Cumene; CASRN 98-82-8

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 Cumene

File First On-Line 09/07/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/01/1997
Inhalation RfC (I.B.)	yes	08/01/1997
Carcinogenicity Assessment (II.)	yes	08/01/1997

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Cumene
CASRN — 98-82-8
Last Revised — 08/01/1997

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
Increased average kidney weight in female rats **Rat Oral Gavage Study** **Wolf et al., 1956**	NOAEL: 154 mg/kg-day adjusted to 110 mg/kg-day LOAEL: 462 mg/kg-day adjusted to 331 mg/kg-day	1000	1	1E-1 mg/kg-day

*Conversion Factors and Assumptions — Dose adjustments based on dosing schedule given in study, where 139 doses were administered in 194 days. NOAEL(ADJ) = 154 mg/kg-day x 139/194 = 110 mg/kg-day, and LOAEL(ADJ) = 462 mg/kg-day x 139/194 = 331 mg/kg-day.

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

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzenes. Arch. Ind. Health. 14: 387-398.

Groups of 10 female Wistar rats were administered 139 doses of cumene by gavage in olive oil at 154, 462, or 769 mg/kg-day over a 194-day period; 20 rats given olive oil served as controls. Body weights, food consumption and mortality were noted throughout the study, although no results are shown. Hematological evaluations were conducted after the 20th, 40th, 80th, and 130th doses, and blood urea nitrogen determinations and gross and histological examinations (lungs, heart, liver, kidneys, testes, spleen, adrenals, pancreas, and femoral bone marrow) were conducted at the end of the study. No compound-related histopathological results were noted at any dose level. An increase in average kidney weight was noted as a "slight effect" at 462 mg/kg- day. A more pronounced weight increase in average kidney weight, noted as a "moderate effect," occurred at 769 mg/kg-day, although no quantitative data is presented. Effects were not observed at 154 mg/kg-day. Similar weight alterations have

been reported in other less-than-lifetime exposures to cumene (Cushman et al., 1995), in which they also have shown limited reversibility. These alterations are considered toxicologically significant and adverse, because such persistence indicates limited reversibility and uncertainty about the progression and fate of these alterations under true chronic exposures. The weight increase described at the middle dose is considered a LOAEL, and the low dose in this study (154 mg/kg-day), at which no effects were noted in any systems examined, was designated the NOAEL. Benchmark dose analysis was not attempted for this endpoint because no quantitative data are presented.

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

UF — 1000. The following uncertainty factors are applied: 10 for extrapolation for intraspecies differences and 10 for consideration of interspecies variation. A partial UF of 3 is applied for subchronic-to- chronic duration extrapolation. Justification for the use of a partial UF for subchronic-to-chronic extrapolation was that the duration of the study (6 to 7 months) is intermediate between subchronic (3 months) and chronic (24 months) duration. A partial UF also is used for database deficiencies (lack of reproductive information). The total UF = 10 x 10 x 3 x 3, which is rounded to 1000.

MF — None

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

No human information on the toxicity of this compound was located. There is a pharmacokinetic study in which humans were exposed head-only for 8 hours to concentrations of cumene as high as 720 mg/cu.m (Senczuk and Litewka, 1976). The results from this study show that cumene is well absorbed from the respiratory tract (approximately 50%), and that excretion of cumene, estimated from urinary amounts of 2-phenyl-2-propanol, was maximal after 6 to 8 hours of exposure and approached zero at 40 hours postexposure. These results concur with those reported in rats (Research Triangle Institute, 1989), showing efficient absorption, distribution, and metabolism of cumene following single administration by both the oral and inhalation routes.

Increased organ weights have been noted in other toxicity studies with cumene. The inhalation RfC also is based on increased renal and adrenal weights observed after a 13-week inhalation study with cumene (Cushman et al., 1995). Increases in kidney weights also were reported in another 4-week inhalation study (Monsanto Company, 1986) and a 2-week inhalation study (Chemical Manufacturers' Association, 1989). These independent observations reinforce and corroborate the findings of the principal study.

