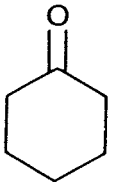
CYCLOHEXANONE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 108-94-1
Chem. Abstr. Name: Cyclohexanone
IUPAC Systematic Name: Cyclohexyl ketone
Synonyms: Ketohexamethylene; pimelic ketone; pimelin ketone

1.2 Structural and molecular formulae and molecular weight



$C_6H_{10}O$ Mol. wt: 98.14

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with peppermint and acetone odour (Krasavage *et al.*, 1982; Windholz, 1983)

(*b*) *Boiling-point*: 155.6°C; 47°C at 15 mm Hg (Weast, 1985)

(*c*) *Melting-point*: -16.4°C (Weast, 1985)

(*d*) *Density*: 0.948 at 20°C/4°C (Weast, 1985)

(*e*) *Spectroscopy data*: Nuclear magnetic resonance, infrared and ultraviolet spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983, 1985).

(*f*) *Solubility*: Miscible with most organic solvents. Soluble in ethanol, diethyl ether, benzene, chloroform and other common organic solvents; soluble in water (150 g/l at 10°C, 50 g/l at 30°C) (Krasavage *et al.*, 1982; Windholz, 1983; Weast, 1985)

(*g*) *Volatility*: Vapour pressure: 5.2 mm Hg at 25°C (Krasavage *et al.*, 1982)

(*h*) *Refractive index*: 1.4507 at 20°C (Weast, 1985)

(*i*) *Flash-point*: 44°C (closed-cup; Krasavage *et al.*, 1982)

(*j*) *Conversion factor*: mg/m^3 = 4.0 x ppm[1]

1.4 Technical products and impurities

Trade Names: Anon; Anone; Hexanon; Hytrol O; Nadone; Sextone

Cyclohexanone is available in various grades of purity (98% min, >99.8%). Impurities reported include formic acid (up to 0.05%) and water (up to 0.2%; Fisher & Van Peppen, 1979; Riedel-de Haën, 1984; Eastman Kodak Co., 1985; Aldrich Chemical Co., Inc., 1988).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Cyclohexanone is produced commercially in several major ways. One widely used process yields cyclohexanol and cyclohexanone by the catalytic oxidation of cyclohexane. The cyclohexanol/cyclohexanone product mixture, also called KA oil, is further reacted to produce adipic acid and hexamethylene diamine, intermediates in the manufacture of nylon 66. Pure cyclohexanone can be produced in high yields by this process either by distillation or by catalytic dehydrogenation of the cyclohexanol (Considine, 1974).

Another important and very efficient process is based on the hydrogenation of phenol. The cyclohexanone produced is further reacted to produce cyclohexanone oxime, an intermediate which then can undergo a Beckmann rearrangement to yield caprolactam (see IARC, 1986; Considine, 1974; Fisher & Van Peppen, 1979), the important intermediate for nylon 6 (see IARC, 1979).

Cyclohexanone production and consumption are determined by the demand for raw materials for nylon. Other uses are minor and have little effect on overall production.

In 1979, approximately 318 000 tonnes of cyclohexanone were produced in the USA (Mannsville Chemical Products Corp., 1979). The US International Trade Commission (1985, 1986, 1987) reported production of approximately 360 000 tonnes each year in 1984 and 1985 and 404 000 tonnes in 1986.

Production of cyclohexanone elsewhere in the world has not been documented.

(*b*) *Use*

Cyclohexanone is used predominantly (about 95% of production in the USA) for the synthesis of raw materials used in the production of nylon. The remainder is used as a chemical intermediate in other processes, as an additive or as a high-boiling, slow-drying solvent.

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) x ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

Cyclohexanone is used as a solvent in insecticides, wood stains, paint and varnish removers, spot removers, cellulosics, and natural and synthetic resins and lacquers. Additive uses include detergents, degreasing of metals, mould release agent for paints or varnishes, levelling agent in dyeing and delustering silk, and lube oil additive, especially for aircraft piston-type engines. Cyclohexanone is also used as a monomer in the synthesis of cyclohexanone resins, polyvinyl chloride and its copolymers (see IARC, 1979), and methacrylate ester polymers (International Technical Information Institute, 1979; Hawley, 1981; Windholz, 1983; Sittig, 1985; American Chemical Society, 1987).

(c) *Regulatory status and guidelines*

Occupational exposure limits for cyclohexanone in 28 countries or regions are presented in Table 1.

