EPA

TOXICOLOGICAL REVIEW

of

CUMENE

(CAS No. 98-82-8)

In Support of Summary Information on the Integrated Risk Information System

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA (U.S. EPA, 1994a). Subsequent to external review and incorporation of comments, this assessment has undergone an Agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Air and Radiation; Office of Policy, Planning, and Evaluation; Office of Prevention, Pesticides, and Toxic Substances; Office of Research and Development; Office of Solid Waste and Emergency Response; Office of Water; and the Regional Offices.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix B.

FOREWORD

The purpose of this review is to provide scientific support and rationale for the hazard identification and dose-response assessments for both cancer and noncancer effects (the oral reference dose and the inhalation reference concentration) from chronic exposure to cumene. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of cumene.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose-response (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the individual assessments and to aid and guide the risk assessor in the ensuing steps of the risk assessment process. For other general information about this assessment or other questions relating to the Integrated Risk Information System (IRIS), the reader is referred to EPA's Risk Information Hotline at (513)569-7254.

1.0 INTRODUCTION

This document presents the derivation of the noncancer dose-response assessments for oral exposure (the oral reference dose or RfD) and for inhalation exposure (the inhalation reference concentration or RfC) and the cancer hazard and dose-response assessments.

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects, such as some carcinogenic responses. The RfD is expressed in units of milligrams per kilogram per 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. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is expressed in units of mg/m^3.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question: (1) the U.S. Environmental Protection Agency (EPA) classification and (2) quantitative estimates of risk from oral exposure and (3) inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. 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 µg/L of drinking water or risk per $µg/m^3$ of air breathed. The third form in which risk is presented is drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identifications and dose-response assessments for cumene has followed the general guidelines for risk assessments as set forth by the National Research Council (1983). Other EPA guidelines that were used in the development of this assessment include Risk Assessment Guidelines of 1986 (U.S. EPA, 1987a), (proposed) Guidelines for Carcinogen Risk Assessment, 1996 (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991c), (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994b), (proposed) Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995b), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994c), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b) Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995c).

Literature search strategy employed for this compound were based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC,

EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, and MEDLINE and MEDLINE backfiles.

Any pertinent information submitted by the public to the Integrated Risk Information System (IRIS) submission desk also was considered in the development of this document.

2.0 CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

Cumene also is known as isopropyl benzene, (1-methylethyl)-benzene, and 2-phenylpropane. Some relevant physical and chemical properties of cumene are listed below (Mackay and Shui, 1981; Hansch and Leo, 1985).

CASRN: 98-82-8
Empirical formula: C_9H_{12}
Molecular weight: 120.2
Vapor pressure: 4.6 mm Hg at 25 °C
Water solubility: 50 mg/L at 25 °C
Log K_{OW}: 3.66
Conversion factor: 1 ppm = 4.9 mg/m^3, 1.0 mg/m^3 = 0.2 ppm

Points to be made from these properties include that, at room temperature, cumene is a volatile liquid, that airborne concentrations of over 6,000 ppm (29,400 mg/m^3) may be attained, and that cumene is nearly insoluble in water. Structurally, cumene is a member of the alkyl aromatic family of hydrocarbons, which also includes toluene (methylbenzene) and ethylbenzene.

3.0 TOXICOKINETICS RELEVANT TO ASSESSMENTS

Inhalation tests conducted in humans indicate that cumene is absorbed readily via the inhalation route, that it is metabolized efficiently to water soluble metabolites within the body, and that these metabolites are excreted efficiently into the urine with no evidence of long-term retention within the body. These results concur with the results of animals studies. The combined findings indicate that neither cumene nor its metabolites are likely to accumulate within the body.

Human volunteers (five men and five women) were exposed head-only for 8-h periods to cumene vapors (Sećzuk and Litewka, 1976). Every 10 days, each subject was exposed to one of three different concentrations of cumene, 240, 480, or 720 mg/m^3. Samples of exhaled air were collected (method not clear from text) during exposures for estimation of respiratory tract retention, and urine was collected from each subject during exposure and for 40 h thereafter. The mean respiratory tract retention was reported to be 50% (range, 45 to 64%), even at the highest concentration, although no data is given to support derivation of these values. Excretion of cumene, estimated from urinary amounts of 2-phenyl-2-propanol, was maximal after 6 to 8 h of exposure and approached zero at 40 h postexposure. The plot of time against urinary excretion of this metabolite revealed a rapid early phase ($t_{½} \approx 2$ h) and a slower later phase

($t_{½} \approx 10$ h). Approximately 35% of the calculated absorbed dose was excreted as 2-phenyl-2-propanol during the 8 h of exposure and 40 h postexposure.

Groups of Fischer 344 rats (minimum 4/sex/group) were studied after being exposed to radiolabeled cumene (>98% purity) either by single intravenous dose (35 mg/kg); single oral gavage doses (33 or 1,350 mg/kg); single 6-h nose-only inhalation (100, 500, or 1,500 ppm); or eight daily oral gavage doses (33 mg/kg), with the eighth dose being radiolabeled (Research Triangle Institute, 1989). The inhalation studies indicated rapid absorption, with detectable levels of cumene appearing in the blood within 5 min of the beginning of exposure. The gavage studies showed that cumene was absorbed readily via this route, with maximum blood levels occurring at the earliest time point sampled (4 h) for the lower dose and at 8 to 16 h for the higher dose. Elimination of cumene from the blood appeared as monoexponential with a half-life calculated between 9 to 16 h for the gavage doses. The pattern of cumene disappearance from the blood in the inhalation studies also appeared to be monoexponential with the half-lives increasing with dose, from 3.9 h at 100 ppm, to 4.6 h at 500 ppm, to 6.6 h at 1,200 ppm. Analysis of tissues (presumably immediately after exposure) indicated that several tissues, including adipose, liver, and kidney, all had elevated tissue/blood ratios of cumene, regardless of the route of cumene administration, indicating thorough distribution of cumene throughout the body independent of administration route. In general, very similar rates of elimination were observed across routes and exposure concentrations, with urine being the major route of elimination ($\geq$70%) at any dose administered by any route. Total body clearance was rapid and complete, less than 1% of the absorbed fraction being present in the body 72 h after the highest exposure regime examined, 1,200 ppm for 6 h. Metabolism of cumene by cytochrome P-450 is extensive and takes place within hepatic and extrahepatic tissues, including lung (Sato and Nakajima, 1987), with the secondary alcohol 2-phenyl-2-propanol being a principal metabolite. Over all doses and routes examined in the Research Triangle Institute study (1989), >50% of urinary excretion in rats was accounted for by 2-phenyl-2-propanol and its glucuronide or sulfate conjugates. The balance of excretion in the urine of these exposed rats was accounted for by conjugates of 2-phenyl-1,2-propanediol and an unknown metabolite, possibly a dicarboxylic acid metabolite of cumene.

4.0 HAZARD IDENTIFICATION

4.1 Studies in Humans—Epidemiology, Case Reports, and Clinical Controls

No such studies were located for this compound.