Neurotoxicological effects from long-term exposure to cumene warrant examination. Short-term exposures of mice to high concentrations (20 minutes at 2000 to 8000 ppm) of cumene produce transient symptoms typical of CNS depression typical of many other solvents (Tegeris and Balster, 1994). Longer term exposures to smaller concentrations, such as in the Cushman et al. (1995) study, did not elicit detectable neurotoxic effects. Extensive examinations in the latter study, including repeated functional observational batteries, motor activity tests, and neurohistopathology, produced no objective reproducible indications of neurotoxicological effects in rats that had undergone repeated exposures to cumene for 13 weeks at concentrations as high as 1202 ppm.

Inhalation developmental studies with cumene are reported in the inhalation RfC for cumene. The kinetics of cumene via oral and inhalation exposure have been examined in rats (Research Triangle Institute, 1989) and indicate similar quantitative and qualitative results of absorption, distribution, elimination, and metabolism of cumene between these routes, thereby providing at least a partial scientific basis for the use of the inhalation studies to judge the developmental toxicity of cumene via the oral route.

No indications of developmental toxicity were observed in a pair of studies in which pregnant rats and rabbits were exposed to vapors of cumene. Pregnant Sprague-Dawley rats (25/group) were exposed to 0, 487, 2399, or 5953 mg/cu.m cumene for 6 hours/day on Days 6 through 15 of gestation (Bushy Run Research Center, 1989a). Clinical signs of toxicity were observed in some dams at the two highest concentrations. There were no statistically significant adverse effects on reproductive parameters or fetal development. New Zealand White rabbits (15/group) were exposed to 0, 2418, 5928, or 11,292 mg/cu.m cumene for 6 hours/day on Days 6 through 18 of gestation (Bushy Run Research Center, 1989b). Two does died at the highest exposure concentration.

Other clinical signs of toxicity were observed at this exposure level only. Nonsignificant alterations observed in several gestational parameters (increases in nonviable implants, early resorptions, and percent of live fetuses) were consistent with adverse developmental effects occurring among animals exposed to the highest exposure concentration. The highest exposure level is considered a LOAEL for both maternal and developmental effects. The next lower level, 5928 mg/cu.m, is considered a NOAEL for both developmental and maternal effects.

No multigenerational or other reproductive studies exist for this compound. However, Cushman et al. (1995) conducted morphological evaluation of epididymal and testicular sperm in rats exposed for 13 weeks to cumene vapors. No cumene-related differences in count, morphology, or stages of spermatogenesis were noted, although one high-dose rat did have diffuse testicular atrophy. (The IRIS entry for the structurally related compound toluene

(methyl benzene) reports occurrence of a significant decrease in weight of offspring in a one-generation reproductive study at a NOAEL of 1885 mg/cu.m.)

For more detail on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Medium
RfD — Low

The overall confidence in this RfD assessment is low to medium. The confidence in the principal study is low. For purposes of quantitative assessment, the quality of the principal study (Wolf et al., 1956) is marginal because the group sizes are minimal and little quantitative information is presented. The confidence in the database, judged here as medium to low, is improved from the earlier version of this assessment on IRIS, principally because of the availability of inhalation developmental studies, some reproductive measures, and kinetic information. Kinetic information on oral and inhalation routes of exposure (Research Triangle Institute, 1989) justifies utilization of the inhalation developmental studies performed in two species, rats and rabbits, in which marginally adverse results were noted in the rabbit study. Neither 2-year chronic nor multigenerational reproductive studies are available for this compound. Results on some male reproductive parameters were, however, documented in Cushman et al. (1995), the principal study for the inhalation RfC. The critical effect, altered tissue weights, was the same across routes of exposure (this was also the critical effect for the RfC) and was observed in several studies giving confidence in the consistency of this effect. The major areas of scientific uncertainty in this assessment are the lack of both full-scale reproductive and 2-year chronic animal studies and the absence of any human toxicity information. These areas are compensated for by the UFs indicated above.

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, 1997

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, 1997. ***To review this appendix, exit to the***

toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF).

