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ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR

CUMENE
(CAS Reg. No. 98-82-8)

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Cumene is a colorless flammable liquid with a sharp, penetrating, aromatic odor. It is insoluble in water, but is soluble in many organic solvents. Cumene is a ubiquitous environmental pollutant since it is a natural component of petroleum and is present in tobacco smoke. Cumene vapor can be readily absorbed by the respiratory tract. At sufficiently high exposures, cumene causes CNS depression leading to narcosis and death, internal hemorrhage of numerous organs, as well as irritation of the eyes and respiratory system, skin, and mucous membranes. Cumene is a high production volume chemical.

AEGL-1 values were based on a brief chemical company report that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers (Dow 1948). A modifying factor of 2 was applied to 300 ppm to obtain a concentration (150 ppm) that would cause effects within the scope of AEGL-1, i.e., mild eye and respiratory irritation. An uncertainty factor of 3 was applied for intraspecies variability, because mild eye and respiratory irritation is not expected to vary greatly among humans. The resulting AEGL value (i.e., 50 ppm) was adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. The AEGL-1 is supported by human data (volunteers willingly tolerated exposure to 49-146 ppm cumene for an 8-hour period with two 30-minute breaks, but observations were not recorded; Senczuk and Litewka 1976), and several rat studies (a single or multiple exposures for 6 hours to 100 ppm caused no toxic effects; Bushy Run 1989; Darmer et al. 1997).

AEGL-2 values were based on a neurotoxicity functional observational battery (FOB) study in which rats were exposed to 100, 500, or 1200 ppm cumene for 6 hours (Bushy Run 1989). No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused gait abnormalities and decreased rectal temperature. The AEGL-2 was based on exposure to 500 ppm, which caused mild reversible neurological changes and was a NOEL for ataxia and an impaired ability to escape. Data were not available to determine the cumene toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using n=3 and n=1 to extrapolate to exposure times less than and greater than 6 hours. A total uncertainty factor (UF) of 3 was applied, consisting of 1 for interspecies and 3 for intraspecies uncertainty. An interspecies UF of 1 was used because the key study tested the most sensitive species (rat), and the critical endpoint was mild and not seen at similar exposure concentrations (~500 ppm) in several non-FOB rat studies from one 6-hour exposure. Additionally, a UF of 3 would yield all AEGL-2 values below a concentration that had no effect on body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans.

AEGL-3 values were based on the same FOB study as the AEGL-2 values (Bushy Run 1989), and one 6-hour exposure to 1200 ppm was considered an estimate of the lethality threshold because (1) inhalation of 2000 ppm for 6 hours/day caused severe CNS depression and

100% mortality in rats and mice in 2 days (NTP 2004), and (2) up to 90 days of exposure to 1200 ppm for 6 hours/day, 5 days/week caused some toxicity but no lethality in several rat studies (Bushy Run 1989, 1991; Darmer 1997). Scaling to different exposure times was performed using $C^n \times t = k$ (ten Berge et al. 1986) and n=3 or n=1, as was done to derive AEGL-2 values. A total uncertainty factor of 3 was used: 1 for interspecies and 3 for intraspecies uncertainty. An interspecies UF of 1 was used because the animal data clearly showed that inhalation of 1200 ppm for 6 hours was not lethal for the most sensitive species; additionally, use of a UF of 3 would yield AEGL-3 values below AEGL-2 values, and would yield 4 and 8-hour AEGL-3 values that humans tolerated over an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans. The developed 10-minute and 30-minute AEGL-3 values exceed 10% of the LEL (lower explosive limit) of cumene of 9000 ppm.

The derived AEGL-1, AEGL-2, and AEGL-3 values are summarized in the table below.

TABLE 1. Summary of AEGL Values for Cumene

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1[a] (Non-disabling)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	Mild eye and respiratory irritation in humans (Dow 1948)
AEGL–2 (Disabling)	550 ppm (2700 mg/m^3)	380 ppm (1900 mg/m^3)	300 ppm (1300 mg/m^3)	190 ppm (930 mg/m^3)	130 ppm (640 mg/m^3)	Mild reversible neurological changes and NOEL for ataxia in rats, and impaired ability to escape (Bushy Run 1989)
AEGL–3 (Lethal)	1300 ppm* (6400 mg/m^3)	920 ppm* (4500 mg/m^3)	730 ppm (3600 mg/m^3)	460 ppm (2300 mg/m^3)	300 ppm (1500 mg/m^3)	Lethality threshold from CNS depression in rats (Bushy Run 1989)

[a] Reported human odor thresholds ranged from 0.005-1.3 ppm, although values of 0.008-0.132 ppm were considered most reliable (AIHA 1989).

*These values exceed 10% of the cumene LEL (lower explosive limit) of 9000 ppm.