Table 1. Occupational exposure limits for cyclohexanone[a]

Country or region	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Australia	1984	200	TWA
Austria	1985	200	TWA
Belgium	1984	200	TWA
Bulgaria	1984	10	TWA
China	1985	50	TWA
Commission of the European Communities	1986	200	TWA
		1000	Maximum
Czechoslovakia	1985	200	Average
		400	Maximum
Denmark	1988	100	TWA
Finland	1987	200	TWA
		250	STEL (15 min)
France	1986	100	TWA
Germany, Federal Republic of	1988	200	TWA
Hungary	1985	20	TWA
		40	TWA
Indonesia	1985	200	TWA
Italy	1984	200	TWA
Japan	1988	100	TWA
Mexico	1985	200	TWA
Netherlands	1986	200	TWA
Norway	1981	100	TWA
Poland	1984	20	TWA
Rumania	1984	100	Average
		200	Maximum
Sweden	1984	S 100	TWA
		S 200	STEL (15 min)
Switzerland	1985	100	TWA
Taiwan	1985	200	TWA
UK	1987	100	TWA
		400	STEL (10 min)

Table 1 (contd)

Country or region	Year	Concentration[b] (mg/m^3)	Interpretation[c]
USA[d]			
OSHA	1983	200	TWA
NIOSH	1983	100	TWA
ACGIH	1988	S 100	TWA
USSR	1986	10	Ceiling
Venezuela	1985	200	TWA
Yugoslavia	1985	200	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); US Occupational Safety and Health Administration (1983); International Labour Office (1984); Arbeidsinspectie (1986); Commission of the European Communities (1986); Institut National de Recherche et de Sécurité (1986); Cook (1987); Health and Safety Executive (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; NIOSH, National Institute for Occupational Safety and Health; ACGIH, American Conference of Governmental Industrial Hygienists

2.2 Occurrence

(a) *Natural occurrence*

Cyclohexanone is not known to occur as a natural product.

(b) *Occupational exposure*

On the basis of a US National Occupational Exposure survey, the National Institute for Occupational Safety and Health (1983) estimated that 336 200 workers were potentially exposed to cyclohexanone in the USA in 1981–83.

Mean time-weighted average (TWA) concentrations of 6–28 ppm (24–112 mg/m^3; personal samples) and 2.8–23.4 ppm (11–94 mg/m^3; area samples) cyclohexanone were detected in a screen-printing plant (Samimi, 1982). Personal 8-h TWA air concentrations of cyclohexanone ranging from 0.4 to 1.1 ppm (1.6–4.4 mg/m^3) with a mean of 0.7 ppm (2.8 mg/m^3) and area samples containing 0.1–2.0 ppm (0.4–8.0 mg/m^3) were reported in a plant that produced paper and vinyl wall coverings (Ordin *et al.*, 1986).

(c) *Air*

Few data are available on ambient air concentrations of cyclohexanone. Its presence was reported in the air of one house near an offset printing office, but the concentration was not given (Verhoeff *et al.*, 1987).

2.3 Analysis

Cyclohexanone is readily analysed by collecting vapours in air samples by adsorption on chromosorb, desorption with carbon disulfide and determination by gas chromatography with flame-ionization detection. The detection limit was 0.8 ng (equivalent to 0.05 ppm; 0.2 mg/m^3) for a 10-l sample (Elskamp, 1979). Another air sampling method involved extraction of cyclohexanone in distilled water, condensation with furfural in an alkaline medium, acidification with sulfuric acid and colorimetric determination at 550 nm (Domanski, 1977).

An electrometric or colorimetric titration method, which can be used when no other carbonyl compound is present, is based on the reaction of cyclohexanone with hydroxylamine hydrochloride to form the oxime and hydrogen chloride (Fisher & Van Peppen, 1979).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 52, 52 and 47 male and 52, 50 and 50 female B6C3F$_1$ mice, seven to eight weeks old, were given 0, 6500 or 13 000 mg/l (ppm) cyclohexanone (96% pure) in the drinking-water for 104 weeks. A further group of 41 female mice received 25 000 mg/l (maximum tolerated dose) cyclohexanone over the same period. Survival in the respective groups was 88%, 90% and 70% in males and 86%, 85%, 40% and 15% in females. The incidences of liver-cell adenomas or carcinomas [only combined figures reported] were 16/52, 25/51 and 13/46 in males and 3/52, 6/50, 3/50 and 2/41 in females, respectively. The incidence in low-dose males was statistically significant ($p = 0.041$, adjusted for differences in mortality). In female mice, a statistically significant increase ($p = 0.036$; life-table method) in the incidence of malignant lymphomas and leukaemia was observed in the low-dose group: 8/52 controls, 17/50 at 6500 ppm, 4/50 at 13 000 ppm and 0/41 at 25 000 ppm (Lijinsky & Kovatch, 1986).