Other EPA Documentation — U.S. EPA, 1987

Agency Consensus Review Date -- 06/06/1997

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 Cumene 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 — Cumene
CASRN — 98-82-8
Last Revised — 08/01/1997

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Increased kidney weights in female rats and adrenal weights in male and female rats **Rat 13-Week Inhalation Study** **Cushman et al., 1995**	NOAEL: 2438 mg/cu.m (496 ppm) NOAEL(ADJ): 435 mg/cu.m NOAEL(HEC): 435 mg/cu.m LOAEL: 5909 mg/cu.m (1202 ppm) LOAEL(ADJ): 1055 mg/cu.m LOAEL(HEC): 1055 mg/cu.m	1000	1	4E-1 mg/cu.m

*Conversion Factors and Assumptions — MW = 120.2. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m) = 496 ppm x 120.2/24.45 = 2438 mg/cu.m. NOAEL(ADJ) = NOAEL (mg/cu.m) x 6 hours/24 hours x 5/7 days = 435 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory (systemic) effect assuming periodicity was obtained. Because the b:a lambda values are unknown for the experimental animal species and humans, a default value of 1 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x b:a lambda(a) / b:a lambda(h) = 435 mg/cu.m.

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

Cushman, J.R., J.C. Norris, D.E. Dodd, K.I. Darmer, and C.R. Morris. 1995. Subchronic inhalation toxicity assessment of cumene in Fischer 344 rats. J. Am. Coll. Toxicol. 14(2): 129-147.

Two successive subchronic inhalation toxicity studies with cumene vapor (>99.9% pure) were conducted on Fischer 344 rats. In the first study, groups, (21/sex) were exposed to 0, 100, 496, or 1202 ppm (0, 492, 2438, or 5909 mg/cu.m, respectively) cumene vapor for 6 hours/day, 5 days/week, for 13 weeks (duration adjusted to 0, 88, 435, and 1055 mg/cu.m). In the second study, the group size was decreased to 15/sex, an additional group (50 ppm, duration adjusted to 44 mg/cu.m) was added, and a 4-week postexposure recovery period was incorporated at the end of the experiment. Animals were sacrificed a few days after the last exposure in the first study and after the 4-week postexposure period in the second study. Parameters monitored included clinical signs of toxicity, body weight, food and water consumption, hematology and serum chemistry, organ weights, gross and histopathology (including examination of all respiratory tract tissues, including three sections of the lungs and four sections of the nasal turbinates). Extensive neurotoxicity (including motor activity tests and neurohistopathology) and auditory brain stem responses were assessed in the second study. Some quantitative and morphologic evaluations of spermatogenesis also were examined in the first study (epididymal tissue was taken from 15 rats/group in the first study, and the left testis was taken from each male) in an effort to judge the potential of cumene to cause reproductive toxicity.

Both absolute and relative weights were increased significantly (>10%, $p < / = 0.05$) in the kidneys and adrenal glands of both sexes at the highest concentration in the first study. The results of the second study, with a 4- week postexposure period, indicated limited reversibility to these alterations. In this second study, significant mean weight increases were present 4 weeks postexposure in adrenals from females exposed to the highest concentration. These alterations are considered toxicologically significant and adverse, because such persistence indicates limited reversibility and uncertainty about the progression and fate of these alterations under chronic exposures. No reproducible or dose-related neurotoxicological

effects or neurohistopathology were noted. Morphological evaluation of epididymal and testicular sperm showed no cumene-related differences in count, morphology, or stages of spermatogenesis, although one high-dose rat did have diffuse testicular atrophy. The only microscopic effect associated with these organ weight changes was increased incidence of kidney lesions at the two highest exposure concentrations in male rats only. The renal histopathology reported in this study fulfill several criteria for assignation to male specific renal nephropathy caused by chemicals that induce excessive accumulation of alpha- 2u-globulin (U.S. EPA, 1991; Hard et al., 1993): lesions were limited to males; hyaline droplet formation was noted, which increased in severity in a dose-related fashion; and lesions associated with the pathologic sequence of alpha-2u-globulin nephropathy were noted, including tubular proteinosis (presumably from exfoliation of epithelial cells into the proximal tubular lumen) and tubular epithelial cell hyperplasia/hypertrophy (presumed to be regenerative from tubular necrosis). Although one criterion is not met within the study, positive identification of the accumulating protein in the hyaline droplets as alpha-2u-globulin, the pattern described strongly suggests male rat specific nephropathy. The U.S. EPA does not consider nephropathy associated with accumulation of alpha-2u-globulin as an appropriate endpoint to determine noncancer toxicity. Chronic progressive nephropathy, which also occurs predominantly in male rats, also is characterized by tubular hyperplasia and proteinosis (Montgomery and Seely, 1990), and this condition also may contribute to these renal lesions. These lesions, as well as the renal weight increases in males, which may be confounded by this species and sex-specific nephropathy, thus are not used in this assessment. The critical effects in this subchronic study are increased relative and absolute kidney weights in females and increased relative and absolute adrenal weights in both sexes at the highest concentration tested, 1202 ppm, the LOAEL. The next lower concentration, 496 ppm, is the NOAEL.