1. INTRODUCTION

Cumene is a colorless liquid with a with a sharp, penetrating, aromatic odor. Cumene is a natural component of petroleum and is present in tobacco smoke. It is insoluble in water, but is soluble in alcohol and many organic solvents (O'Neil et al. 2001). It can be synthesized chemically by alkylation of benzene with propylene using a solid acidic catalyst (NRC 1981). Cumene major industrial uses are in the synthesis of phenol and acetone. Other uses include acetophenone and α-methylstyrene synthesis, as a paint and enamel thinner, in high-octane aviation and automobile fuel, and as a perfume component (Lee 1987). Cumene is a high production volume chemical: in 1995, U.S. production capacity for cumene was ~6.4 billion lbs (Darmer et al. 1997). Cumene vapor can be readily absorbed by the respiratory tract. Symptoms of exposure include irritation of the eyes, skin, and mucous membranes, narcosis, dizziness, ataxia, and headache (NIOSH 2004; IPCS 2004). At sufficiently high exposures (concentration and/or time), animals studies have shown that cumene causes CNS depression leading to narcosis and death and internal hemorrhage of numerous organs (NTP 2004).

TABLE 2. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	(1-methylethyl)benzene, cumol, isopropylbenzene, 2-phenyl propane	O'Neil et al. 2001; NIOSH 2004
Chemical formula	$C_6H_5CH(CH_2)_2$	O'Neil et al. 2001
Molecular weight	120.19	O'Neil et al. 2001
CAS Reg. No.	98-82-8	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Solubility in water	Insoluble (0.005 g/100 mL)	NIOSH 2004
Vapor pressure	3.2 mm Hg at 20°C; 4.6 mm Hg at 25°C	IPCS 2004; U.S. EPA 2004
Vapor density (air =1)	4.2	IPCS 2004
Liquid density (water =1)	0.862 @ 20°C	O'Neil et al. 2001
Melting point	-96°C	IPCS 2004
Boiling point	152-153°C	O'Neil et al. 2001
Flammability limits (volume % in air)	Flash point, closed cup is 31°C; upper and lower explosive limits are 6.5% and 0.9%, respectively	IPCS 2004; NIOSH 2004
Conversion factors	1 mg/m^3 = 0.203 ppm 1 ppm = 4.92 mg/m^3	NIOSH 2004; also calculated as: ppm = (24.45/MW) mg/m^3

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of death resulting from inhalation of cumene were located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

A list of 9 cumene odor thresholds, ranging from 0.005-1.3 ppm, were reported in a secondary source, which stated that values of 0.008, 0.047, and 0.132 ppm were the most reliable (AIHA 1989). Amoore and Hautala (1983) reported a cumene odor threshold of 0.088 ppm.

2.2.2. Workplace Monitoring Data

Personal samples collected over a 7 to 8-hour period for a number of years by a chemical company had a mean concentration of 0.65 ppm ± 4.7 ppm standard deviation (SD) for the 614 samples (Gulf Oil Corp. 1985a). Concentrations ranged from ~0.02 ppm to 78 ppm, and 75% of the samples were ≤0.13 ppm. Area samples (555) had a mean of 0.26 ppm ± 0.93 ppm, and 75% of the samples were ≤0.18 ppm. This report does not address potential health effects or the presence of other compounds in the air. The ACGIH TLV at the time was 50 ppm.

A survey of producers and users of cumene conducted by the Chemical Manufacturers Association (CMA 1985) reported that 86 area samples collected from 1981-1984 at seven companies had a mean of <1 ppm (range of 0.0001-5.58 ppm). Of 1487 personal monitoring samples collected at 10 companies, 89.3% were ≤1.0 ppm, 99.6% were ≤4.0 ppm, and all were ≤30.0 ppm. The presence of other chemicals in the air or of toxic effects were not addressed. All companies used the OSHA PEL of 50 ppm as the guideline exposure limit.

Leach et al. (1987) determined that cumene air concentrations at two small coal liquefaction plants were either below or at the limit of detection (69/70 and 1/70 samples, respectively) of 0.05 mg/m^3 (0.01 ppm). Both stationary area samples and personal samples of operators were collected and analyzed for cumene and several dozen other chemicals, all of which were below their respective recommended exposure limits (50 ppm for ACGIH TLV-TWA). No toxic effects to workers were discussed in the report.

The cumene concentrations in breath (alveolar), blood, and the environment (workplace infirmaries, 8-hour samples) were determined in 58 hospital staff and 28 chemical (benzene) workers not occupationally exposed to cumene (Brugnone et al. 1989). Statistically significant differences were not seen between the chemical plant and hospital workers in the mean cumene environmental levels (0.008 vs. 0.002 ppm) or alveolar concentrations (0.002 vs 0.001 ppm), but the chemical workers had significantly greater cumene blood concentrations (762 vs. 176 ppm). Levels of all three parameters were independent of smoking status. There was a linear correlation ($p<0.01$) between alveolar and environmental concentrations of cumene in both sets of workers, but these were directly correlated to blood levels only in the chemical workers. The concentration of cumene was ~ 40-fold greater in the blood than in alveolar air, which is consistent with the *in vitro* blood/air partition coefficient of 37 (Sato and Nakajima 1979).

A chemical company reported that daily exposure to unspecified cumene concentrations that were “readily tolerated” for 1-2 years caused “no toxic injury” (Dow 1948). It was stated that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most

workers, although some could tolerate "considerably" greater concentrations, although how this information was obtained was not stated.

2.2.3. Experimental Studies

In a study of the absorption of inhaled cumene and excretion of its metabolite dimethylphenylcarbinol (DMPC), 10 healthy volunteers (5/sex) 20-35 years old were exposed to 240, 480, or 720 mg/m^3 (49, 98, or 146 ppm) for 7 hours over an 8-hour period (Senczuk and Litewka 1976; see Section 4.1. for more details). Each individual was exposed to one of the concentrations every 10 days. The toxicity to the volunteers of these cumene exposures was not addressed in the study report. No other parameters were evaluated that could have provided evidence of toxicity (only measured cumene air concentration and urinary DMPC).