4.2 Prechronic and Chronic Studies and Cancer Bioassays in Animals—Oral and Inhalation

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 were conducted with cumene vapors (>99.9% pure) on Fischer 344 rats. In the first study, groups (21/sex) were exposed to 0, 100, 496, or 1,202 ppm (0, 492, 2,438, or 5,909 mg/m^3) cumene vapor for 6 h/day, 5 days/week, for 13 weeks (duration adjusted for continuous exposure to 0, 88, 435, and 1,055 mg/m^3). The second study was a repeat of the first, except that the group size was decreased to 15/sex, and an additional group (50 ppm, duration adjusted to 44 mg/m^3) and a 4 week postexposure period were added. 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; and gross pathology and histopathology, including examination of all respiratory tract tissues (three sections of the lungs and four sections of the nasal turbinates). In both studies, evaluations of neurological function (functional observation battery [FOB] and motor activity) were conducted. In the first study, an FOB was performed on 10 rats/sex/group, and motor activity tests were conducted on 15 rats/sex/group. In the second study, motor activity tests only were performed on 15 rats/sex/group. The FOBs were performed prior to the exposure and on the weekends following Weeks 1, 2, 4, 9, and 13 of exposure; motor activity was determined prior to exposure and on the weekend following Weeks 4, 9, and 13 of exposure. The same animals were examined at each evaluation. Also in the first study, 6 rats/sex/group were perfusion-fixed for analysis of the nervous system tissues. Because cataracts were detected in the first study, a more thorough protocol was used in the second study. In the first study, the eyes were examined once by a single ophthalmologist during the last week of exposure. In the second study, eyes were examined independently by two ophthalmologists preexposure and at Weeks 4, 9, and 13, and at Week 4 postexposure, and any cataracts detected were confirmed histopathologically. In the first study, sperm from epididymides (taken from 15 male rats/group) and the left testis from each male were evaluated for sperm count and sperm morphology, and cross-sections of testes were examined for evaluation of the stages of spermatogenesis in an effort to judge the potential of cumene to cause reproductive toxicity. Auditory brain stem responses were measured at 4, 8, 16, and 30 kHz during Postexposure Week 1 of the second study.

Transient, reversible cage-side observations during exposure periods included hypoactivity, blepharospasm, and a delayed or absent startle reflex at the highest concentration. Rats exposed to 496 ppm were reported as being hypoactive during exposure, although no further specifics were given. An increased incidence of cataracts was observed in males at all exposure concentrations in the first study. These results were not observed in the second study, in which incidence of cataractous changes were not different from historical controls nor confirmed by more extensive histopathological analysis. In the first study, statistically significant ($p < 0.05$) exposure-related decreases in motor activity (ambulatory and total activity) were observed in male rats exposed to the two highest concentrations of cumene, but these results were not

reproduced in the second study. There were no exposure-related changes in the FOBs in either study. No effects were observed in the neurohistopathological examinations. Evaluation of the auditory brain stem responses revealed no changes in the auditory function of the exposed animals, although 3/10 female rats in the highest exposure group were noted to have variability in their waveforms recorded at 4 kHz. These results were judged by the authors not to be indications of ototoxicity because of the variability of the responses. It also is noted that the ototoxicity known to occur with toluene, a structural analog of cumene, is evident only at frequencies of 8 kHz and higher. The only gross histopathology noted was periocular swelling, which occurred in animals at the two highest concentrations (and for which neither incidence nor severity was reported).

In the first study, both absolute and relative weights were increased significantly (>10%, $p \leq 0.05$) in the kidneys, adrenal glands, and livers of both sexes at the highest concentration. In females, mean kidney weights were increased 11% (absolute) and 16% (relative), adrenal weights 19% (absolute) and 26% (relative), and liver weights 34% (absolute) and 40% (relative). In males, mean renal weights were increased 12% (absolute) and 10% (relative), adrenal weights 20% (absolute) and 27% (relative), and liver weights 33% (absolute) and 30% (relative). These changes also were noted in the liver at the next lower concentration (500 ppm) for both females (7% absolute, 11% relative) and males (20% absolute, 17% relative). The results of the second study, with a 4-week postexposure period, indicated limited reversibility of these alterations because significant mean weight increases still were present in female liver (13% absolute, 11% relative) and female adrenals (12% absolute, 8% relative) of the highest exposure group. Only male relative kidney weights (6%) and absolute liver weights (11%) remained increased significantly. These alterations in weight are considered toxicologically significant and adverse because such persistence indicates limited reversibility and uncertainty about the progression and fate of these alterations under chronic exposure. There were no cumene-related differences in weights of lungs, testes, ovaries, or brain at any exposure level in either study. At the end of the exposure in the first study, water consumption was increased by as much as 40% in male rats at the two highest exposure concentrations. Alterations were noted in a number of hematological parameters, including a concentration-related increase in leukocytes (which is consistent with the study of Jenkins et al., 1970, below) and platelets in males and females, as well as in lymphocytes in males at 496 and 1,202 ppm, and significant ($p < 0.05$) decreases in erythrocyte parameters (erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) in male rats at these concentrations. All of these alterations (except for the platelet count, which was increased by around 20% over controls, in males exposed to the highest concentration) were within normal ranges (Mitruka and Rawnsley, 1981), with no accompanying indications of hematological toxicity, and therefore are considered of minimal toxicological importance. Morphological evaluation of epididymal and testicular sperm showed no cumene-related differences in either 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 an increased incidence of kidney lesions in male rats at the two highest exposure concentrations. The incidence of hypertrophy and hyperplasia of proximal tubular epithelial cells and interstitial nephritis were increased significantly at 496 ppm (12/15 and 13/15, respectively) and 1,202 ppm (14/15 and 13/15, respectively) compared to controls (1/15 for each effect). There was also an

increase in severity with dose in exposed renal tissues, including hyaline droplet formation, where dose-related increases in the incidence of moderate and marked severities were 2/15, 3/15, 14/15, and 14/14 in controls and dose groups in ascending order of exposure concentration.

The relevance of these renal effects to human toxicity is questionable because the lesion described relates closely to the male rat specific nephropathy. The EPA has established scientific policy and several criteria for assignation of male specific renal nephropathy caused by chemicals that induce excessive accumulation of α_{2u}-globulin (U.S. EPA, 1991a; Hard et al., 1993). The renal histopathology reported in this study fulfills several of these criteria: lesions were limited to males; hyaline droplet formation (as confirmed by the Mallory-Heidenheim method) was noted and increased in severity in a dose-related fashion; lesions associated with the pathologic sequence of α_{2u}-globulin nephropathy were noted, including tubular proteinosis (presumably from exfoliation of epithelial cells into the proximal tubular lumen) and tubular epithelial cell hyperplasia and hypertrophy (presumed to be regenerative from tubular necrosis). Although a major criterion is not met in the study, positive identification of the accumulating protein in the hyaline droplets as α_{2u}-globulin, the pattern described strongly suggests male rat specific nephropathy. Chronic progressive nephropathy, which also occurs predominately in male rats, also is characterized by tubular hyperplasia and proteinosis (Montgomery and Seely, 1990), and this also may be contributory to these renal lesions. The weight alterations in the adrenals and female kidney are considered potentially adverse. The increased water consumption noted also may indicate potential for renal effects, although this effect was present at dose levels at which renal weights were not altered. Although the progression of these weight alterations from continued exposure cannot be ascertained from this subchronic study, data from the second (postexposure) study indicate limited reversibility to the adrenals, at least in females. The liver weight alterations are not viewed as adverse because increase in liver weight without accompanying pathology is a trait of common microsomal-inducing agents (Sipes and Gandolfi, 1991). Based on the lowest dose at which both relative and absolute weight alterations are statistically ($p < 0.05$) and biologically (>10%) significant, 1,202 ppm is a lowest-observed-adverse-effect level (LOAEL) based on weight alterations observed in the first study in the adrenal tissues of both sexes and the kidneys in females. The next lower dose, 496 ppm, is a no-observed-adverse-effect level (NOAEL).

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

In an inhalation study, Wistar rats were exposed to 2,500 mg/m^3 cumene vapor for 8 h/day, 6 days/week, for up to 180 days (duration adjusted to 714 mg/m^3), and rabbits were exposed to 6,500 mg/m^3 using the same exposure regimen (duration-adjusted concentration is 1,857 mg/m^3). Clinical signs of toxicity, body weight, blood and bone marrow parameters, and histopathological effects (brain, cerebellum, heart, stomach, liver, pituitary, intestine, spinal cord, bone marrow, ovary, pancreas, parathyroid, lung, spleen, kidney, adrenals, testicle, thymus, thyroid, and bladder) were monitored. In the rat, the number of red blood cells decreased slightly, but no test for statistical significance was performed. Histological effects reported were "passive congestion" in the lungs, liver, spleen, kidney, and adrenals and the presence of hemorrhagic zones in the lung, hemosiderosis in the spleen, and lesions from epithelial nephritis "in some

cases". It was not clear if these effects occurred in both species. Both of these exposure levels induced adverse effects.

