Cyclohexanone; CASRN 108-94-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Cyclohexanone

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

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The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Body weight depression **Chronic Rat Oral Study** **Lijinsky and Kovatch, 1986**	NOAEL: 3300 ppm in water (converted to 462 mg/kg/day) LOAEL: 6500 ppm in water (converted to 910 mg/kg/day)	100	1	5E+0 mg/kg/day

*Conversion Factors: Water intake = 49 mL/day; rat body weight = 0.35 kg

I.A.2. Principal and Supporting Studies (Oral RfD)

Lijinsky, W. and M. Kovatch. 1986. A chronic toxicity study of cyclohexanone in rats and mice (NCI study). J. Natl. Cancer Inst. 77(4): 941-949.

A chronic bioassay study with cyclohexanone was conducted with F344 rats and B6C3F1 mice (Lijinsky and Kovatch, 1986). Cyclohexanone was administered as a solution in the drinking water; rats were dosed at 3300 or 6500 ppm levels, male mice at 6500 or 13,000 ppm, and female mice at 6500, 13,000 or 25,000 ppm levels. Each treatment group consisted of 52 animals/sex for both mice and rats. Survival and weight gain were similar to the controls in both sexes of either species treated with the lowest dosage of cyclohexanone, but weight gain was depressed at all of the higher doses. Female mice treated with both the higher doses (13,000 or 25,000 ppm) and male mice treated with the high dose (13,000 ppm) exhibited increased mortality as compared with controls; 50% of the females treated with 25,000 ppm cyclohexanone survived beyond 1 year. Based on these effects, the 3300 ppm cyclohexanone (converted to 462 mg/kg/day) in rats is considered the NOAEL, whereas the high dose (6500 ppm or 910 mg/kg/day) that causes decreased body weight gain was considered the LOAEL in rats.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was applied; 10 for interspecies extrapolation and 10 for intraspecies variability among the human population.

MF — None

I.A.4. Additional Comments (Oral RfD)

In a French study by Gondry (1973), pregnant mice were administered a diet containing 1% (approximately 1300 mg/kg/day) cyclohexanone throughout their gestation and lactation period. An increased rate of neonatal mortality was observed during the first 21 days of life. Details of this study were unavailable. Schroeder (1984) evaluated the embryotoxic and teratogenic effects of cyclohexanone in rats exposed through inhalation at 0, 320, 680, and 1430 ppm levels during 9-16 days of gestation. Evaluation of teratologic data showed no incidence of teratogenicity in rats treated with any of the above doses, whereas the high dosage caused significant depression of both maternal and fetal body weights. Therefore, the high dose, 1430 ppm (457 mg/kg/day) was a LOAEL and the mid dose, 686 ppm (219 mg/kg/day) was considered to be a NOEL for maternotoxicity and fetotoxicity in rats.

The National Cancer Institute conducted subchronic toxicity studies of 95 to 175 days duration in mice and rats, respectively (NCI, 1979). The doses were: 0, 200, 425, 850, 1700, 3500, 5000, or 7000 ppm for rats; and 0, 425, 2400, 7000, 14,000, 26,000, 36,000, or 50,000 ppm for mice. The toxicologic endpoints in this study included mortality, body and organ weight changes, clinical observations, and histopathologic evaluations of the target organs. The results of the rat study indicated no effect on survival in either sex at any of the dosage levels, but a depression of body weight was seen in both sexes exposed to 7000 ppm cyclohexanone. The study with mice indicated depression of weight gain at 14,000 ppm or higher levels in males, at 36,000 ppm or higher levels in females, and decreased survival in both sexes at the high-dose level (50,000 ppm). Cyclohexanone was administered in water (v/v). Assuming a 0.35 kg rat drinks 49 mL water/day, and applying a correction factor of 0.95 (to account for the specific gravity), 5000 ppm cyclohexanone dosage was converted to 665 mg/kg/day. This dose was considered to be the highest NOEL. However, this dose is higher than the dose of 457 mg/kg/day (LOAEL), which produced fetal and maternal weight gain depression in the inhalation study of Schroeder (1984). Furthermore, the derivation of an oral RfD using inhalation data may present uncertainties associated with route-to- route extrapolation. Therefore, the NOAEL (462 mg/kg/day) from the Lijinsky and Kovatch (1986) study is preferred as the basis for RfD derivation.

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

The principal study was based on an NCI cancer bioassay oral study with adequate toxicologic endpoints where mice and rats were used; high confidence is assigned. Adequate supporting subchronic studies and other reproductive studies were available in the database to warrant medium confidence. Therefore, the RfD is assigned a medium confidence level.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 06/11/1986, 09/02/1986

Verification Date — 09/02/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Cyclohexanone conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Cyclohexanone
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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Cyclohexanone
CASRN — 108-94-1

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Cyclohexanone
CASRN — 108-94-1

VI.A. Oral RfD References

Gondry, E. 1973. Toxicity of cyclohexylamine, cyclohexanone, and cyclohexanol and metabolites of cyclamate. J. Environ. Toxicol. 5: 227-238.

Lijinsky, W. and M. Kovatch. 1986. A chronic toxicity study of cyclohexa- none in rats and mice (NCI study). J. Natl. Cancer Inst. 77(4): 941-949.

NCI (National Cancer Institute). 1979. Summary and experimental design of subchronic studies of cyclohexanone. Final Report.

Schroeder, R.E. 1984. An inhalation teratology study in rats with cyclohexanone. Bio/Dynamics, Division of Biology and Safety Evaluation. Submitted to Industrial Health Foundation, Pittsburgh, PA. Final report. Project No. 83-2719.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Cyclohexanone
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Date	Section	Description
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Cyclohexanone
CASRN — 108-94-1
Last Revised — 09/30/1987

- 108-94-1
- ANONE
- CICLOESANONE
- CYCLOHEXANON
- Cyclohexanone
- CYKLOHEKSANON
- HEXANON
- HYTROL O

- KETOHEXAMETHYLENE
- NADONE
- NCI-C55005
- PIMELIC KETONE
- PIMELIN KETONE
- RCRA WASTE NUMBER U057
- SEXTONE
- UN 1915