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

UF — 1000. The following full uncertainty factors are applied to the NOAEL: 10 for subchronic-to-chronic extrapolation and 10 for consideration of intraspecies variation. Partial uncertainty factors also are applied to this effect level for consideration of interspecies extrapolation (which already has been addressed partially through the calculation of an HEC) and for database deficiencies (lack of reproductive studies). The total UF = 10 x 10 x 3 x 3, which is rounded to 1000.

MF — None

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

No information on the toxicity of this compound in humans was located. There does exist a pharmacokinetic study where humans were exposed head-only for 8 hours to concentrations of

cumene as high as 720 mg/cu.m (Senczuk and Litewka, 1976). The results of this study show that cumene is well absorbed from the respiratory tract (approximately 50%), and that excretion of cumene, estimated from urinary amounts of 2-phenyl-2-propanol, was maximal after 6 to 8 hours of exposure and approached zero at 40 hours postexposure. These results concur with those reported in rats (Research Triangle Institute, 1989), showing efficient absorption, distribution, and metabolism of cumene following administration by both the oral and inhalation routes.

Neurotoxicological effects from long-term exposure to cumene warrant examination. Short-term exposures of mice to high concentrations (20 minutes at 2000 to 8000 ppm) cumene produced transient symptoms typical of CNS depression typical of many other solvents (Tegeris and Balster, 1994). Longer term exposures to smaller concentrations do not appear to result in detectable neurotoxic effects because extensive examinations, including repeated functional observational batteries, motor activity tests, and neurohistopathology, produced no objective reproducible indications of neurotoxicological effects in rats that had undergone repeated exposures to cumene for 13 weeks at concentrations as high as 1202 ppm (Cushman et al., 1995).

Results from two short-term inhalation studies corroborate the results of organ weight alterations reported in Cushman et al. (1995). Male and female Sprague-Dawley rats (10/sex/group) were exposed to cumene vapor concentrations of 0, 516, 1475, or 2945 mg/cu.m for 6 hours/day, 5 days/week for approximately 4 weeks, for a minimum exposure of 20 days (Monsanto Company, 1986). Among exposed males, increases ($p < 0.05$) in mean absolute left and right kidney weights were observed at the highest dose and, in left kidney weights, in the mid- and low-dose groups. Among high-dose females, the mean absolute weight of left kidneys was greater ($p < 0.05$) than in controls. No compound-related pathological changes were detected during gross or microscopic examination of these or other organs. Fischer 344 rats (10/sex/group) were exposed to cumene at 0, 1234, 2689, 5147, or 6342 mg/cu.m, for 6 hours/day, 5 days/week for 2 weeks (Chemical Manufacturers' Association, 1989). Among females in the two highest dose groups, the average relative kidney weight and relative and absolute adrenal weights all were increased significantly over control values.

Fabre et al. (1955) exposed Wistar rats to a single concentration of cumene vapor, 2500 mg/cu.m, for 8 hours/day, 6 days/week for up to 180 days (duration adjusted to 714 mg/cu.m), and rabbits were exposed to 6500 mg/cu.m, using the same exposure regimen (duration-adjusted concentration is 1857 mg/cu.m). Histological effects reported were "passive congestion" in the lungs, liver, spleen, kidney, and adrenals, the presence of hemorrhagic zones in the lung and hemosiderosis in the spleen, and lesions from epithelial nephritis "in some cases". It was not clear if these effects occurred in both species.

