Cyclohexane; CASRN 110-82-7

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 Cyclohexane

File First On-Line 09/11/2003

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	09/11/2003
Inhalation RfC (I.B.)	yes	09/11/2003
Carcinogenicity Assessment (II.)	yes	09/11/2003

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Cyclohexane
CASRN — 110-82-7
Last Revised — 09/11/2003

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

No adequate oral exposure studies of humans or animals exist from which an oral RfD may be derived. There are no adequate data for using route-to-route extrapolation from inhalation toxicity studies to derive an RfD.

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

Not applicable.

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

Not applicable.

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

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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

Source Document — U.S. EPA, 2003

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2003.***To review this appendix, exit to the***

toxicological review, Appendix A, Summary of External Peer Review of Comments and Disposition (PDF).

Date of Agency Consensus — 08/20/2003

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 (email address).

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

Substance Name — Cyclohexane
CASRN — 110-82-7
Last Revised — 09/11/2003

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are 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.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Reduced pup weights in the F1 and F2 generations	NOAEL: 6,886 mg/m^3 LOAEL: 24,101 mg/m^3	300	1	6 mg/m^3
Rat, 2-generation reproductive/ developmental toxicity study (DuPont HLR, 1997a)	NOAEL$_{HEC}$: 1,722 mg/m^3 LOAEL$_{HEC}$: 6,025 mg/m^3 BMCL$_{(1sd)}$ (HEC): 1,822 mg/m^3			

*Conversion Factors and Assumptions: Exposure concentrations in the reproductive toxicity study (DuPont HLR, 1997a) were reported in ppm and converted to mg/m^3 using the following formula: $mg/m^3 = (ppm)(MW)/24.45$; where, the molecular weight (*MW*) used for cyclohexane was 84.2 g/mol (U.S. EPA, 1994a). The exposure concentrations in the reproductive toxicity assay (6-hour exposure per day) were duration-adjusted to derive exposure levels corresponding to 24-hour daily exposure by multiplying by a factor of 6/24 (or 1/4). When calculating the human equivalent concentration (HEC) for category 3 gases causing respiratory effects the guidance (U.S. EPA 1994a, b) indicates that the default value of the $(H_{b/g})_A/(H_{b/g})_H$ ratio should be set equal to 1 if the calculated value is greater than 1. The average ratio of the animal-blood:air partition coefficient (rat heparinized blood 1.39 ± 0.09 [Gargas et al., 1989]) divided by the human-blood:air partition coefficient (human heparinized blood 1.41 ± 0.14, [Gargas et al., 1989] and 1.3 ± 0.1 [Perbellini et al., 1985]) would be marginally greater than 1. However, the calculations are not included since the available animal and human values cannot be distinguished statistically. Therefore, the default value of 1 was used and HEC values for cyclohexane were set equal to the duration adjusted exposure concentrations expressed as mg/m^3. The RfC was derived by dividing the HEC benchmark concentration limit of 1,822 mg/m^3 by the product of uncertainty factors (UFs) or 300, equaling 6 mg/m^3.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

A two-generation reproduction inhalation toxicity study of rats conducted with cyclohexane that involved the production of one set of litters in each generation was selected as the principal study (DuPont HLR, 1997a; Kreckmann et al., 2000). Male and female Crl:CD BR rats (Sprague-Dawley strain; 30/sex/concentration) were exposed by whole body inhalation to

cyclohexane vapor at 0, 500, 2,000 or 7,000 ppm (0, 1,721, 6,886, or 24,101 mg/m^3). After 10 weeks of exposure (generally 6 hrs/day and 5 days/wk, excluding holidays), the animals were bred within their respective treatment groups and allowed to deliver and rear their offspring until weaning. With the exception of gestation day 21 until day 4 of lactation, when they were not exposed, females were exposed daily after breeding throughout pregnancy and lactation. Neonate rats were not directly exposed to cyclohexane. At weaning, F1 rats were randomly selected to produce the next generation and were treated to the same exposure schedule as the P1 generation. At least 11 weeks after weaning, the F1 rats were bred to produce the F2 litters.