2.3. Neurotoxicity

Elfimova (1967) reported that cumene concentrations $\geq$0.05 mg/m^3 (0.01 ppm) altered (presumably decreased) the light sensitivity and reflex adaptation of the eye to light. The study tested 3 humans of unspecified age and sex and further description of the study methods was not provided. Stern (1968) listed 0.028 mg/m^3 (0.006 ppm) as the lowest concentration that negatively affected optical chronaxy, dark adaptation, and/or electrocortical reflex, but no other information was provided.

2.4. Developmental/Reproductive Toxicity

No human developmental studies with cumene were located.

2.5. Genotoxicity

Human genotoxicity studies were not located.

2.6. Carcinogenicity

Studies examining the carcinogenic activity of cumene were not located. The U.S. EPA currently places cumene in Classification D; not classifiable as to human carcinogenicity because no adequate data, such as well-conducted long-term animal studies or human epidemiological studies, are available for assessment (U.S. EPA 2004). Concern for the carcinogenic potential of cumene is judged to be limited because (1) 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, (2) cumene has been examined in a relatively complete battery of *in vivo* and *in vitro* mutagenicity tests in which only a single test, a micronucleus assay, was mildly positive, and then at a dose that resulted in mortality in some animals, and (3) with respect to metabolism, cumene is more analogous to toluene than to ethyl benzene, and toluene showed no evidence of carcinogenic activity in rats or mice in a 2-year NTP inhalation study.

2.7. Summary

No human lethality studies were located. Reported human odor thresholds ranged from 0.005-1.3 ppm, although values of 0.008-0.132 ppm were considered most reliable. Workplace monitoring data showed that occupational exposure was generally well below the OSHA PEL of 50 ppm, as the vast majority of personal and area samples collected at 11 companies were <1.0 ppm. Cumene was also found in ambient air (≤0.008 ppm) and in the blood and exhaled air of persons not occupationally exposed to cumene. An anecdotal report (experimental method not reported) stated that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers. Volunteers tolerated exposure to 49, 98, or 146 ppm cumene for seven hours in an absorption and excretion study although toxicity was not addressed. Two studies reported that cumene concentrations ≥0.01 ppm and 0.006 ppm decreased the light sensitivity and dark adaptation of the eye to light. No human developmental, genotoxicity, or carcinogenesis studies were located. The U.S. EPA places cumene in Classification D; not classifiable as to human carcinogenicity due to absence of adequate data.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Animal lethal toxicity studies are summarized in Table 3.

TABLE 3. Cumene Acute Lethality Animal Studies

Species	Exposure time	Conc. (ppm)	Mortality[1] M	Mortality[1] F	Effects, Comments (Reference)
Rat	4 hrs	8000*	4/6		▸ Narcosis at both doses; 14 day observation; sex of animals not specified (Smyth et al. 1951)
		4000	0/6		
Rat	8 hrs	saturated	6/6		▸ Effects other than death not reported; sex of animals and cumene conc. not specified but calculated by AEGL author from vapor pressure of 4.6 at 25°C (Union Carbide Co. 1985)
	4 hrs	vapor	2/6		
	2 hrs	(~6100)	1/6		
Rat	8 hr/d x 6d?	508	no		▸ Rats appeared normal; sex unknown; total exposure time unclear
	8 hr/d x 6d?	813	no		▸ Somnolence, motor disturbances; exposure time unclear
	6-16 hrs	1321	yes (3/10?)		▸ As above but seen sooner, death rate unclear (Fabre et al. 1955)
Rat	6 hr/d x 5d	2000	0/5	0/5	▸ Nominal concs of 6354* and 12333* ppm but disparity not addressed. Similar signs as at 5000 ppm but lower incidence; no gross lesions.
		5000	5/5	5/5	▸ On day 1, all were lethargic, hypothermic, had ocular irritation, rales, dyspnea; all died on day 2. Congestion in many tissues and eye, nose; red fluid-filled bladders (Gulf Oil Co. 1985b)
Rat	6 hr/d x 14d (5d/wk)	250	0/5	0/5	▸ No effects
		500	0/5	0/5	▸ "Ataxia" on day 1 only (finding is likely incidental)
		1000	0/5	0/5	▸ Ataxia during all or part of study; inc liver wt; one lung lesion
		2000	2/5	3/5	▸ Death on days 2-4; all lethargic starting day 1, dyspnea on day 3 and later, lowered BW gain; dec testes and thymus wt, inc liver wt; lesions in lungs, liver, kidneys, urinary bladder
		4000	5/5	5/5	▸ All die after 1 day; lesions in lung, respiratory pleura (NTP 2004)
Rat	6 hr/d x 90d (5d/wk)	62.5	0/10	0/10	▸ No effects
		125	0/10	0/10	▸ M had inc incidence kidney medullary granular casts
		250	0/10	0/10	▸ Inc liver wt; M had kidney lesions
		500	0/10	0/10	▸ As at 250 ppm
		1000	0/10	0/10	▸ As for 500 ppm but more severe; two F had ovarian cysts (NTP 2004)
Mouse	6 hr/d x 14d (5d/wk)	250	0/5	0/5	▸ No effects
		500	0/5	0/5	▸ Inc liver wt
		1000	0/5	4/5	▸ F died day 3 or 4; all had ataxia or lethargy from day 1; inc liver wt
		2000	5/5	5/5	▸ All died day 2; all lethargic starting on day 1; inc liver wt
		4000	5/5	5/5	▸ All died day 1 (NTP 2004)
Mouse	6 hr/d x 90d (5d/wk)	62.5	0/10	0/10	▸ F had inc incidence of liver minimal chronic focal inflammation
		125	0/10	0/10	▸ As for 62.5 ppm
		250	0/10	0/10	▸ As for 125 ppm; also F had forestomach inflammation
		500	0/10	0/10	▸ As for 250 ppm; also F had inc eye polymorphonuclear infiltration
		1000	0/10	8/10	▸ As for 500 ppm; also F died on days 3-5; M and/or F had inc liver wt, lesions of liver, eye, thymus, lung, or nose (NTP 2004)
Mouse	7 hr	1972-5122 (≥95% pure)	LC_{50}= 1900		▸ Individual test concs (≥5 per series) and results not specified; obs. period not clear but possibly 3 days. Mice had CNS depression (incoordination, analgesia, loss of reflexes, respiratory depression, unconsciousness) to death. Most deaths were 8-24 hr after exposure start. Mice had liver, kidney, and spleen lesions but no lung irritation. Older mice were ~27 g vs. ~21g for others. (Werner et al. 1944)
		2098-2642 (≥99% pure)	LC_{50}= 2000		
Mouse, older	7 hr	1972-5122 (≥95% pure)	LC_{50}= 2300		
Mouse	2 hr	3110-8028	LC_{50}= 5020		▸ No other study details available in report (Izmerov 1982)