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

In an inhalation exposure study, groups of Sprague-Dawley or Long-Evans rats (n = 15), Princeton-derived guinea pigs (n = 15), beagle dogs (n = 2), and squirrel monkeys (n = 2) were exposed to cumene at concentrations of 18 or 147 mg/m^3 continuously for 90 days. Initial and terminal body weight, hematologic and clinical chemistry parameters, and histopathologic data were collected. The only effect noted was a slight degree of leukocytosis in rats at both concentrations, which is consistent with the results of Cushman et al. (1995). The same effect occurred in a similar group of rats exposed to cumene at 1,200 mg/m^3 for 8 h/day, 5 days/week for 30 exposures, although none were indicated as statistically significant. No other toxicologically significant effects were noted in either guinea pigs, dogs, or monkeys. This single concentration defines a LOAEL for this study.

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.

Male and female Sprague-Dawley rats (10/sex/group) were exposed to cumene vapor concentrations of 0, 105, 300, or 599 ppm (0, 517, 1,475, or 2,946 mg/m^3) for 6 h/day, 5 days/week, for approximately 4 weeks (minimum exposure, 20 days). Urinalysis, hematology, and clinical biochemistry on serum (including BUN, SGOT, LDH, and total bilirubin) were performed. Animals were observed daily for signs of toxicity. Necropsy was performed on 5 rats/sex/group at the end of the exposure. No deaths occurred during the study. Cage-side observations included hypoactivity in the high-concentration animals on some days during the exposure period. Signs of toxicity observed during the pre- or postexposure checks included concentration-related increases in side-to-side head movements in both males and females in all dose groups (combined total incidence during exposure of 0, 14, 21, and 48 for controls and the three dose groups), head tilt (total incidence in all dose groups of 0, 5, 4, and 8 for controls and the three dose groups), and arched back in one female in the high-dose group. Other less significant observations included dried, reddish discharge around the nose and near the eyes in nearly all dose groups and controls. Other effects observed in males include alopecia (mid-dose group during Weeks 2, 3, and 4 of exposure) and swollen conjunctiva during Week 4 in the high-dose group. Increases ($p < 0.05$) in mean absolute left and right kidney weights were observed high-dose males, as were increases in left kidney in low and mid-dose males. In 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. Assuming that the renal changes among the males were associated with male rat specific nephropathy (see above), the cage-side observations of head tilt and head movements become the critical effects for this short-term study with a LOAEL of 105 ppm. This study confirms that renal weight changes occur in females, thereby corroborating similar effects reported in the study of Cushman et al. (1995). It should be noted that the effects associated with

central nervous system perturbation (i.e., head movements) were not noted in several other longer term studies, including that of Cushman et al. (1995) where neurotoxicity was specifically assessed.

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 (6- to 7-mo) period (duration adjusted dose × 139/194 = 110, 331, or 551 mg/kg/day). Rats given olive oil served as controls (n = 20). Body weights, food consumption and mortality were noted throughout the study, although no results are shown. Hematological evaluations were conducted after doses 20, 40, 80, and 130, and blood urea nitrogen determinations and gross and histological examinations (lungs, heart, liver, kidneys, spleen, adrenals, pancreas, and femoral bone marrow) were conducted at the end of the study. Effects were not observed at 154 mg/kg/day. 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. The LOAEL is considered to be 462 mg/kg/day, and the NOAEL is 154 mg/kg-day.

4.3 Reproductive/Developmental Studies—Oral and Inhalation

Bushy Run Research Center. 1989b. 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.

Sprague-Dawley rats (25/group) were exposed to 0, 99, 488, or 1,211 ppm (0, 487, 2,399, or 5,953 mg/m^3) cumene for 6 h/day on Days 6 through 15 of gestation. Dams were observed for clinical signs of toxicity, body weight, gravid uterine weight, liver weight, abnormalities of the respiratory tract, numbers of corpora lutea, implantation sites, resorptions, and living and dead fetuses. Fetuses were examined for external, visceral, and skeletal malformations and variations. At the two highest concentrations, perioral wetness and encrustation, hypoactivity and blepharospasm, and significantly ($p < 0.05$) decreased food consumption were observed in the dams. At the highest concentration, there was a significant ($p < 0.01$) decrease in body weight gain on Gestation Days 6 through 9 (accompanied by a significant decrease in food consumption) and a slight increase (7.7%) in relative liver weight. There were no statistically significant adverse effects on reproductive parameters or fetal development. For this study, 1,211 ppm is a developmental NOAEL, and 488 ppm (2,399 mg/m^3) is a maternal NOAEL.

Bushy Run Research Center. 1989c. 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.

New Zealand White rabbits (15/group) were exposed to 0, 492, 1,206, or 2,297 ppm (0, 2,418, 5,928, or 11,292 mg/m^3) cumene for 6 h/day on Days 6 through 18 of gestation. Dams were observed for clinical signs of toxicity, body weight, gravid uterine weight, liver

weight, abnormalities of the respiratory tract, numbers of corpora lutea, implantation sites, resorptions, and living and dead fetuses. Fetuses were examined for external, visceral, and skeletal malformations and variations. Two does died at the highest exposure concentration. There were significant ($p < 0.01$) reductions in body weight gain (178.11 g lost compared to 31.55 g gained in the control group) and food consumption at the highest exposure level. Significantly ($p < 0.05$) reduced food consumption also was observed in the 492- and 1,206-ppm exposure groups. Clinical signs of toxicity observed in the does included significant ($p < 0.01$) increases in perioral and perinasal wetness and blepharospasm at the high concentration. At necropsy, there were color changes in the lungs of 33% of the does exposed to 2,297 ppm. Relative liver weight was significantly ($p < 0.01$) elevated (16.8% of control weight) at the highest exposure level. There were no statistically significant effects on gestation parameters; however, there were nonsignificant increases in nonviable implants, and early resorptions and a nonsignificant decrease in the percent of live fetuses at 2,297 ppm. The only variation observed was an increase in ecchymosis (hemorrhagic areas of the skin) of the head that occurred in all exposed animals (0, 5.4, 3.7, and 4.9% of the fetuses and 0, 35.7, 28.6, and 25.0% of the litters at 0, 492, 1,206, and 2,297 ppm, respectively), which was not concentration-related. On further analysis, EPA (1991b) determined that the rates of ecchymosis in this study were within the ranges observed for the historical controls of this test facility. No other malformations or variations differed from control values. Although the alterations observed in gestational parameters were not significant, they were consistent in indicating possible developmental effects. Based on this consistency, the highest exposure level is considered a LOAEL. The next lower level, 1,206 ppm, is considered a NOAEL for both developmental and maternal effects.

No multigeneration reproductive study exists for this compound by either oral or inhalation route. Neither are there any data concerning cumene exposure prior to mating, from conception to implantation, or during late gestation, parturition, or lactation. The principal study (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 (methylbenzene) reports occurrence of a significant decrease ($p < 0.05$) in weight relative to controls in the offspring in a one-generation reproductive study at a NOAEL of 1,885 mg/m^3 (U.S. EPA, 1997).

Cumene was a minor component of aromatic naphtha vapors that were tested in a inhalation reproductive toxicity study in rats and a developmental toxicity study in mice (McKee et al., 1990). These studies were read as part of this assessment but were not considered further because the concentration of cumene was less than 3% (about 2 to 40 ppm maximum concentration) of the vapors tested.

4.4 Other Studies

Neurotoxicology

Cumene appears to be similar to many solvents that produce a profile of acute effects similar to those of known central nervous system (CNS) depressants such as alcohol. The occurrence of neurological effects from inhalation exposure to cumene has been confirmed in several studies, some of which are described below. These studies are acute exposures that show neurotoxicological effects only at quite high concentrations (>500 ppm). Neurotoxicological effects were not observed, however, in the longer term inhalation study by Cushman et al. (1995; Section 4.2), which included complete batteries of functional and motor activity tests and neurohistopathology.