Clinical observations during exposure showed a diminished response or absent response to a sound stimulus beginning at exposure 15 in animals exposed to 6,886 or 24,101 mg/m^3. Rats were evaluated for their response to an auditory altering stimulus prior to cyclohexane exposure, during cyclohexane exposure, and during the time required to clear the exposure chamber. Groups, rather than individual animals, were observed for normal, diminished, or hyperresponsive behavior in response to the auditory stimulus. The sedation was transient and was no longer apparent shortly after the rats were removed from the chamber. The animals in these two groups also showed salivation, stained perioral area, and wet chin. These clinical signs may have been related to the sedation.

The study concluded that inhalation exposure of rats to 24,101 mg/m^3 cyclohexane vapors produced significant reductions in body weights in P1 and F1 females and F1 males, and significant reductions in pup weights from lactation days 7 to 25 for F1 and F2 litters. At the 6,886 or 24,101 mg/m^3 level, diminished response to a sound stimulus or absent sound stimulus was observed during exposure. The principal study authors noted that the most suggestive evidence of maternal toxicity was the altered response to an altering sound stimulus. The authors indicate that the effects appeared to be transient and compound-related. They also noted that the effects would be expected and were consistent with overexposure to cyclohexane. Maternal toxicity was also indicated by decreased maternal body weight gain at 24,101 mg/m^3. The relevance of these effects and maternal toxicity to this assessment of cyclohexane is questionable. Specifically, effects on altering response were evaluated with knowledge of dosage group and on a group (rather than individual) basis. In addition, decreased maternal weight gain was attributed to preexisting body weight differences.

Based on the reduced pup weights during lactation in the two generations, generally $\geq$ 10% less than controls, the NOAEL for developmental effects in this reproductive toxicity study was 6,886 mg/m^3.

In an inhalation developmental toxicity study of cyclohexane with rats (DuPont HLR, 1997b; Kreckmann et al., 2000), adult maternal body weights were significantly reduced at 24,101 mg/m^3 as were both adult male and female body weights in the two-generation reproduction

inhalation toxicity study of rats (DuPont HLR, 1997a; Kreckmann et al., 2000). While developmental toxicity was not detected, the standard prenatal developmental study did not extend into the lactation period, where the reduced pup weight effect was found in the two-generation reproductive toxicity study. Maternal- and fetal-effects were not detected in a similar developmental toxicity study of rabbits (DuPont HLR, 1997c; Kreckmann et al., 2000).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 300

A factor of 3 (equivalent to approximately $10^{1/2}$) was applied to account for interspecies differences between humans and laboratory test animals. The factor for interspecies differences has two components: pharmacokinetics and pharmacodynamics. In this assessment the pharmacokinetic component was addressed by the calculation of the human equivalent concentration (HEC) according to the RfC methodology for a category 3 gas (U.S. EPA, 1994a, 1994b, 2002). Accordingly, only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty.

A factor of 10 was used to account for intraspecies variation among humans. Although the RfC is based on a sensitive lifestage (developing offspring), the uncertainty factor is appropriate because of the lack of any information on the range of responses in humans exposed to cyclohexane.

A factor of 10 was also applied to account for database deficiencies. There is a lack of long-term or chronic studies of animals in the database available for deriving the RfC (U.S. EPA, 1994b). The subjective clinical observation of altered response to an alerting stimulus by adult mice and rats increases concern for developmental neurotoxicity, although specific neurotoxicity testing of adult rats did not reveal significant changes (DuPont HLR, 1996a, b, c, d; Christoph et al., 2000; Malley et al., 2000). Similarly, the increased liver size detected in mice and rats in 90-day studies (Malley et al., 2000), although not accompanied by pathological changes in necropsy, may be early indications of changes that might progress to frank liver toxicity with long-term exposure.