[1]The sex of animals that died is stated, if reported in study.
*Exceeds the cumene saturated vapor concentration of ~6100 ppm at 25°, therefore the actual cumene vapor exposure concentration is unclear.

3.1.1. Rats

Treatment of rats (6/group; sex not specified) with 8000 ppm cumene for four hours was lethal to 4/6 of the animals, but all survived a 4-hour exposure to 4000 ppm (Smyth et al. 1951). It is notable that 8000 ppm exceeds the cumene saturated vapor concentration of ~6100 ppm at 25°C, therefore, the actual cumene vapor concentration the animals were exposed to is unclear. The rats were observed for 14 days. Narcosis of unspecified duration was observed following exposure at both test concentrations. In the same study, exposure of rats to "substantially saturated vapor" (not defined) for 8 hours caused 100% mortality, whereas 4 hours caused 1/3 mortality, and 2 hours caused 1/6 mortality.

Wistar rats (8-10 weeks old) exposed to 1321 ppm at first appeared nervous, but within the first hours of exposure had symptoms including somnolence, motor disturbances, and loss of equilibrium, and death occurred "after one exposure for 6-16 hours" (Fabre et al. 1955). The study did not state what fraction of exposed animals died at which exposure duration. Exposure to 813 ppm caused similar signs as 1321 ppm, although they were slower to develop (not quantified). Rats exposed to 508 ppm appeared normal, and their treatment was continued for up to 180 days (see section 3.2.2. for further study details).

Fischer 344 rats (5/sex/dose, 14 weeks old) were exposed whole-body to 0, 2000, or 5000 ppm cumene (nominal concentrations of 0, 6354, and 12333 ppm) 6 hours/day for 5 days (Gulf Oil Co. 1985b). The discrepancy between the nominal and analytical concentrations was not addressed, but is likely due to the fact that the cumene saturated vapor concentration is ~6100 ppm at 25°C. Necropsy was conducted on day 8 or as soon as possible after premature death. Chamber air cumene concentrations were determined at least three times per exposure by GC (gas chromatography) of 100 µL air samples. On study day 1, all high-dose rats were lethargic and hypothermic, had clear ocular discharge, rales, and labored respiration, and some had ocular porphyrin, red material around the eyes, nose, and mouth, partially closed eyes, and perianal soiling. All 5000 ppm rats died on the second exposure day. The 2000 ppm animals had similar signs but with lower incidence over the course of the study, some being seen on the first exposure day (red or clear ocular discharge and red material around the nose and mouth). Low-dose females lost weight over the 8-day study. Necropsy of 5000 ppm rats revealed congestion in many tissues, abnormal intestinal contents, excessive ocular and nasal accumulations, and red fluid-filled bladders. No gross lesions were reported at 2000 ppm.