Cumene was one of six alkylbenzenes tested at 0, 2,000, 4,000, or 8,000 ppm that all produced a short-lived profile of neurobehavioral effects in mice, indicating CNS depressant activity (Tegeris and Balster, 1994). Effects noted from brief (20-min) exposures to cumene included those on CNS activity (decreased arousal and rearing at $\geq$2,000 ppm) muscle tone/equilibrium (changes in grip strength and mobility $\geq$4,000 ppm), and sensorimotor activity (including decreased tail pinch and touch response $\geq$4,000 ppm).

In an acute experiment accompanying the subchronic exposures, Cushman et al. (1995) exposed Fischer 344 rats once to 0, 100, 500, or 1,202 ppm for 6 h and conducted functional observations 1 h postexposure. Gait abnormalities and decreased rectal temperatures were noted for both sexes at the highest exposure level only. Decreased activity levels were noted for both sexes at the highest levels and for females only at the next highest level (500 ppm) of exposure. Males, but not females, from the highest exposure group had decreased response to toe pinch at 6 h postexposure.

In a 5-day inhalation study, Fischer 344 rats exposed to 2,000 or 5,000 ppm (9,832 or 24,580 mg/m^3) cumene vapor for 6 h/day showed toxic effects from exposure (Gulf Oil Corp., 1985). All rats in the high-exposure group died after 2 days. At the lower dose, females demonstrated CNS effects (hypothermia and staggering). Similar, but more severe, symptoms were observed in the high-exposure animals before they died.

Fischer 344 rats (10/sex/group) were exposed to cumene at 0, 251, 547, 1,047, or 1,290 ppm (0, 1,234, 2,689, 5,147, or 6,342 mg/m^3) for 6 h/day, 5 days/week for 2 weeks (Chemical Manufacturers Association, 1989). Initial exposures to 2,000 ppm (9,832 mg/m^3) for 1 to 2 days resulted in such severe neurological and respiratory effects that the concentration levels were reduced to those given above. During the remainder of the 2-week exposure period, clinical observations (ocular discharge, decreased motor activity or hyperactivity, and ataxia) were noted sporadically at all levels except 251 ppm. For females in the two highest dose groups, the average relative kidney weight and relative and absolute adrenal weights were increased significantly over control values. These data provide corroboration for these same effects reported in the study of Cushman et al. (1995).

Respiratory Irritation

The concentration of cumene causing a 50% reduction in the respiratory rate in mice was determined to be 2,058 ppm (10,117 mg/m^3) (Kristiansen et al., 1986). This concentration is quite high and in the range where repeated exposure caused death and morbidity in rats (Gulf Oil Corp., 1989; Chemical Manufacturer's Association, 1989) and rabbits (Bushy Run Research Center, 1989c).

Genotoxicity

Cumene was tested at concentrations up to 2,000 μg/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 3,606 μg/plate (Florin et al., 1980). Cumene also tested negative, with and without metabolic activation, in a set of HGPRT assays (using Chinese hamster ovary cells) at concentrations up to 225 μg/mL (Yang, 1987; Gulf Life Sciences Center, 1985a).
A micronucleus assay performed in mice given up to 1 g/kg cumene by gavage was negative (Gulf Life Sciences Center, 1985b).

A recent micronucleus assay done in Fisher 344 rats, however, gave values that were weakly positive, although little dose response was seen, and deaths occurred at the highest dose (5/10 animals at 2.5 g/kg ip, an extraordinarily high dose; NTP, 1996). In the first of two duplicate NTP experiments, the average number of micronuclei per thousand polychromatic erythrocytes at 72 h was 0.5 for controls, 1.2 at 78 mg/kg, 1.2 at 156 mg/kg, 1.3 at 313 mg/kg, 0.8 at 625 mg/kg, 2.6 at 1,250 mg/kg, and 1.3 at 2,500 mg/kg cumene and 17.3 in the positive control (25 mg/kg cyclophosphamide). A similar lack of dose-response was noted in the second experiment.

Cumene failed to induce significant rates of transformation in BALB/3T3 cells (without activation) at concentrations up to 500 μg/mL (Putnam, 1987) but tested positive in an earlier cell transformation test also using BALB/3T3 cells, in which an increase in transformations was observed 60 μg/mL (Gulf Oil, 1984a). One test for unscheduled deoxyribonucleic acid (DNA) synthesis (UDS) in rat primary hepatocytes, using exposures of up to 24 μg/mL cumene (without activation), was negative (Curren, 1992), whereas results from an earlier test indicated UDS at doses of 16 and 32 μg/mL cumene (Gulf Oil, 1984b). Those tests indicating positive mutagenic potential (Gulf Oil, 1984a,b) were considered equivocal because they were not reproducible.

4.5 Synthesis and Evaluation of Major Noncancer Effects and Mode of Action (If Known)—Oral and Inhalation

The overall hazard profile presented by cumene is one of low toxicity. Short-term acute exposures of animals to high concentrations (>1,000 ppm) demonstrate that cumene, like other solvents, can induce transient reversible neurotoxic effects. However, neither neurotoxicity, portal-of-entry effects, developmental effects, nor markedly adverse systemic toxicity are observed after long-term repeated dose studies conducted in animals at lower concentrations ($\leq$500 ppm).

The increased renal weights in female rats reported by Cushman et al. (1995) to occur at the highest concentrations tested are considered toxicologically significant under the conditions of less than lifetime exposure because the fate and progression of such effects with longer exposure are not known. Increased renal weights also have been reported in female rats in the 2-week inhalation study of the Chemical Manufacturer's Association (1989), the 4-week inhalation study of Monsanto (1986), and the oral gavage study of Wolf et al. (1956), although none observed or reported renal histopathology.

Renal histopathology that included hyaline droplet formation and an increase in the incidence of proximal tubular hypertrophy was observed in males only by Cushman et al. (1995). These findings, along with others documented in this study (see Section 4.2) are among criteria used to identify chemically induced male rat α_{2u}-globulin-specific nephropathy (U.S. EPA, 1991a; Hard et al., 1993), which EPA does not consider an appropriate endpoint to determine noncancer toxicity. Although it is not shown conclusively that the renal effects in the male rats are attributable to an α_{2u}-globulin mechanism, the available evidence strongly suggests that such a mechanism is operable with this compound.

Renal weight changes also were noted in the male rats by Cushman et al. (1995). However, the extent of association of the renal weight increase in males with the α_{2u}-type histopathology is not clear. The increase may either precede or be independent of renal histopathology. Nevertheless, these weight changes noted in kidneys of male rats may be confounded by indications of an α_{2u}-globulin mechanism or exacerbation of rat chronic progressive nephropathy (Montgomery and Seely, 1990); therefore, they are not used in this assessment.

The study of Cushman et al. (1995) with inhaled cumene showed that, in addition to increases in kidney weights, liver weights also were increased in both sexes of rats in a concentration-dependent manner. Increased liver weight is also an effect observed in rats exposed to toluene (methylbenzene) a structural analog of cumene (NTP, 1990). Liver weight increases without accompanying histopathology often are considered to result from both hyperplastic and hypertrophic parenchymal changes associated with metabolism of the toxicant, with the increases usually being reversible on discontinuance of the toxicant (Sipes and Gandolfi, 1991). Cushman et al. (1995) observed no hepatic histopathology. In addition, the 4-week recovery period incorporated in the second subchronic study by Cushman demonstrated that the liver changes were reversible. In male rats exposed to the highest concentration of cumene, the 33% increase in absolute liver weight relative to controls observed at the end of the first study was decreased to only 11% at the end of the second study. In female rats, the results were similar, with a 34% increase at the end of the first study, as compared to a 13% increase at the end of the second study. Thus, although Cushman et al. (1995) did not document actual increases in hepatic metabolism, other characteristics of the hepatic response indicate that the liver responses were highly likely to be adaptive in nature and nonadverse.

