley 2000	7,000	2,000
subchronic inhal	Rats	Acute behavioral and motor activity	Malley 2000	Highest dose	7,000
subchronic inhal	Rats, Mice	Acute diminished auditory response (response to rap on side of cage)	Malley 2000	2,000	500
Subchronic inhal	Rats	Giant axonal degeneration	Frontali 1981	Highest dose	2,500
Subacute IP	Rats	Nephrotoxicity via beta 2-microglobulinuria urine levels, no glomerular filtration rate effects.	Bernard 1989	5,600	2,800
Chronic inhal	Rats, Rabbits	Developmental toxicity	Kreckman 2000	Highest dose	7,000
Chronic inhal		F1 and F2 pup weight, day 7 to 25.	Kreckman 2000	7,000	2,000*
Chronic inhal	Rats	Maternal effects: transient diminished auditory stimulus response (females)	Kreckman 2000	2,000(male NOAEL)	500 (female)
Chronic inhal	Rabbits	Maternal behavioral effects	Kreckman 2000	Highest dose	7,000