The inhalation toxicity of cumene was examined by NTP (2004) in a 14-day study for which the report is not available, but for which the in-life phase was completed in 2000 and most study results are available online. Male and female F344 rats were treated 6 hours/day for 14 days (5 days/week) with 0 (vehicle), 250, 500, 1000, 2000, or 4000 ppm cumene vapor. Respective mortality for males was 0/5, 0/5, 0/5, 0/5, 2/5 (died day 2 or 4), 5/5 (all died day 1), and for females was 0/5, 0/5, 0/5, 0/5, 3/5 (died day 2- 4), 5/5 (all died day 1). All 500 ppm rats had "ataxia" on day 1 but not thereafter. [Ataxia was defined as "movement in an uncharacteristic gait", and differed from "lethargy", the only other neurological descriptor used, which meant "lack of movement".] At ≥1000 ppm, some males and females had ataxia starting on day 1 and throughout the study, whereas others had ataxia occasionally during the second week only. At 2000 ppm, all rats were lethargic starting on day 1, three males had abnormal breathing on day 3

and later, and both sexes had lowered weight gain. The finding of ataxia after only day 1 at 500 ppm appears to be an anomaly: either a non-specific response, or due to an error in the achieved cumene chamber concentration. This is concluded because (1) there is no logical explanation for ataxia occurring after day 1 but not after 2 or day 90, if anything, one would expect the toxicity to increase with time; (2) concentrations of cumene that caused ataxia (i.e. ≥1000 ppm) in the NTP (2004) study in rats and mice did so on many days throughout the study, or during only the latter portion of the study, which is consistent with their increased cumulative dose; and (3) other rat studies that did not specifically examine neurological effects by FOB during and/or immediately after exposure, did not report ataxia at ~500 ppm, but did see it at 813-1480 ppm (Fabre et al. 1955; RTI 1989).

Organ weight changes in the NTP (2004) 14-day study included decreased (-31%) testis weight in 2000 ppm males, increased (+31-47%) liver weight in 1000 and 2000 ppm males and females, and decreased thymus weight in 2000 ppm males (-63%) and females (-51%). Lesions were seen at necropsy at 1000 ppm in the lungs (hemorrhage, 1/5 F) and at 2000 ppm in the lungs (alveolar inflammation, 2/5 F, 2/5 M; hemorrhage 1/5 F; histiocyte infiltration 1/5 F), liver (congestion, 3/5 M; hemorrhage 1/5 M) kidneys (hemorrhage 1/5 M, 1/5 F, tubular degeneration 1/5 F), and urinary bladder (hemorrhage 1/1 F, 1/1 M). At 4000 ppm, males had lung alveolar edema (2/5) or inflammation (2/5), and the one examined female had inflammation of the respiratory pleura.

NTP (2004) also conducted a 13-week subchronic inhalation toxicity rat study for which the report is not available, but for which the in-life phase was completed in 2000 and most study results are available online. Male and female F344 rats were treated 96 days with 0 (vehicle), 62.5, 125, 250, 500, or 1000 ppm cumene vapor, 6 hours/day, 5 days/week. All animals survived to study termination and there were no test agent-related clinical observations or effects on body weight gain or biologically significant effects on hematology or clinical chemistry. Liver weight was increased at 1000 ppm in both sexes (25-33%) and slightly in males at 250 and 500 ppm (17-22%). Females had a slightly increased incidence of ovarian cysts (1/10 at 125 ppm, 2/10 at 1000 ppm) and males had an increased incidence of kidney medullary granular casts at ≥125 ppm and increased severity of kidney hyaline droplet formation at ≥250 ppm.

3.1.2. Mice

Young, mature white mice of an unreported strain (~21g; 16/dose, ~ equally divided between the sexes) were exposed to technical cumene (≥95% pure) or "relatively pure" cumene vapor for seven hours (Werner et al. 1944). The chamber air cumene concentrations were checked ≥2X per day with a Rayleigh-Jeans interference refractometer. The individual concentrations tested and their results were not reported, but per the study text test concentrations appeared to range from 5.5-25.2 mg/L (1100-5122 ppm) for technical cumene (≥5 doses) and from 6.5-13.0 mg/L (1300-2642 ppm) for the pure cumene (≥6 doses). The total observation period was not clearly stated but may have been 3 days. The most notable clinical sign was central nervous system (CNS) depression manifest as slight incoordination to deep narcosis (analgesia, loss of reflexes, complete relaxation, respiratory depression, unconsciousness) to death. The response developed slowly (seen towards end of exposure) and had a long duration (up to 36 hours), and was dose-related. Most deaths occurred 8-24 hours

after the beginning of exposure. The LC_{50} values for technical and pure cumene were 9.5 and 10.0 mg/L, respectively (1900 and 2000 ppm), although it was not stated how these values were determined. Technical cumene was also given to a group of "old" mice (~27 g), which had an LC_{50} of 11.5 mg/L (2300 ppm). A fraction of treated mice (22 mice across all dose groups) were examined histopathologically including the heart, lungs, liver, spleen, and kidneys. All animals had moderate or small amounts of fat in the centrolobular region of the liver, congested capillaries, and lymphocytes in the portal zone with occasional necrotic cells in their midst. Kidney findings consisted of fat globules in proximal and distal convoluted tubules or the cortical collecting tubules in six animals, and a few mice (number not specified) had moderate numbers of basophilic casts in the kidney cortex convoluted and collecting tubules. All examined spleens (19) had slight, moderate, or marked phagocytosis of nuclear fragments and/or hemosiderin in the follicles. Evidence of pulmonary irritation was not present.

A two-hour LC_{50} of 5020 ppm (3110-8028 ppm was tested) was reported for mice by Izmerov (1982). No study details were available in this report.