Ototoxicity also is an effect observed in rats exposed to toluene but that was not observed in the study of Cushman et al. (1995) at cumene concentrations as high as 1,200 ppm.

Neurotoxicological effects from long-term exposure to cumene warranted examination. After short-term exposures to high concentrations (20 min at 2,000 to 8,000 ppm), cumene, along

with many other solvents, has been shown to produce transient symptoms typical of CNS perturbation typical of many other solvents (Tegeris and Balster, 1994), such as those reported in the principal study (appearance of hypoactivity, blepharospasm, and delayed startle reflex) and in the study by Monsanto (1986), in which head movements and hypoactivity were noted. Longer term exposures to lesser concentrations do not appear to result in detectable effects because the extensive examinations conducted in the Cushman et al. (1995) study produced no objective reproducible indications of neurotoxicological adversity in rats that had undergone repeated exposures to cumene for 13 weeks at concentrations as high as 1,202 ppm.

Cumene has a superficial similarity (an aromatic ring) to benzene. Nevertheless, blood toxicity (a known effect of benzene) has been a focus of both short- and long-term studies. Although clinical blood parameters were monitored in several long-term studies of several species exposed to cumene (Fabre et al., 1955; Jenkins et al., 1970; Wolf et al., 1956), only Cushman et al. (1995) detected any significant hematological perturbations. Due to the relatively small alterations and the wide-ranging normal values for a number of these parameters, these alterations were considered to be of minor toxicological significance.

4.6 Weight of Evidence Evaluation and Cancer Classification—Synthesis of Human, Animal, and Other Supporting Evidence; Conclusions About Human Carcinogenicity; and Likely Mode of Action

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 to perform any assessment. Under the current Risk Assessment Guidelines (U.S. EPA, 1987a), cumene is assigned carcinogen category D (not classifiable), indicating inadequate or no human or animal data.

The metabolic pathways of this compound are, by and large, known and do not appear to involve any suspect reactive species. One *in vivo* mutagenicity test (micronucleus) did give a weakly positive result with a dose that produced mortality, although cumene gave negative results in a relatively complete battery of in vitro and in vivo mutagenicity tests, including gene mutation, chromosomal aberration, and primary DNA damage. Trends in structure-activity relationships are unclear as neither toluene (methylbenzene) or ethylbenzene has been classified by EPA with respect to carcinogenicity. It is clear, with respect to metabolism, however, that cumene is more analogous to methylbenzene (toluene) than to ethylbenzene, and toluene showed no evidence of carcinogenic activity in rats or mice in a 2-year inhalation study (NTP, 1990). At present, there is no likely genotoxic mode-of-action to consider for carcinogenic activity by cumene. In summary, there is not much suspicion that cumene would pose a significant carcinogenic hazard.

4.7 Other Hazard Identification Issues

4.7.1 Possible Childhood Susceptibility

A number of factors may differentially affect childrens' responses to toxicants. The only toxicity information on cumene of possible relevance to this issue is that from developmental studies, one study in rats (Bushy Run Research Center, 1989a) and another in rabbits (Bushy Run Research Center, 1989b), in which no adverse fetal effects were observed. There is too little information to make any further statements about how children may be differentially affected by cumene, as there are no data regarding cumene exposure prior to mating, from conception through implantation, or during late gestation, parturition, or lactation.

4.7.2 Possible Gender Differences

The only gender-related difference observed in the current data on cumene is the occurrence of renal histopathology in male rats only. However, this phenomenon is more than likely related to or confounded by the male specific nephropathy (U.S. EPA, 1991a; Hard et al., 1993) and has no relevance to humans.

5.0 DOSE RESPONSE ASSESSMENTS

5.1 Oral Reference Dose

5.1.1 Choice of Principal Study and Critical Effect—with Rationale and Justification

The study of Wolf et al. (1956) is a repeated dose study (6 to 7 mo) of cumene via the oral route. The study suffers from several deficiencies, including small group sizes and the lack of any quantitative data reporting. The only significant effect observed in this study is a description of dose-related increases in average renal weights observed in the animals exposed to the middle and high dosages (462 and 769 mg/kg/day). Too, the observations of Wolf et al. were in female rats (the only sex tested) so that the renal effects are not likely to be confounded as are those reported for males in the study of Cushman et al. (1995). Similar weight alterations have been reported in other less-than-lifetime exposures to cumene (Cushman et al., 1995), in which they have been shown to have 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 exposure. The lack of any such effect at the lowest dose tested (154 mg/kg/day; duration adjusted, 110 mg/kg/day) defines the NOAEL of this study.

An alternative possibility for the principal study would be to use the results of the Cushman et al. (1995) subchronic inhalation study after performing a route-to-route extrapolation. Limited interroute kinetic information (blood levels of total metabolites only) is available in rats, from which comparable blood levels and tissue levels possibly could be calculated for oral versus inhalation exposures (Research Triangle Institute, 1989). However, the Wolf et al. (1956) study, although limited in quality, is via the oral route and is of longer exposure duration than the inhalation study (6 versus 3 mo). Based on these facts, it is judged to be more appropriate to use the study of Wolf et al. (1956).

5.1.2 Methods of Analysis—No-Observed-Adverse-Effect Level and

Lowest-Observed-Adverse-Effect Level

The increase in renal weight in female rats observed at the middle dose (462 mg/kg/day) of the Wolf et al. (1956) study is considered a LOAEL, and the low dose in this study (154 mg/kg/day), at which no adverse 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.

5.1.3 Oral Reference Dose Derivation—Including Application of Uncertainty Factors and Modifying Factors

The NOAEL for increased kidney weight in the Wolf et al. (1956) study is 154 mg/kg/day, and the NOAEL(ADJ), based on adjustment for the stated dosing schedule of 139 doses/ 194 days, equals 110 mg/kg/day.

Uncertainty factors (UFs) are applied to account for recognized uncertainties in extrapolation from experimental conditions to the assumed human scenario (i.e., chronic exposure over a lifetime). Historically, UFs are applied as values of 10 in a multiplicative fashion (Dourson and Stara, 1983). Recent EPA practice, however, also includes use of a partial UF of $10^{1/2}$ (3.333; U.S. EPA, 1994b) on the assumption that the actual values for the UFs are lognormally distributed. Application of these factors in the assessments is that, when a single partial UF is applied, the factor is rounded to 3, such that the total factor for a UF of 3 and 10, for example, would be 30 (3 × 10). When two partial UFs are evoked, however, they are not rounded, such that a UF of 3, 3, and 10 would result in a total uncertainty of 100 (actually $10^{1/2} \times 10^{1/2} \times 10^{1}$).

Uncertainty factors and the justification for their use are as follows. A factor of 10 is used for extrapolation of intraspecies differences in response (human variability) as a means of protecting potentially sensitive human subpopulations. A factor of 10 is applied for consideration of interspecies variation. A full factor is considered necessary for this variation as no human toxicity information currently exists. Partial UFs also are applied for 6 mo to chronic duration extrapolation and for database deficiencies. The partial database deficiency is evoked because of the lack of a full-scale multigeneration reproductive study. Cushman et al. (1995) provides evidence for a lack of concern that cumene may be a reproductive toxicant. However, these data are limited in that they can not provide a complete scientific argument that would definitively exonerate cumene as a reproductive toxicant. For example, there are no data regarding cumene exposure to mating, from conception through implantation, or during late gestation, parturition, or lactation. The wide tissue distribution demonstrated after inhalation of cumene, which included the reproductive organs (Research Triangle Institute, 1989), demonstrates that these tissues would be as highly exposed as the remainder of the body. The IRIS entry for the structurally related compound toluene (methylbenzene) reports occurrence of a significant decrease ($p < 0.05$) in weight relative to controls in the offspring in a one-generation reproductive study at a NOAEL of 1,885 mg/m^3 (U.S. EPA, 1997). The total UF = $10 \times 10 \times 10^{1/2} \times 10^{1/2} = 1{,}000$. No modifying factor (MF) is considered necessary.