In an inhalation exposure study, groups of Sprague-Dawley or Long-Evans rats (n = 15), Princeton-derived guinea pigs (n = 15), beagles (n = 2), and squirrel monkeys (n = 2) were exposed to cumene at concentrations of 18 or 147 mg/cu.m continuously for 90 days (Jenkins et al., 1970). A group of rats also was exposed to cumene at 1200 mg/cu.m for 8 hours/day, 5 days/week for 30 exposures (duration adjusted concentration = 286 mg/cu.m). No toxicologically significant findings were reported.

No indications of developmental toxicity were observed in a pair of studies in which pregnant rats and rabbits were exposed to vapors of cumene. Pregnant Sprague-Dawley rats (25/group) were exposed to 0, 487, 2399, or 5953 mg/cu.m cumene for 6 hours/day on Days 6 through 15 of gestation (Bushy Run Research Center, 1989a). Clinical signs of toxicity were observed in some dams at the two highest concentrations. There were no statistically significant adverse effects on reproductive parameters or fetal development. New Zealand White rabbits (15/group) were exposed to 0, 2418, 5928, or 11,292 mg/cu.m cumene for 6 hours/day on Days 6 through 18 of gestation (Bushy Run Research Center, 1989b). Two does died at the highest exposure concentration.

Nonsignificant alterations observed in several gestational parameters (increases in nonviable implants, early resorptions, and percent of live fetuses) were consistent with adverse developmental effects occurring among animals exposed to the highest exposure concentration. The highest exposure level is considered a LOAEL for both maternal and developmental effects. The next lower level, 5928 mg/cu.m, is considered a NOAEL for both developmental and maternal effects.

No multigenerational reproductive study exists for this compound. Cushman et al. (1995), however, conducted morphological evaluation of epididymal and testicular sperm in rats exposed for 13 weeks to cumene vapors. No cumene- related differences in count, morphology, or stages of spermatogenesis were noted, although one high-dose rat did have diffuse testicular atrophy. The IRIS entry for the structurally related compound toluene (methyl benzene) reports occurrence of a significant decrease in weight of offspring in a one-generation reproductive study at a NOAEL of 1885 mg/cu.m.

For more detail on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. The principal study was performed with adequately sized groups, had extensive and thorough histopathological analyses, and included ancillary studies for neurotoxicity and ocular pathology. The quality of this evidence is high in comparison to the study of Fabre et al. (1955), who used only a single exposure concentration, and to the study of Jenkins et al. (1970), who used small groups of animals. Neither 2-year chronic nor multigenerational reproductive studies are available for this compound. Results on some male reproductive parameters were, however, documented in the principal study of Cushman et al. (1995). The critical effect, altered tissue weights, was the same across routes of exposure (this was also the critical effect for the oral RfD) and was observed in several studies, giving confidence in the consistency of this effect.||The major areas of scientific uncertainty in this assessment are the lack of 2-year chronic and full-scale reproductive studies and the absence of any information on human toxicity. These areas are compensated for by partial UFs. Assessment of the renal lesions observed in male rats in the principal study requires special attention. As noted above, the renal histopathology reported in this study fulfills several criteria for assignation to male- specific renal nephropathy caused by chemicals that induce excessive alpha-2u- globulin, such as d-limonene and decalin (U.S. EPA, 1991; Hard et al., 1993). Although positive identification of the accumulating protein in the hyaline droplets as alpha-2u-globulin was not accomplished, the pattern described strongly suggests male-rat-specific alpha-2u-globulin nephropathy. This assessment has discounted these histopathological lesions in establishing an effect level for derivation of the RfC because the U.S. EPA has expressed the opinion that these lesions are not an appropriate endpoint to determine noncancer toxicity. So, too, have the increased renal weights observed in the male rats been discounted because this effect may be confounded by the presence of the factors involved in the progression of the nephropathy or by another mechanism altogether, such as rat chronic progressive nephropathy, which is known to be exacerbated by certain compounds (Montgomery and Seely, 1990). What has been accepted as toxicologically relevant from the profile of kidney toxicity in the principal study is the increase in female renal weights. Other repeated-dose studies with cumene also have reported increased renal weights among female rats (Wolf et al., 1956; Monsanto Company, 1986; Chemical Manufacturers' Association, 1989). These independent observations, coupled with their persistence postexposure and uncertainty about the progression/outcomes of these alterations (because of the absence of any chronic studies), justify considering the weight alterations in kidneys and adrenals as toxicologically significant.