Rat: Groups of 52 male and 52 female Fischer 344 rats, seven to eight weeks old, received 0, 3300 or 6500 mg/l (ppm; maximum tolerated dose) cyclohexanone (96% pure) in the drinking-water for 104 weeks. A slight decrease in survival was observed in high-dose females but was not statistically significant. Dose-related reductions in body weight were observed in treated groups. A significant increase ($p = 0.03$) in the incidence of adrenal cortical adenomas was observed in low-dose males (controls, 1/52; low-dose, 7/52; high-dose, 1/51). The incidences of thyroid follicular-cell adenomas-carcinomas [reported in combination] were 1/52, 0/51 and 6/51 ($p = 0.053$) in control, low-dose and high-dose males, respectively. No difference in the incidence of liver tumours was observed between treated and control groups (Lijinsky & Kovatch, 1986).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Cyclohexanone is metabolized in rats, rabbits and dogs to cyclohexanol, which is conjugated with glucuronic acid and excreted mainly in urine; very little cyclohexanone or free cyclohexanol is found in urine (Elliott *et al.*, 1959; Martis *et al.*, 1980; Greener *et al.*, 1982). Cyclohexanone did not accumulate in the body (Martis *et al.*, 1980).

(ii) *Toxic effects*

The acute oral LD_{50} for cyclohexanone has been reported to be 2.07 and 2.11 g/kg bw in male and female mice, respectively, and 1.80 g/kg bw in male and female rats. The intraperitoneal LD_{50} has been reported to be 1.23 g/kg bw in male mice, 1.13 g/kg bw in male rats, 1.54 g/kg bw in male rabbits and 0.93 g/kg bw in male guinea-pigs. Oral and intraperitoneal administration of cyclohexanone caused narcosis, and death due to central nervous system depression and respiratory arrest. Autopsy revealed peritoneal and intestinal congestion in mice, suggesting an irritant effect (Gupta *et al.*, 1979).

Cyclohexanone did not induce skin allergy in the guinea-pig maximization test (Bruze *et al.*, 1988). Application of 0.2 ml undiluted cyclohexanone to the shaved back of rabbits for 24 h induced marked irritation, which totally disappeared only six days later. Instillation of 99, 80 or 40% cyclohexanone in cottonseed oil caused eye irritation in rabbits. No significant difference was observed in the pentobarbital sleeping-time test in mice that received 120 or 250 mg/kg bw cyclohexanone intraperitoneally on three consecutive days, suggesting no major effect of the compound on hepatic drug metabolizing enzymes (Gupta *et al.*, 1979). These enzymes were not induced by cyclohexanone in beagle dogs (Martis *et al.*, 1980).

Groups of mice received 400–47 000 mg/l (ppm) cyclohexanone in the drinking-water for 13 weeks; one-third of the females and two-thirds of the males in the highest-dose group died during treatment. One male in the group receiving 34 000 mg/l died; the other animals had 15–24% depression of body weight gain, depending on sex. With 47 000 mg/l, focal liver necrosis and hyperplasia in the thymus were observed in some animals. Pathological changes at lower doses were minimal (Lijinsky & Kovatch, 1986).

Exposure of rabbits by inhalation to about 12 000 mg/m^3 cyclohexanone for 6 h per day on five days per week for three weeks and to 1200–5560 mg/m^3 for ten weeks induced narcosis, loss of coordination and death (2/4 animals) only in the highest exposure group; slight conjunctival irritation was seen at doses of 1200–3000 mg/m^3. No toxic effect was observed with exposure to 750 mg/m^3 (Treon *et al.*, 1943).

Intravenous administration of about 280 mg/kg bw per day cyclohexanone to beagle dogs for 18–21 days produced a moribund condition and central nervous system effects and liver and kidney toxicity. No significant change in body weight was observed (Koeferl *et al.*, 1981).

Intravenous administration of 50 or 100 mg/kg bw cyclohexanone to rats for 28 consecutive days caused no significant ophthalmological or haematological toxicity or alterations in clinical chemistry, gross pathology or histopathology (Greener *et al.*, 1982).

Guinea-pigs and rabbits were administered 0.5 or 5 mg/kg bw cyclohexanone intravenously or 0.5 ml percutaneously three times a week for three consecutive weeks; lenticular alterations (anterior subcapsular vacuoles) were observed in all groups of guinea-pigs but not in rabbits (Greener & Youkilis, 1984).

Electrophysiological and neuropathological examination of rats receiving intraperitoneal injections of 200 mg/kg bw cyclohexanone twice daily on five days per week for up to 13 weeks revealed no damage to the peripheral nervous system (Perbellini *et al.*, 1981).

(iii) *Effects on reproduction and prenatal toxicity*

Chick embryos were exposed to cyclohexanone vapours [concentration unspecified] either for 3 or 6 h prior to incubation or for 3, 6 or 12 h after 96 h of incubation. Growth retardation was noted in day-13 embryos following exposure for 3 or 6 h prior to or after incubation. In some hatchings exposed after incubation, an abnormal gait was seen (Griggs *et al.*, 1971).