The inhalation toxicity of cumene was examined by NTP (2004) in mice in a 14-day study for which the report is not available, but for which the in-life phase was completed in 2000 and most study results are available online. Male and female B6C3F1 mice were treated 14 days with 0 (vehicle), 250, 500, 1000, 2000, or 4000 ppm cumene vapor, 6 hours/day, 5 days/week. Respective mortality rates were 0/5, 0/5, 0/5, 0/5, 5/5 (all died day 2), 5/5 (all died day 1) for males and 0/5, 0/5, 0/5, 4/5 (died day 3 or 4), 5/5 (all died day 2), 5/5 (all died day 1) for females. No observations were reported at 250 or 500 ppm in either sex. At 1000 ppm, ataxia or lethargy were present in all females starting on day 1, and ataxia in all males starting on day 1. At 2000 ppm, all mice were lethargic on day 1 (and died on day 2). The 250, 500, and 1000 ppm mice that survived gained weight normally over the 2 weeks. There were no treatment-related effects at necropsy or on organ weights except liver weight was increased 19-37% in both sexes at 500 and 1000 ppm.

NTP (2004) also conducted a 13-week subchronic inhalation toxicity mouse study for which the report is not available, but for which the in-life phase was completed in 2000 and most study results are available online. Male and female B6C3F1 mice were treated 96 days with 0 (vehicle), 62.5, 125, 250, 500, or 1000 ppm cumene vapor, 6 hours/day, 5 days/week. All males survived and all females exposed to ≤500 ppm survived. Females exposed to 1000 ppm (8/10) died on study days 3-5. There were no test agent-related clinical observations, effects on body weight gain, or biologically significant effects on hematology. Liver weight was increased at 1000 ppm in both sexes (25-32%). Males had an increased incidence of liver necrosis and a slight increase in the incidence and severity of eye polymorphonuclear infiltration at 1000 ppm. Females had an increased incidence of liver minimal chronic focal inflammation (≥62.5 ppm), forestomach inflammation (≥250 ppm), marked thymus necrosis (1000 ppm), lung or nose inflammation (1000 ppm), and eye minimal polymorphonuclear infiltration (≥500 ppm).

3.2. Nonlethal Toxicity

Animal nonlethal toxicity studies are summarized in Table 4 (rats) and 5 (other species).

TABLE 4. Cumene Nonlethal Toxicity Rat Studies

Exposure time	Conc. (ppm)	Effects, Comments (Reference)
8 hr/d x 180d (6d/wk)	508	▸ Rats appeared normal, had lower weight gain for week 1. Lesions found in lungs, liver, spleen, and kidneys (Fabre et al. 1955)
6 hr	3577	▸ All survived for 14 days with no toxic signs or gross abnormalities; most study details were not provided; males only (Monsanto 1982)
1 hr	4400	▸ Signs included excitation, lacrimation, tremors, ataxia, prostration and sedation by 15 min; most study details not provided; males only (Ciba-Geigy 1985)
6 hr, nose-only	580 1480	▸ No effect; evaluated only respiratory frequency (measured as pressure changes at the nose-ports) relative to controls, and clinical signs ▸ Respiratory frequency was statistically lower by 3-5 hrs of exposure. After exposure, rats had severe motor impairment and narcosis. (RTI 1989)
244ppm: 8 hr/d x 30d (5d/wk) 3.7, 30 ppm: 90d non-stop		▸ No effects on BW gain, hematology, necropsy, histopathology. One rat exposed to 3.7 ppm cumene died on day 11, but this appeared incidental. (Jenkins et al. 1970)
6 hr/d x 20d (5d/wk)	105.1 300.1 or 599.3	▸ Increased liver and kidney weight w/o histopathology ▸ Red discharge by nose and eyes, hypoactivity starting wk 1; by wk 2 had side-to-side head motion and salivation. Had inc kidney and liver weight w/o histopathology. (Monsanto 1985)
All concs: 6 hr/d, 5d/wk 250 ppm: 10d 750 ppm: 4d, 500 for 6d 1500 ppm: 3d, hold 1d, then 1000 for 6d 2000 ppm: 1-2d, hold 4d, then 1200 for 4-5d		▸ No toxicity at 250 ppm (F=female; M=male) ▸ Three highest concs lowered due to high toxicity at 2000 ppm after 1 or 2 exposures (ataxia, dec. motor activity, eye discharge, collapse, abnormal respiratory sounds, corneal opacity). Signs generally disappeared overnight. One M died on day 3. Necropsy on day 2: F had liver lesions. During/after 2-week study, top three doses had eye and anogenital discharge, dec. BW gain and food consumption, inc. liver, kidney, and/or adrenal weights, and high-dose rats had ataxia. (Chevron 1989)
6 hr/d x 90d (5d/wk for 13 wk)	100 500 1200	▸ No toxicity ▸ Dec. motor activity, hypoactivity, periocular tissue swelling, urogenital stains, inc. water consumption, cataracts (possibly), inc. liver and kidney weight , kidney lesions ▸ As for 500 ppm; also blepharospasm, delayed/absent startle reflex, ataxia, inc. adrenal weight (Bushy Run 1989; Cushman et al. 1995).
6 hr	100 500 1200	▸ No effects (study only tested FOB at 1, 6, and 24 hr post-exposure) ▸ Inc. total activity and horizontal activity at 1 hr post-exposure only, dec. toe-pinch withdrawal reflexes at 6 hr only ▸ As for 500 ppm; also at 1 hr had inc. incidence/severity of gait abnormalities and dec. rectal temperature (Bushy Run 1989 study; Cushman et al. 1995).
6 hr/d x 90d (5d/wk for 13 wk) + 4-wk recovery	50 or 100 500 1200	▸ Swollen periocular tissue after ≥18d ▸ As for 100 ppm; also inc. liver weight (histopathology not evaluated) ▸ As for 500 ppm; also dec. BW gain, inc. lung, adrenal weight (histopath unknown). No cataracts or neurotoxicity (Bushy Run 1991; Dow 1991; Cushman et al. 1995).
6 hr/d x 10d (GD 6-15)	100 500 1200	▸ No effect on dams or offspring (gravid females exposed on gestation days 6-15). ▸ Dec. maternal food consumption ▸ As for 500 ppm; also dec. maternal BW gain, inc. relative liver weight, perioral wetness (Darmer et al. 1997)