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, 1997

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary in June 1997. A record of these comments is included as an appendix to U.S. EPA, 1997. ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — U.S. EPA, 1987

Agency Consensus Review Date -- 06/06/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Cumene 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.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 (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Cumene
CASRN — 98-82-8
Last Revised — 08/01/1997

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 from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking

water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

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

Classification — D; not classifiable as to human carcinogenicity

Basis — Under the current Risk Assessment Guidelines (U.S. EPA, 1987a), cumene is assigned carcinogen category D, not classifiable, indicating no or inadequate human or animal data. Under the proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), it is concluded that the carcinogenic potential of cumene cannot be determined because no adequate data, such as well-conducted long-term animal studies or reliable human epidemiological studies, are available for any assessment.

Concern for the carcinogenic potential of cumene is judged to be limited from several standpoints. The metabolic pathways of this compound are, for the most part, known for both rats and humans and do not involve any suspect reactive species. Cumene has been examined in a relatively complete battery of in vivo and in vitro mutagenicity tests, including gene mutation, chromosomal aberration, and primary DNA damage. Only a single test, a micronucleus assay, was mildly positive, and then at a dose that resulted in mortality in some animals. Trends in structure-activity relationships are unclear for cumene. It is, however, clear with respect to metabolism that cumene is more analogous to methyl benzene (toluene) than to ethyl benzene, and that toluene showed no evidence of carcinogenic activity in rats or mice in a 2-year inhalation study (NTP, 1990). In summary, there is not much suspicion that cumene would pose a significant carcinogenic hazard.

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

For more details on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate; none are available.

II.A.3. Animal Carcinogenicity Data

Inadequate; none are available.

II.A.4. Supporting Data for Carcinogenicity

Cumene was tested at concentrations up to 2000 ug/plate in a S. Typhimurium reverse mutation assay (modified Ames test); negative results were observed with and without metabolic activation (Lawlor and Wagner, 1987). Cumene was negative in an Ames assay at concentrations up to 3606 ug/plate (Florin et al., 1980). Cumene also tested negative, with and without metabolic activation, in a set of hypoxanthine-guanosine phosphoribosyltransferase assays (using CHO cells) at concentrations up to 225 ug/mL (Yang, 1987; Gulf Life Sciences Center, 1985a). A micronucleus assay performed in mice gavaged up to 1 g/kg cumene was negative (Gulf Life Sciences Center, 1985b). A recent micronucleus assay performed in rats (NTP, 1996) gave a weakly positive result at an extraordinarily high dose (2.5 g/kg ip).

Cumene failed to induce significant rates of transformation in BALB/3T3 cells (without activation) at concentrations up to 500 ug/mL (Putnam, 1987) but tested positive in an earlier cell transformation test that also used BALB/3T3 cells, in which an increase in transformations was observed at 60 ug/mL (Gulf Oil Corporation, 1984a). One test for unscheduled DNA synthesis (UDS) in rat primary hepatocytes, using exposures of up to 24 ug/mL cumene (without activation), was negative (Curren, 1992), whereas results from an earlier test indicated UDS at cumene doses of 16 and 32 ug/mL (Gulf Oil Corporation, 1984b).

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

Not available.

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

Not available.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987b, 1997

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, 1997. ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

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

Agency Consensus Review Date -- 06/06/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Cumene 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.

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 (internet address).

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

VI. Bibliography

Substance Name — Cumene
CASRN — 98-82-8

VI.A. Oral RfD References

Bushy Run Research Center. 1989a. Developmental toxicity study of inhaled cumene vapor in CD (Sprague-Dawley) rats. Final project report 52-621. TSCATS/0522881; EPA/OTS Doc. No. 40-8992172.