RfD = 110 mg/kg/day ÷ 1,000 = 1E – 1 mg/kg/day

5.2 Inhalation Reference Concentration

5.2.1 Choice of Principal Study and Critical Effect—with Rationale and Justification

The pair of 3-mo subchronic inhalation studies reported by Cushman et al. (1995) are designated together as the principal study for derivation of the RfC. Although the inhalation study of Fabre et al. (1955) had a longer exposure regime (around 6 mo), only a single exposure concentration was employed versus the four in the principal study. The study of Jenkins et al. (1970) used more species than the principal study and attained nearly continuous exposure for 90 days. In comparison, the principal study used larger groups of animals and conducted thorough and extensive cage-side observations, neurotoxicological examinations, and auditory function tests. Also, neither Fabre et al. (1955) nor Jenkins et al. (1970) reported any significant adverse effects, unlike the principal study. The choice of Cushman et al. (1995) as the principal study is considered justified because of these methodological and analytical attributes.

The critical effects are the increases ($p \leq 0.05$, changes >10% relative to controls) in both absolute and relative mean weights in the adrenal glands of both sexes and in the kidneys of female rats at the highest concentration tested. Although both absolute and relative liver weights also were increased, this effect was not considered adverse because an increase in liver weight, without accompanying pathology, is a trait of common microsomal-inducing agents (Sipes and Gandolfi, 1991). The next lower concentration is designated as the NOAEL, although some other effects were described somewhat subjectively and generally at this concentration (hypoactivity and some periorbital swelling); these are not deemed sufficient to warrant consideration of this concentration a LOAEL, primarily because of their occurrence in controls.

5.2.2 Methods of Analysis—No-Observed-Adverse-Effect Level and Lowest-Observed-Adverse-Effect Level

The highest concentration tested, 1,202 ppm, is designated the LOAEL. The next lower dose, 496 ppm, is designated the NOAEL.

Analyses for benchmark concentrations (BMCs) were performed on the absolute weight alterations in male and female adrenal and female renal weights (Appendix A). An overview of the benchmark dose approach for health risk assessments is given in U.S. EPA (1995c). The only data set of the three that could be modeled to a level of statistical significance ($F < 0.01$) was male adrenal weights. The BMC_{10} (the lower 95% confidence bound on the concentration from the maximum likelihood estimate of a 10% relative change) values obtained for these data were identical to one another for the two models, 484 ppm.

The critical effect that was the most corroborated by the cumene database, however, was the increase in female kidney weight, which was not modeled successfully. Rather than rely on unsuccessful modeling results or on results from a possibly inappropriate endpoint, the NOAEL of 496 ppm is used for all further quantitative analysis. It should be noted that the BMC_{10} of 484 ppm obtained for the only data set that was successfully modeled, male adrenal weight gain, is nearly the same as the NOAEL.

Calculation of the human equivalent concentration (HEC) from the NOAEL of 496 ppm is shown below.

- The NOAEL first is converted to milligrams per cubic meter and duration adjusted; then, assuming 25 °C and 760 mm Hg,

  NOAEL (milligrams per cubic meter) = 496 ppm × MW/24.45 = 2,438 mg/m^3.

- This converted value then is duration adjusted to continuous exposure, which equals the NOAEL(ADJ).

  2,438 mg/m^3 × 6h/day × 5 days/7 days = 435 mg/m^3 = NOAEL(ADJ)

- The scenario for this effect was a gas causing a systemic or extrarespiratory effect that assumed attainment of periodicity for the blood/air (b/a) cumene concentrations. Because no b/a lambda (i.e., partition coefficient) values for cumene are known for either animals or humans, a default value of one is used for this ratio, which indicates that there exist no differences between animals and humans in blood concentrations attained for the same air concentration of cumene.

- Therefore, NOAEL(HEC) = NOAEL(ADJ) × [b:a lambda(a) / b:a lambda (h)] = 435 mg/m^3 × 1 = 435 mg/m^3.

5.2.3 Inhalation Reference Concentration Derivation—Including Application of Uncertainty Factors and Modifying Factors

The NOAEL(HEC) for increased kidney and adrenal weights in the Cushman et al. (1995) study is 435 mg/m^3.

Uncertainty factors are applied to account for recognized uncertainties in extrapolation from experimental conditions to the assumed human scenario (i.e., chronic exposure over a lifetime). Historically, UFs are applied as values of 10 in a multiplicative fashion (Dourson and Stara, 1983). Recent EPA practice, however, also includes use of a partial UF of $10^{1/2}$ (3.333; U.S. EPA, 1994b) on the assumption that the actual values for the UFs are lognormally distributed. Application of these factors in the assessments is that, when a single partial UF is applied, the factor is rounded to 3, such that the total factor for a UF of 3 and 10, for example, would be 30 (3 × 10). When two partial UFs are evoked, however, they are not rounded, such that a UF of 3, 3, and 10 would result in a total uncertainty of 100 (actually $10^{1/2} \times 10^{1/2} \times 10^{1}$).

The UFs applied and the justification for their use are as follows. A factor of 10 is used for extrapolation of intraspecies differences in response (human variability) as a means of protecting potentially sensitive human subpopulations. A factor of 10 is applied for subchronic to chronic extrapolation as the progression or fate of observed effects in kidney and adrenals resultant from true chronic administration is uncertain. A partial ($10^{1/2}$) UF is applied for consideration of interspecies extrapolation, which already has been addressed partially through the calculation of an HEC. A partial UF also is used for database deficiencies, principally because of the lack of a

full-scale multigeneration reproductive study (as discussed above in the section on UF for the RfD). The total UF = $10 \times 10 \times 10^{1/2} \times 10^{1/2} = 1{,}000$.

No MF is proposed for this assessment.

RfC = 435 mg/m^3 ÷ 1,000 = 4E – 1 mg/m^3.

5.3 Cancer Assessment

As discussed above (Section 4.5), there are no epidemiological, occupational, or long-term in vivo animal studies addressing the issue of cancer. No data exist to support any quantitative cancer assessment for this compound.

6.0 MAJOR CONCLUSIONS IN CHARACTERIZATION OF HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENTS

6.1 Hazard Identification

Cumene is a water insoluble petrochemical used in the manufacture of several chemicals, including phenol and acetone. It is metabolized primarily to the secondary alcohol, 2-phenyl-2-propanol, in both animals and humans. This alcohol and conjugates thereof are excreted readily by both rodents and humans.

No human toxicity data exists for cumene. Increases in organ weights (most notably kidney) are the most prominent effects observed in rodents exposed repeatedly to cumene by either the oral (Wolf et al., 1956) or the inhalation (Cushman et al., 1995) routes. No adverse effects were observed in rat or rabbit fetuses whose mothers had been exposed to aerosolized cumene during development.

The sparsity of long-term repeated dose toxicity data and the absence of any human toxicity data both constitute areas of scientific uncertainty in this assessment. The longest repeated-dose study is the oral study of Wolf et al. (1956), at about 7 mo, followed by the 3-mo subchronic inhalation study of Cushman et al. (1995). Neither of these studies is sufficient in duration to reveal the fate of the observed alterations in organ weights. Although there exists no multigeneration reproductive study for cumene, its rapid metabolism and excretion, coupled with the information on sperm morphology reported by Cushman et al. (1995), indicate that cumene has low potential for reproductive toxicity.

The potential human hazard for carcinogenicity of cumene has not been determined, although there is some evidence that suggests this compound may not be likely to produce a carcinogenic response (i.e., numerous genotoxic tests, including gene mutation, chromosomal aberration, and primary DNA damage tests, all but one of which were negative or not reproducible, were conducted). No highly reactive chemical species are known to be generated during the metabolism of cumene. Although structure-activity relationships to cumene are problematic, it is clear that cumene, with respect to metabolism, is more analogous to

methylbenzene (toluene) than to ethylbenzene. Toluene has been tested in a 2-year inhalation protocol and showed no evidence of carcinogenic activity in either rats or mice (NTP, 1990). No dose-response assessment was performed on this compound because no data are available.