Consistent with EPA practice (U.S. EPA, 1991, 1996), an additional uncertainty factor was not used to account for the extrapolation from endpoints in less-than-chronic studies to chronic effects since developmental toxicity (reduced pup body weight during lactation) was used as the critical effect. The developmental period is recognized as a sensitive lifestage where exposure during critical developmental time windows may induce effects not caused by lifetime adult exposure.

The resulting RfC calculated with the HEC $BMCL_{(1sd)}$ of 1,822.48 mg/m^3 is 6 mg/m^3:

RfC = 1,822.48 mg/m^3 / 300 = 6 mg/m^3

MF = 1

I.B.4. Additional Studies/Comments (Inhalation RfC)

No adequate human studies were available for the calculation of the RfC. No chronic or lifetime animal studies are available in the database. Subchronic, 90-day inhalation toxicity studies were conducted with cyclohexane in mice and rats (DuPont HLR, 1996a, b; Malley, et al., 2000). In mice, altered response (diminished or absent) to an alerting stimulus was observed at 6,886 or 24,101 mg/m^3 while in the exposure chamber. In addition, hyperactivity was observed at the high dose (24,101 mg/m^3) in mice. In rats, diminished response to an alerting stimulus also was observed at 6,886 and 24,101 mg/m^3. However, these were subjective observations of a few animals and the data reported per exposure group per day, not per individual animal. As such, while the observations have value for the qualitative characterization of cyclohexane as having properties of central nervous system depression that is consistent with many organic solvents, the data are not of adequate quality for quantitative use to calculate the RfC. Relative liver weights increased in rats and mice treated with 24,101 mg/m^3 cyclohexane, but they were less than 20% different and the study authors state that the changes were reversible in mice and mostly reversed in rats during recovery. Other effects noted in histopathology and clinical chemistry of the high-dose group in the 90-day rodent inhalation exposure studies (hepatocellular hypertrophy and changes in liver enzymes) were also characterized as largely reversible and judged by the study authors to reflect adaptive changes. On the other hand, these effects may be evidence suggestive of the first changes that might result in hepatic toxicity with chronic exposure, but the absence of long-term studies precludes making reliable conclusions.

Because neurological effects were seen in people exposed occupationally to mixed solvents containing cyclohexane, an acute operant behavior study of cyclohexane by inhalation in rats and a 90-day inhalation neurotoxicity study of cyclohexane in the adult rat were conducted by DuPont HLR (1996c, d; Christoph, et al., 2000; Malley, et al., 2000). Neither study showed neurotoxicity or impaired response caused by the inhalation of cyclohexane beyond the diminished response to an alerting stimulus observed in the 90-day study at the time of exposure. In the 90-day adult rat neurotoxicity study, the screening battery included a functional observational battery, motor activity, and neuropathology. There were no statistically significant compound-related effects on functional observational battery, motor activity, or neuropathology measures following exposure to any concentration (maximum 24,101 mg/m^3) in this study. Clearly there was some change of the normal central nervous

system associated with the clinical observation of sedation and/or hyperactivity of rodents in the exposure chambers; however, the available standard neurotoxicity study methods were either not targeted to the relevant changes or not sensitive enough to detect subtle changes that may have existed.

There is lack of data on the effects of cyclohexane on potentially susceptible populations. Developmental neurotoxicity is of particular concern, when considering the clinical observation of altered response to an altering stimulus by adult mice and rats.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Low to Moderate
RfC -- Low to Moderate

The overall confidence in this RfC assessment is low to moderate, reflecting the lack of data regarding chronic duration exposure by any pathway, as well as a lack of developmental neurotoxicity testing in animals.