Bushy Run Research Center. 1989b. Developmental toxicity study of inhaled cumene vapor in New Zealand White rabbits. Final project report 52-622. TSCATS/0522881; EPA/OTS Doc. No. 40-8992172.

Chemical Manufacturers' Association. 1989. A two-week pilot inhalation toxicity study of cumene vapors in rats, with attachments and cover letter dated September 7, 1989. TSCATS/0522867; EPA/OTS Doc. No. 40-8992168.

Cushman, J.R., J.C. Norris, D.E. Dodd, K.I. Darmer, and C.R. Morris. 1995. Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J. Am. Coll. Toxicol. 14(2): 129-147.

Monsanto Company. 1986. One-month study of cumene vapor administered to male and female Sprague-Dawley rats by inhalation. U.S. EPA/OTS Public Files, 8D submission. Microfiche No. OTS0513229.

Research Triangle Institute. 1989. Metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, IV administration or nose-only inhalation exposure. Report RTI/4353-01F. CMA Reference No. CU-5.0-PK-RTI.

Senczuk, W. and B. Litewka. 1976. Absorption of cumene through the respiratory tract and excretion of dimethylphenylcarbinol in urine. Br. J. Ind. Med. 33: 100-105.

Tegeris, J.S. and R.L. Balster. 1994. A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fund. Appl. Toxicol. 22: 240-250.

U.S. EPA. 1987. Health and Environmental Effects Document on Cumene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC. August.

U.S. EPA. 1997. Toxicological Review of Cumene. U.S. Environmental Protection Agency, Washington, DC. Contact the IRIS Hotline at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (internet address).

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

VI.B. Inhalation RfC References

Bushy Run Research Center. 1989a. Developmental toxicity study of inhaled cumene vapor in CD (Sprague-Dawley) rats. Final project report 52-621. TSCATS/0522881; EPA/OTS Doc. No. 40-8992172.

Bushy Run Research Center. 1989b. Developmental toxicity study of inhaled cumene vapor in New Zealand White rabbits. Final project report 52-622. TSCATS/0522881; EPA/OTS Doc. No. 40-8992172.

Chemical Manufacturers' Association. 1989. A two-week pilot inhalation toxicity study of cumene vapors in rats, with attachments and cover letter dated September 7, 1989. TCCATS/0522867: EPA/OTS Doc. No. 40-8992168.

Cushman, J.R., J.C. Norris, D.E. Dodd, K.I. Darmer, and C.R. Morris. 1995. Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J. Am. Coll. Toxicol. 14(2): 129-147.

Fabre, R.R. Truhaut, J. Bernuchon, and F. Loisillier. 1955. Toxicologic studies of solvents to replace benzene. III. Study of isopropylbenzene or cumene. Arch. Mal. Prof. 16(4): 285-299.

Hard, G.C., I.S. Rodgers, K.P. Baetcke, W.L. Richards, R.E. McGaughy, and L.R. Valcovic. 1993. Hazard evaluation of chemicals that cause accumulation of alpha2-microglobulin, hyaline droplet nephropathy, and tubular neoplasia in the kidneys of male rats. Environ. Health Perspect. 99: 313-349.

Jenkins, L.J., Jr., R.A. Jones, J. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, ortho-xylene, and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16: 818-823.

Monsanto Company. 1986. One-month study of cumene vapor administered to male and female Sprague-Dawley rats by inhalation. U.S. EPA/OTS Public Files, 8D submission. Microfiche No. OTS0513229.

Montgomery, C.A., Jr. and J.C. Seely. 1990. Chapter 10, Kidney, in Pathology of the Fischer Rat, Reference and Atlas, G.A. Boorman, et al., Eds. Academic Press. p. 127-153.

Research Triangle Institute. 1989. Metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, IV administration or nose-only inhalation exposure. Report RTI/4353-01F. CMA Reference No. CU- 5.0-PK-RTI.

Senczuk, W. and B. Litewka. 1976. Absorption of cumene through the respiratory tract and excretion of dimethylphenylcarbinol in urine. Br. J. Ind. Med. 33: 100-105.