6.2 Dose Response

The quantitative estimates of human risk as a result of low-level chronic exposure to cumene are based on animal experiments because no human data exist.

The human dose that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (the RfD) is 0.1 mg/kg-day. This amount is 1/1000 of the dose, adjusted for the stated schedule, at which no adverse effects were noted in female rats dosed orally with cumene over a period of about 7 mo (Wolf et al., 1956).

The overall confidence in the 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 comprise females only, and little quantitative information is presented. The confidence in the database, judged here as medium to low, is improved from the earlier version on IRIS, principally because of the availability of inhalation developmental studies; some reproductive measures; corroboration of the critical effect by other studies, including those using oral dosing; and kinetic information. Kinetic information on oral and inhalation routes of exposure (Research Triangle Institute, 1989) justifies utilization of inhalation developmental studies performed in two species, rats and rabbits, in which no adverse results were noted. However, no 2-year chronic study is available via the oral or inhalation route. No multigeneration 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 RfC. The rapid metabolism and excretion of cumene in both animals and humans, coupled with the information on sperm morphology reported by Cushman et al. (1995), also indicate cumene to have a low potential for reproductive toxicity. 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.

Justification for the use of a partial uncertainty factor for subchronic to chronic extrapolation was twofold: (1) the duration of the principal study (6 to 7 mo) was intermediate, between subchronic (3mo) and chronic (24 mo) duration, and (2) toxicokinetic data (Section 3) indicate that inhaled cumene and its metabolites are cleared quickly from both humans and rats, which also could indicate low potential for cumulative damage.

The daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime (the RfC) is 4E-1 mg/m^3. This concentration is 1/1000 of the adjusted no-effect level for significant increases (>10%) in renal and adrenal weights in rats exposed to cumene in the subchronic inhalation study of Cushman et al. (1995).

The overall confidence in the RfC assessment is medium. The RfC is based on rat subchronic inhalation studies performed with relatively large group sizes in which thorough

histopathological analyses and ancillary studies of neurotoxicity and ocular pathology were performed. The scientific quality of this evidence is high. The confidence in the database for the cumene RfC is rated as medium. Acceptable developmental studies were carried out (via inhalation route) in two species, rats and rabbits, with no adverse results noted; however, no 2-year chronic studies are available. As with the RfD database, full-scale multigeneration reproductive studies are lacking. The critical effect, altered tissue weights, is consistent across routes of exposure (altered kidney weight was also a critical effect for the RfD).

The use of a partial uncertainty factor for interspecies extrapolation is justified because species-to-species dosimetric adjustments were made and an HEC was calculated.

An area of scientific uncertainty and controversy in this assessment concerns the renal lesions in the male rats observed in the principal study. The descriptions of these lesions strongly suggest the male-specific rat nephropathic response elicited by compounds such as *d*-limonene and decalin (U.S. EPA, 1991a). This assessment has discounted these histopathological lesions in establishing an effect level for derivation of the RfC because EPA does not consider such lesions to be an appropriate endpoint for determining noncancer toxicity. If the male rat renal effects had not been discounted, then the RfD would have been approximately fivefold lower, because the NOAEL would be 100 ppm versus 496 ppm. What has been accepted as toxicologically relevant from the profile of renal toxicity in the principal study is the increase in female renal weight. Other repeated-dose studies with cumene also have reported increased renal weights among female rats (Wolf et al., 1956; Monsanto, 1986; Chemical Manufacturer's Association, 1989). These independent observations, coupled with the uncertainty about the progression and outcomes of these alterations (because of the absence of any true lifetime studies) further justifies considering these weight alterations as toxicologically significant.

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8.0 APPENDIXES

Appendix A: Benchmark Concentration Analyses of Data from Cushman et al. (1995)

(1) Computational Models — Continuous Data

The polynomial mean response regression model (THC, ICF Kaiser, 1990a) and the Weibull power mean response regression model (THWC; ICF Kaiser, 1990b) were used.

THC $F(d) = q_0 + SIGN \times [q_1(d - d_0) + ... + q_k(d - d_0)^k]$

THWC $F(d) = q_0 + SIGN \times q_1(d - d_0)^{q2}$

where

d = dose,
F(d) = average response at dose d,
q_0, q_1, q_2, k = estimated parameters (used to determine degrees of freedom), and
SIGN = input indicating an increasing or decreasing dose-response function.

For THC data inputs, the degree of the polynomial was set to the number of dose groups minus one, the corrected sum of squares for each group = (n – 1) × (standard deviation)^2, the response type was relative [F(d) – F(0)] / F(0), and no threshold was estimated. For THWC, data inputs were the same, except that the lower limit of q_2 was set at 1. Although lower values of q_2 may produce a better fit to the data (i.e., lower SS_f), the shapes of dose-response curves generated from the lower values often lack a reasonable biological motivation.

(2) Data

Group mean absolute organ weights for female kidneys and female and male adrenals listed in the principal study of Cushman et al. (1995) were modeled.

(3) Model Fit

Model fit was judged by comparison of a test statistic (F') with F distribution at specified degrees of freedom [df_f (F table numerator); df_e (F table denominator)]. When F' equals or exceeds the appropriate value in the F distribution tables at 0.01, it is concluded that the model did not fit the data.

$$F' = (Ss_f / df_f) / MS_e)$$

where

Ss_f = sum of squares lack of fit (generated by THC or THWC),
Ms_e = pooled mean square pure error (generated by THC or THWC),

df_f = dose groups minus number of parameters [see (1) above] = 5 – 3 = 2 (numerator

in F table), and
df_e = degrees of freedom generated by THC or THWC (denominator in F table).

(4) Results

The critical effect most correlated with the cumene database, female kidney weight gain, was not modeled successfully (F > 0.01, Table 1). Inspection of the modeling results (Table 2) showed that the model did not predict the dose-response discontinuity in weight observed at the low dose in the female kidney. A similar discontinuity in dose-response occurred with female adrenal weights, such that the model did not fit the data at 500 ppm, where there was a decrease, rather than increase, in weight gain relative to the lower dose.

Organ Weight Data Modeled	THC BMC10 (MLE), ppm	THC Fit (F', F)	THWC BMC10 (MLE), ppm	THWC Fit (F', F)
Male adrenal	484 (656)	<0.01 (0.9, 4.8)	484 (656)	<0.01 (0.9, 4.8)
Female kidney	1,067 (1,229)	>0.01 (5.6, 4.8)	1,072 (1,239)	>0.01 (5.6, 4.8)
Female adrenal	906 (1,067)	>0.01 (7.1, 4.8)	924 (1,168)	>0.01 (6.5, 4.8)

Table 1. BMC_{10} values and statistical analysis of model fits to weight gain data from Cushman et al. (1995), where BMC_{10} is the lower 95% confidence bound on the concentration of the maximum likelihood estimate (MLE) of a 10% relative weight change. Fits for both THC and THWC were based on calculations from ICF Kaiser, Inc. (1990a,b)

(5) Discussion

Rather than rely on results from unsuccessful modeling (F'/F > 0.01) or on results from a possibly inappropriate endpoint, the NOAEL of 496 ppm is used for further quantitative analysis. This NOAEL is nearly the same as the BMC10 of 484 ppm for the only data set that was modeled successfully, male adrenal weight gain. The critical effect that was most correlated with the cumene database, female kidney weight gain, was not modeled successfully.

