CYCLOHEXANONE

Data were last evaluated in IARC (1989).

1. Exposure Data

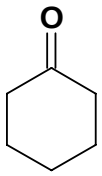
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 108-94-1

Chem. Abstr. Name: Cyclohexanone

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_{10}O$ Relative molecular mass: 98.14

1.1.3 *Physical properties* (for details, see IARC, 1989)

(*a*) *Boiling point*: 155.6°C

(*b*) *Melting point*: –16.4°C

(*c*) *Conversion factor*: $mg/m^3 = 4.0 \times ppm$

1.2 Production, use and human exposure

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 (IARC, 1989).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

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, but 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 (IARC, 1989).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Cyclohexanone is metabolized to cyclohexanol, which is conjugated with glucuronic acid and excreted mainly in urine, where very little cyclohexanone or cyclohexanol is found (IARC, 1989).

The metabolism and kinetics of cyclohexanone were studied in a group of volunteers (four men and four women) during and after 8-h exposures to 101, 207 and 406 mg/m^3. After exposure to 207 mg/m^3, the metabolic yields of urinary cyclohexanol, 1,2- and 1,4-cyclohexanediol and their glucuronide conjugates were 1%, 39% and 18%, respectively. The elimination half-times ($t_{½}$) of the 1,2- and 1,4-diols, respectively, were 16 h and 18 h. Consequently, after repeated exposure over five days, there was no cumulation of urinary cyclohexanol, whereas there was cumulative excretion of the diols. The permeation rate of cyclohexanone liquid through the skin was 37–69 mg/cm^2 per hour, indicating that occupational exposure by this route is of minor importance (Mráz *et al*., 1994).

Monitoring of exhaled breath and urine of workers occupationally exposed to an average of 9 ppm [36 mg/m^3] cyclohexanone (range, 1–40 ppm [4–160 mg/m^3]) throughout an 8-h workshift showed a proportionality between environmental and exhaled breath concentrations; 9 ppm environmental cyclohexanone produced end-of-workshift breath concentrations of approximately 1 ppm cyclohexanone and urinary cyclohexanol of 9 mg/g creatinine (Ong *et al*., 1991).

Following the deliberate ingestion by a 61-kg man of 720 mL sake (ethanol, 10% w/v) and then about 100 mL of liquid cement containing cyclohexanone (39%), methyl ethyl ketone (28%), acetone (18%) and polyvinyl chloride (15%), cyclohexanone was not detectable in blood at the first sampling time (5 h after ingestion), when the plasma level of cyclohexanol was about 215 µg/mL. Urinary excretion of cyclohexanone was minimal, most excretion by this route being of cyclohexanol glucuronide and unconjugated cyclohexanol. For cyclohexanol, the plasma half-life was 4.75 h and the elimination constant (K_e) was 0.145 per hour (Sakata *et al*., 1989).

Isomers of cyclohexanediol were found in 101 of 584 urine samples from newborn babies in a special care unit. The most abundant was *trans*-1,2-cyclohexanediol. No glucuronide conjugates were detected. Cyclohexanone was found as a contaminant in dextrose infusion fluids. From the five samples analysed, at an average concentration of 0.89 mg, cyclohexanone would have been delivered in 150 mL dextrose over 24 h (Mills & Walker, 1990).

4.1.2 *Experimental systems*

Groups of six rabbits were given cyclohexanone (4.8 mmol/kg bw) and ethanol (4.8 mmol/kg bw) either together or separately by gavage. When cyclohexanone was given alone, maximum plasma concentrations of cyclohexanone and cyclohexanol were approximately 100 μg/mL at 15 min and 200 μg/mL at 120–180 min, respectively; after administration of the combined substances, maximum plasma concentrations of cyclohexanone and cyclohexanol were approximately 35 μg/mL at 15 min and 220 μg/mL at 120–180 min, respectively, indicating an interaction between cyclohexanone and ethanol (Sakata *et al.*, 1993).

4.2 Toxic effects

4.2.1 *Humans*

No difference in nervous system function, blood and respiration was reported in workers exposed by inhalation and via skin contact, but there was some indication of liver disorders among a subgroup of workers (30–39 years old) with more than five years' exposure (IARC, 1989).

One report concerning five patients with contact dermatitis caused by a cyclohexanone resin made no attempt to identify the sensitizer (Bruze *et al.*, 1988), while a report of one patient indicated that the patient was reacting to cyclohexanone itself (Sanmartín & De la Cuadra, 1992).

4.2.2 *Experimental systems*

No major effect of cyclohexanone on hepatic drug-metabolizing enzymes was observed in mice and beagle dogs. It is irritant to the eye and skin in rabbits and has been shown to cause central nervous system depression in rabbits and beagle dogs. Target organs for toxicity are kidney in beagle dogs and liver in beagle dogs and mice. No evidence for sensitizing potential has been shown in guinea-pigs (IARC, 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Cyclohexanone did not impair the intrauterine development of mice. Variable results have been reported with regard to postnatal development, but the findings were not reproducible and some of the studies were inadequate (IARC, 1989).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Cyclohexanone did not induce mutations in bacteria, whereas chromosomal aberrations and aneuploidy were induced in cultured human lymphocytes and in the bone-marrow cells of rats treated *in vivo*.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of cyclohexanone were available.

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

Overall evaluation

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

6. References

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Table 1. Genetic and related effects of cyclohexanone

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Haworth *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	0.005	Dyshlovoi *et al.* (1981)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	10	Lederer *et al.* (1971)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	NG	Collin (1971)
AIH, Aneuploidy, human lymphocytes *in vitro*	+	NT	0.005	Dyshlovoi *et al.* (1981)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		100 sc × 1	de Hondt *et al.* (1983)

[a] +, positive;–, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; sc, subcutaneous

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