Tegeris, J.S. and R.L. Balster. 1994. A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fund. Appl. Toxicol. 22: 240-250.

U.S. EPA. 1987. Health and Environmental Effects Document on Cumene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response. August.

U.S. EPA. 1991. Alpha-2 microglobulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Rat. EPA/625/3-91/019F. September.

U.S. EPA. 1997. Toxicological Review of Cumene. U.S. Environmental Protection Agency, Washington, DC. Contact the IRIS Hotline at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (internet address).

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

VI.C. Carcinogenicity Assessment References

Curren, R.D. 1992. Unscheduled DNA synthesis in rat primary hepatocytes - test article: Cumene. Microbiological Associates, Inc. Study No. T4786.380005, May 28, 1987. EPA/OTS 40-8792124. Microfiche No. OTS 0522853.

Florin, I., L. Rutberg, M. Curvall, and C.R Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18: 219-232.

Gulf Life Sciences Center. 1985a. CHO/HGPRT test of cumene. Gulf Project No. 84-2128. EPA/OTS Doc. No. 878216011. Microfiche No. OTS 0206775.

Gulf Life Sciences Center. 1985b. Micronucleus test of cumene. Gulf Project No. 84-2129. EPA/OTS Doc. No. 878216015. Microfiche No. OTS 0206782.

Gulf Oil Corporation. 1984a. TSCA 8(e) submission 8EHQ-11840536 88-8500694. Project No. 84-2131: Cell transformation test of cumene. Office of Toxic Substances, U.S. EPA, Washington, DC. Microfiche No. OTS 0509712.

Gulf Oil Corporation. 1984b. TSCA 8(e) submission 8EHQ-11840536 88-8500694. Project No. 84-2130: Hepatocyte primary culture/DNA repair test of cumene. Office of Toxic Substances, U.S. EPA, Washington, DC. EPA/OTS Doc. No. 40- 8492086 or Microfiche No. OTS 0512292.

Lawlor, T.E. and V.O. Wagner. 1987. Salmonella/Mammalian-microsome preincubation mutagenicity assay (Ames test); test article: Cumene. Microbiological Associates, Inc., Study Number T4786.502009, March 23. EPA/OTS Doc. No. 40-8792121. Microfiche No. OTS 0522851.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice. (Available from National Toxicology Program, NIEHS, Research Triangle Park, NC.)

NTP (National Toxicology Program). 1996. In-vivo cytogenetics testing results for cumene, micronucleus induction results. (Available from National Toxicology Program, NIEHS, Research Triangle Park, NC.)

Putnam, D.L. 1987. Chromosome aberrations in Chinese hamster ovary (CHO) cells - test article: Cumene. Microbiological Associates, Inc., Study No. T4786.337012, May 12. EPA/OTS Doc. No. 40-8792123. Microfiche No. OTS 0922892.

U.S. EPA. 1987a. Risk Assessment Guidelines of 1986. EPA/600/8-87/045, August. Prepared by the Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA. 1987b. Health and Environmental Effects Document on Cumene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC, August.

U.S. EPA. 1996. (New proposed) Guidelines for Carcinogen Risk Assessment, 1996. (Currently, these guidelines are available only as a draft).

U.S. EPA. 1997. Toxicological Review of Cumene. U.S. Environmental Protection Agency, Washington, DC. Contact the IRIS Hotline at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (internet address).

Yang, L.L. 1987. CHO/HGPRT mutation assay; test article: Cumene. Microbiological Associates, Inc., Study Number T4786.332010, June 1. EPA/OTS Doc. No. 40-8792124. Microfiche No. OTS 0522853.

VII. Revision History

Substance Name — Cumene
CASRN — 98-82-8

Date	Section	Description
09/07/1988	I.A.	Oral RfD summary on-line
08/01/1997	I.A.	Oral RfD replaced; RfD changed
08/01/1997	I.B.	Inhalation RfC on-line
08/01/1997	II.	Carcinogenicity assessment on-line

Date	Section	Description
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Cumene
CASRN — 98-82-8
Last Revised — 09/07/1988

- 98-82-8
- Cumene
- isopropyl benzene
- isopropylbenzol
- 2-phenylpropane