Confidence in the principal inhalation study is high because it used an adequate number of study animals and exposure levels to evaluate an adequate set of endpoints. Confidence in the remainder of the inhalation toxicity database is low to moderate because, although it contains a number of well-designed 90-day toxicity, neurotoxicity, and developmental toxicity animal bioassays, no data were available for evaluating long-term or lifetime exposures or for developmental neurotoxicity. There is also no specific study of immunotoxicity, although no abnormalities of immune system tissues have been noted in necropsies of test animals. The database included some evidence of neurological effects in occupationally exposed humans, but these subjects were exposed to mixtures of chemicals, including those more clearly demonstrated to have such effects (*n*-hexane and toluene). Rats and mice exhibited altered responses to an alerting stimulus at the mid-level and high doses tested in subchronic studies. However, the observations were subjective (the observers knew what dose group they were watching), the observations were not on an individual animal basis, and no significant effects were detected in the neurotoxicity test batteries conducted on adult rats. Therefore, confidence in the RfC is low to moderate, reflecting primarily the lack of chronic duration exposure and a lack of developmental neurotoxicity testing.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2003

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2003. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review of Comments and Disposition (PDF).***

Date of Agency Consensus — 08/20/2003

I.B.7. EPA Contacts (Inhalation RfC)

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 (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Cyclohexane
CASRN — 110-82-7
Last Revised — 09/11/2003

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F0644, July. Risk Assessment Forum.) The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per

unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per mg/kg-day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per $\mu g/m^3$ air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

II.A. Evidence for Human Carcinogenicity

No data were located regarding the existence of an association between cancer and cyclohexane exposure in humans. The are no adequate animal studies of cancer or of chronic duration by any exposure route. The genotoxicity studies that have been performed are generally negative. Therefore, cyclohexane is characterized as "Data are inadequate for an assessment of human carcinogenic potential" (U.S. EPA, 1999). See discussion in U.S. EPA (2003).

II.A.1. Weight-of-Evidence Characterization

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

No cancer epidemiology studies in humans were located for this assessment.

II.A.3. Animal Carcinogenicity Data

No carcinogenicity assays in animals were located for this assessment.

II.A.4. Supporting Data for Carcinogenicity

Not applicable.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

Not applicable.

II.D.1. EPA Documentation

Source Documents -- U.S. EPA, 2003

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2003. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review of Comments and Disposition (PDF).***.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 08/20/2003

II.D.3. EPA Contacts (Carcinogenicity Assessment

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 (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Cyclohexane
CASRN — 110-82-7

VI.A. Oral RfD References

U.S. EPA (Environmental Protection Agency) (2003). Toxicological review of cyclohexane in support of summary information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. EPA 635/R-03/008. Available on-line at: http://www.epa.gov/iris.

VI.B. Inhalation RfC References

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DuPont HLR. (1996b) 90-Day inhalation toxicity study with cyclohexane in rats, with cover letter dated 11/18/96. Submitted by Chemical Manufacturers Association, Cyclohexane Panel; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine to U.S. EPA under TSCA. Section 4. U.S. EPA Document No. 44634. Fiche No. OTS0558873.

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Kreckmann, KH; Baldwin, JK; Roberts, LG; et al. (2000) Inhalation developmental toxicity and reproduction studies with cyclohexane. Drug Chem Toxicol 23(4):555-73.

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VI.C. Carcinogenicity Assessment References

U.S. EPA (U.S. Environmental Protection Agency). (1999) Guidelines for carcinogen risk assessment, review draft. NCEA-F-0644. Risk Assessment Forum. Available at http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm.

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VII. Revision History

Substance Name — Cyclohexane
CASRN — 110-82-7

Date	Section	Description
09/11/2003	All	IRIS Summary first posted

VIII. Synonyms

Substance Name — Cyclohexane
CASRN — 110-82-7
Last Revised — 09/11/2003

- 110-82-7
- benzenehexahydride
- benzene, hexahydro-cicloesano (Italian)
- cyclohexaan (Dutch)
- cyclohexan (German)
- cykloheksan (Polish)
- hexahydrobenzene
- hexamethylene
- hexanaphthene