Dietary administration of 1% cyclohexanone to TB or NMRI mice for several generations was reported to affect the viability and growth of first-generation males and females. No such effect was seen in animals of the second generation (Gondry, 1972). [The Working Group noted that the viability of both control and treated animals was low.]

CF1 mice received daily intraperitoneal injections of 50 mg/kg bw cyclohexanone for 28 days; beginning on the tenth day of treatment and throughout the exposure period, females were housed with an untreated male. On the last day of treatment, females were killed and the uterus examined for dead, resorbed and viable fetuses. No adverse effect was noted in the seven exposed litters (Hall *et al.*, 1974).

CD-1 mice were exposed by oral intubation to 0 (25 mice) or 800 (24 mice) mg/kg bw cyclohexanone per day on days 8–12 of gestation and the offspring were evaluated for growth and viability over the first three postnatal days. No treatment-related maternal or developmental effect was observed in this teratology screening assay (Chernoff & Kavlock, 1983), nor were effects detected when the offspring were observed until 250 days of age (Gray & Kavlock, 1984; Gray *et al.*, 1986).

In a similar study, groups of 28 ICR mice were exposed by oral intubation to 0 or 2200 mg/kg bw cyclohexanone per day on days 8–12 of gestation. The treatment was lethal to 6/28 females, but no maternal mortality was observed in the control group. Maternal weight gain during the treatment period was significantly reduced in the treated group, and two females had completely resorbed litters. Pup weight at birth and on postnatal day 3 was significantly reduced in the treated group, but litter size and viability were normal (Seidenberg *et al.*, 1986)

(iv) *Genetic and related effects*

Cyclohexanone was not mutagenic to four strains (TA1535, TA1537, TA98 and TA100) of *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system in a plate incorporation assay (Haworth *et al.*, 1983).

It was reported in an abstract (Aaron *et al.*, 1985) that exposure of Chinese hamster ovary cells to cyclohexanone just as they were entering the S-phase induced sister chromatid exchange and gene mutation in the absence, but not in the presence of an exogenous meta-

bolic system. Under these conditions, no chromosomal aberration was induced in the presence or absence of an exogenous metabolic system.

Cyclohexanone at 10^{-2}, 10^{-3} and 10^{-4} M induced chromosomal aberrations in cultured human leucocytes (Collin, 1971; Lederer *et al.*, 1971). It also produced an increase in the frequency of chromosomal damage in human lymphocytes both in terms of ploidy and structural changes (Dyshlovoi *et al.*, 1981).

Chromosomal abnormalities were induced in bone-marrow cells of male rats (*Rattus norvegicus*) 6, 24 and 48 h after subcutaneous injection of three doses each of 0.1, 0.5 and 1.0 g/kg bw cyclohexanone (maximum tolerated dose). Abnormalities increased with dose and decreased with time, and consisted of chromatid gaps, breaks, centric fusions, centromeric attenuation, chromatid exchanges and polyploidy (de Hondt *et al.*, 1983).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

No data were available to the Working Group.

(ii) *Toxic effects*

Allergic contact dermatitis to a cyclohexanone resin [composition unspecified] was reported on patch testing of five patients with paint-related allergies (Bruze *et al.*, 1988). Irritation of the eyes, nose and throat was described in a review in volunteers exposed to cyclohexanone (Krasavage *et al.*, 1982).

In 100 workers exposed by inhalation (3.7 mg/m^3) and *via* skin contact (10^{-4} mg/cm^2 on the hands) during the production of caprolactam to cyclohexanone, no difference in nervous system function, blood and respiration was reported relative to 49 controls. There was some indication of liver disorders among a subgroup of workers, 30–39 years old, with more than five years' exposure to cyclohexanone (Bereznyak, 1984).

(iii) *Effects on fertility and on pregnancy outcomes*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No data were available to the Working Group.

3.3 Epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposures

Cyclohexanone is a synthetic organic liquid used primarily as an intermediate in the production of nylon. Other minor applications are as an intermediate, additive and solvent in a variety of products. Occupational exposure levels have been measured in some industries.

4.2 Experimental carcinogenicity data

Cyclohexanone was tested for carcinogenicity by oral administration in the drinking-water in one strain of mice and one strain of rats. In mice, there was a slight increase in the incidence of tumours that occur commonly in this strain, only in animals given the low dose. In rats, a slight increase in the incidence of adrenal cortical adenomas occurred in males treated with the low dose.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

No significant systemic toxicity was reported in humans or experimental animals. No significant prenatal toxicity was observed in mice.

Cyclohexanone induced chromosomal aberrations and ploidy changes in cultured human cells and in rats. It did not induce mutation in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of cyclohexanone in experimental animals.

No data were available from studies in humans on the carcinogenicity of cyclohexanone.

Overall evaluation

Cyclohexanone *is not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

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[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

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