1
2

TABLE 5. Cumene Nonlethal Toxicity Animal (Other than Rat) Studies

Species	Exposure time	Conc. (ppm)	Effects, Comments (Reference)
Squirrel monkey	8 hr/d x 30d 90 d contin.	244 3.7 or 30	▸ No animals died or had treatment-related effects on BW gain, hematological parameters, or on gross or microscopic pathology (Jenkins et al. 1970)
Mouse	2 hr	4065 5081	▸ Lowest conc causing mice to lie prostrate on their side ▸ Lowest conc causing loss of startle reflex (Lazarew 1929)
Mouse	30 min, head-only	320-4450	▸ RD_{50} = 2490 ppm (conc. causing 50% reduction in respiratory rate). The respiratory rate dec. quickly (≤ 1 minute) and in most cases did not return to normal during 20-min recovery period. (Nielsen and Alarie 1982)
Mouse	30 min, head-only	556-4120	▸ RD_{50} = 2058 ppm. Respiratory inhibition was immediate, and was maximal by 2 min for ≤1812 ppm, and by 10 min for ≥2863 ppm, after which the responses started to fade. (Kristiansen et al. 1986)
Mouse	20 min	2000 4000 8000*	▸ Only FOB evaluated in study. Observed dec. rearing and righting reflex and inc. landing foot splay during and/or after exposure. ▸ As for 2000 ppm; also posture changes, palpebral closure, lacrimation, gait abnormalities, dec. arousal, mobility, forelimb grip strength, and response to sensory stimuli. ▸ As for 4000 ppm; also easier removal, dec. coordination. Effects were reversible and greater during than after exposure (Tegeris and Balster 1994).
Mouse	2 hr	1047-5203	▸ NC_{50} = 2337 (produced narcosis in 50% of tested animals) (Izmerov 1982)
Dog	8 hr/d x 30d 90 d contin.	244 3.7 or 30	▸ No animals died or had treatment-related effects on BW gain, hematological parameters, or on gross or microscopic pathology (Jenkins et al. 1970)
Guinea pig	8 hr/d x 30d 90 d contin.	244 3.7 or 30	▸ No animals died or had treatment-related effects on BW gain, hematological parameters, or on gross or microscopic pathology (Jenkins et al. 1970)
Rabbit	8 hr/d x 5d 8 hr/d x 180d	2439 1321	▸ Slightly dec. urine output (no signs of toxicity) ▸ No toxic effects (Fabre et al. 1955).
Rabbit, gravid	6 hr/d x 13d (GD 6-18)	500; 1200 2300	▸ No developmental effect ; dams had dec. food consumption ▸ As for 1200 ppm; also dams had dec. BW gain during exposure, inc. relative liver weight and incidence of perioral wetness, and two dams died (cause of death not stated) (Darmer et al. 1997)

*Exceeds the cumene saturated vapor concentration of ~6100 ppm at 25°, therefore the actual cumene vapor concentration the animals were exposed to is unclear.
Contin. = continuous

3.2.1. Monkeys

Jenkins et al. (1970) exposed squirrel monkeys (*Saimiri sciurea*) 8 hours/day, 5 days/week for 30 sessions to 244 ppm cumene, or continuously for 90 days to 3.7 or 30 ppm cumene (3 males/group). Chamber cumene concentrations were monitored by GC, infrared analysis, and/or total hydrocarbon analysis (not specified). No animals died on study, or had treatment-related effects on body weight gain, hematological parameters (leukocytes, hemoglobin, hematocrit), necropsy results, or for the histopathology of the brain, spinal cord, heart, lungs, liver, spleen, or kidneys.

3.2.2. Rats

Wistar rats (8-10 weeks old) exposed to 508 ppm for up to 180 days for 8 hours/day, 6 days/week appeared normal. Their body weight gains were decreased during the first week but thereafter recovered. Analysis of blood (RBC, leukocytes, platelets) and bone marrow (myelograms) did not find any toxic effects. Histological tissue examination revealed hyperemia and congestion in the lungs, liver, spleen, and kidneys, and in some cases hemorrhagic areas in the lungs, spleen hemosiderosis, and lesions in the kidney epithelium.

White albino male rats exposed for 6 hours to 17.6 mg/L (3577 ppm) all survived for 14 days with no toxic signs or abnormalities seen in the viscera (Monsanto Co. 1982). It was not stated whether the calculated exposure concentration was verified analytically, and most other study details were not provided.