Appendix B: Summary of and Response to External Peer Review Comments

The Toxicological Review for Cumene (except for Sections 4.7 and 6.0, which were rewritten subsequent to external peer review) and all individual cumene assessments have undergone both internal peer review performed by scientists within EPA or other Federal agencies and a more formal external peer review performed by scientists chosen by EPA in accordance with U.S. EPA (1994a). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this

Organ Data Modeled	Dose (ppm)	Observed Mean Weight (g)	Predicted Mean Weight THC and THWC (g)
Male adrenal	0	0.039	0.040
	50	0.041	0.040
	100	0.040	0.041
	496	0.044	0.043
	1,202	0.047	0.047
Female kidney	0	1.40	1.43
	50	**1.49**	**1.43**
	100	1.41	1.43
	496	1.44	1.44
	1,202	1.56	1.56
Female adrenal	0	0.047	0.048
	50	0.049	0.048
	100	0.048	0.048
	496	**0.043**	**0.048**
	1,202	0.056	0.056

Table 2. Benchmark dose modeling of organ weight data from the study of Cushman et al. (1995). The actual data from the study (Oberved Mean Wt.) is compared against the results obtained from applying both the THC and THWC models (Predicted Mean Wt.). Bolded text highlights differences between predicted and observed values.

appendix. Public comments also were read and carefully considered. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical- specific questions in areas of scientific controversy or uncertainty. A summary of comments made by the external reviewers and EPA's response to these comments follows. All three external peer reviewers (see Contributors and Reviewers) recommended that this document and the accompanying assessments were acceptable with minor revision.

(1) General Comments

The three external reviewers offered editorial comments and many minor, but valuable suggestions, all of which have been incorporated into the text to the extent feasible. Substantive scientific comments are addressed below.

A. Comment: The appropriateness of Wolf et al. (1956) as principal study for deriving the oral RfD

One reviewer states that EPA is forced to rely on the marginal Wolf et al. (1956) study because of the paucity of other studies that use the oral route, but the use of uncertainty factors may in part compensate for the deficiencies of this study. Another reviewer states that EPA appropriately recognizes the severe limitations of the study. This same reviewer suggests the use of the Cushman et al. (1995) inhalation study as an alternative method for deriving an RfD.

Response to Comment: The proposal that the inhalation study of Cushman et al. study be used for derivation of the oral RfD has merit. The reviewer notes correctly that cumene is both readily absorbed and has a similar disposition by both oral and inhalation routes. The EPA, however, feels that this option is outweighed by the short term (90 days) of the Cushman et al. inhalation study (the Wolf et al. study lasted 7 mo and is therefore more in concordance with the intention of the RfD). Therefore, the Wolf et al. (1956) study is retained as the principal study for the RfD assessment.

B. Comment: The potential for hematotoxicity

One reviewer cautioned that myelotoxicity from several compounds, including benzene, has been difficult to reproduce in rodents, and the absence of distinct blood effects in the rat studies does not completely exonerate cumene as a potential myelotoxic agent in humans.

Response to Comment: Minor blood effects noted in the principal, 90-day inhalation study of Cushman are described in this IRIS file. A comparison of these blood effects to those observed with benzene is somewhat problematic. The metabolism of benzene is exceedingly complex. The hematotoxic effects of benzene are thought to be mediated through secondary metabolites, such as catechol and hydroquinone, that can be involved in peroxidative processes (Irons, 1991). On the other hand, the metabolism of cumene is simple, the principal metabolite being a secondary alcohol that has little propensity to be involved in peroxidative processes. It also should be noted that benzene was tested in the same oral study with cumene (Wolf et al., 1956), and that blood effects (leucopenia and erythrocytopenia) were reported in rats exposed to benzene but not in rats exposed to cumene. Moreover, the magnitude of blood effects observed in the Cushman cumene study are within normal limits for rodents. No changes are proposed to the IRIS file.

C. Comment: The absence of liver effects in the oral study of Wolf et al. (1956)

One reviewer expressed concern that liver weight changes (along with possible hepatocellular hypertrophy) were present but not recognized in this investigation.

Response to Comment: The study of Wolf et al. (1956) tested and reported on several benzenoid compounds, in addition to cumene (isopropylbenzene), and the experimental procedures state that livers were weighed and examined. Results of the study report changes in liver weight and pathology and in kidney weights and pathology for ethylbenzene, liver and kidney weight changes for styrene, but only kidney weight changes for cumene. In light of the

experimental description and observed results, it is unlikely that liver alterations by cumene would have been missed. No change is proposed to the IRIS file to accommodate this comment.

(2) Comments on Chemical-Specific Questions

Question 1. Based on the information noted in the currently designated principal study (Cushman et al., 1995), is the discounting of the renal effects in males justified?

Comments: One reviewer stated that it was not clear that all kidney changes in the males could be attributed solely to α_{2u}-globulin, but that EPA had presented a scientific basis for discounting the male effects. Another reviewer indicated that attributing male renal effects to α_{2u}-globulin without identification of the specific protein was problematic, although the rationale presented by EPA for the use of female renal effects was adequate.

The response of the third reviewer was that the organ weight changes in both kidney and liver observed in both sexes were caused primarily by microsomal enzyme induction, with an α_{2u}-globulin-like response in males being merely ancillary to the weight increases. This reviewer notes that α_{2u}-globulin responses do not occur with the structurally related compounds toluene and benzene.

Response to Comments: In response to the third reviewer, liver and kidney weights are increased in female and male rats exposed to toluene, and kidneys from male rats exposed to toluene do not show characteristics of α_{2u}-globulin nephropathy in 14- to 15-week exposures (NTP, 1990). Cumene, in comparison, shows increased liver and kidney weights (and adrenals) in female and male rats, and kidneys from male rats exposed to cumene show some characteristics of α_{2u}-globulin nephropathy (perfusion of uncharacterized hyaline droplets) in 13-week exposures. Thus, responses of rats to cumene exposure show characteristics both of toluene exposure and of agents causing male-specific α_{2u}-globulin nephropathy. Because the relevancy to humans is unclear, EPA policy indicates that male-specific α_{2u}-globulin is not an appropriate toxicological endpoint for use in dose-response assessments. Due to this policy and to the inconclusiveness of the information on the identity of cumene as an α_{2u}-globulin agent, the effects in the male kidney are considered to be confounded and are discounted. This logic is currently presented in the IRIS file, and no change is proposed.

Question 2. Is sufficient rationale given to let stand the organ weight changes in female rats as a critical effect?

Comments: One reviewer considers the rationale adequate. Another reviewer approves of the rationale, while stating that associated renal pathology (none was described in the study) would be more compelling. The third reviewer states that organ weight changes in both kidney and liver, observed in both sexes, should be considered as critical effects. The third reviewer also considered the weight increases observed in kidney and liver of both sexes adverse and caused by microsomal enzyme induction (as apparently is the case for effects from toluene).

Response to Comments: Liver weight increases were carefully considered as a co-critical effect. As a matter of policy, liver weight increases without accompanying pathology may be

indicative of increased liver metabolic capacity and usually are considered by the EPA to be adaptive, not adverse, in nature. As pointed out by the reviewer, both liver and kidney weights are increased in female and male rats exposed to toluene by air or by gavage (NTP, 1990) and liver weight increases are the basis for the current toluene RfD (U.S. EPA, 1997, IRIS Online). In the case of toluene, the liver weight changes were considered more adverse in character because liver damage is a documented sequela of toluene exposure in humans. Nevertheless, increases in hepatic weight are not considered as an adverse, co-critical effect in the case of cumene toxicity because no parallel evidence exists for human hepatic damage from cumene exposure, and because liver weight increases do not appear to be a consistent response in animal studies. Liver weight increases were not observed in the oral study of cumene by Wolf et al. (1956). Future evidence in the area of cumene liver toxicity may be sufficient to justify inclusion of liver weight changes as a critical effect. No changes are proposed to the current IRIS file as a consequence of this comment.

Question 3. Is the information in the toxicological review sufficient to consider that cumene has low potential for causing reproductive effects?

Comments: All reviewers considered cumene as an unlikely reproductive toxicant. One reviewer did not consider cumene as a likely reproductive or developmental toxicant, based on the toxicological evidence (including analysis of the available studies), the rapid elimination from the body, and results of studies with similar but unspecified compounds. This same reviewer recommends that the IRIS file should reflect that not only are multigeneration reproductive studies lacking, but also there are no data regarding cumene exposure prior to mating, from conception through implantation, or during late gestation, parturition, or lactation.

Response to Comments: The above statement on specific absence of data is incorporated into the IRIS file at several locations.

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