Male albino rats exposed for 1 hour to 22.1 mg/L (4400 ppm) cumene displayed signs including excitation, lacrimation hyperpnea, tremors, ataxia, prostration and sedation within the first 15 minutes of exposure but 0/6 died (Ciba-Geigy Co. 1985). No further experimental details were provided.

RTI (1989) evaluated the effect of treatment with 0, 580, or 1480 ppm cumene on respiratory frequency in Fischer 344 rats as an indicator of toxicity in a range finding study. Rats (3/sex/dose, 7-9 weeks old) were treated nose-only for 6 hours. Cumene vapor concentration was monitored by GC. Respiratory frequency was quantified by measuring pressure changes in individual nose-ports of the inhalation apparatus for two 30-second intervals per hour of exposure (each pressure maximum was one respiration). The study authors reported a statistically significant decrease in respiration frequency relative to controls in 1480 ppm males and females, beginning at 3 and 5 hours, respectively, from the start of exposure. Immediately after the 6-hour exposure, severe motor impairment and narcosis were seen in both sexes.

Jenkins et al. (1970) exposed male and female rats 8 hours/day, 5 days/week for 30 sessions to 244 ppm cumene, or exposed rats continuously for 90 days to 3.7 or 30 ppm cumene. The rats were NMRI Sprague-Dawley or Long-Evans (not specified), and each concentration tested a total of 14 or 15 males and females, but the number of each sex was not specified. Chamber cumene concentrations were monitored by GC, infrared analysis, and/or total hydrocarbon analysis (not specified which method was used at which concentration). No treatment-related effects were noted on body weight gain, hematological parameters (leukocytes, hemoglobin, hematocrit), necropsy results, or for the histopathology of the heart, lungs, liver, spleen, or kidneys. One rat continuously exposed to 3.7 ppm cumene died on day 11, but the study did not address the cause of death (lack of death at 8-fold higher test concentrations for longer duration indicates the death was incidental).

Sprague-Dawley rats (10/sex/dose, 44 days old) inhaled 0, 105.1, 300.1, or 599.3 ppm cumene vapor 6 hours/day, 5 days/week for 4 weeks (20-21 exposures) (Monsanto 1985). Analytical concentrations were obtained during exposure using a Miran gas analyzer, and were close to the target concentrations of 100, 300, and 600 ppm, respectively. Cageside observations were made several times per day but were reported on a weekly basis. No rats died on study.

Observations made during the first week at 300 and/or 600 ppm in one or both sexes included dried reddish discharge around the nose (most common), reddish discharge near the eyes, hypoactivity, and reddish color on fur around the nose. These signs were typically also seen during weeks 2-5 at 600 ppm in both sexes and sporadically at lower test concentrations. In addition, side-to-side head movements occurred in all treated groups but no controls for weeks 2-5, and salivation occurred in males at all doses and in one 300 ppm female. Treatment did not affect animal body weight gain or numerous urinalysis, hematology, and clinical chemistry parameters, necropsy results, or the histopathology of internal organs. The statistical increase in weight of the left and right kidney for 100, 300, and/or 600 ppm males, and the increased weight of the liver in 600 ppm males and in 100, 300, and 600 ppm females lacked correlating histopathology and its toxicological significance is unclear.

In a two-week repeat-dose study, Fischer-344 rats (10/sex; 58 days old) were exposed whole-body initially to 0, 250, 750, 1500, or 2000 ppm cumene (99.9% pure) for 6 hours/day, 5 days per week (Chevron 1989). The three highest concentrations were decreased to 500, 1000, and 1200 ppm during the experiment due to excessive toxicity at 2000 ppm. Cumene vapor was generated by vaporizing liquid cumene, and its concentration was measured at least once/day by chemical analysis, and was monitored continuously with a Miran infrared gas spectrophotometer. Rats were observed daily, food consumption and weight were measured weekly, and the clinical pathology, macroscopic and microscopic pathology, and organ weights were evaluated at sacrifice. Severe effects were seen at 2000 ppm after the first exposure in females and after the second exposure in males (study day 2), and included ataxia, decreased motor activity, colorless eye discharge, collapse, abnormal respiratory sounds, yellow anogenital discharge, corneal opacity, and lowered food consumption in many animals and decreased respiration rate in one male that died the next day. The 2000 ppm rats were not exposed for the next 4 days, and 4/10 males and 5/10 females were sacrificed on study day 2. The 2000 ppm females had pale livers with an accentuated lobulation pattern and vacuolar changes (hydropic). On study day 6, the 2000 ppm exposure concentration was lowered to 1200 ppm. The concentrations of the 750 and 1500 ppm groups were lowered to 500 and 1000 ppm, respectively, on study day 5. During or after the 2-week study, toxic effects in the 2000/1200 ppm and 1500/1000 ppm groups included sporadic ataxia, hypo- or hyper-activity, colorless or red eye discharge, yellow anogenital discharge, decreased body weight and food consumption, very slight anemia (not biologically significant), and increased liver weight in both sexes. Males had slightly increased kidney weight at all doses but the response was not clearly dose-related. High-dose females had slightly increased serum chemistry levels (triglycerides, cholesterol, total protein, and albumin) and increased adrenal weight. At 750/500 ppm, both sexes had increased liver weight, and females had ocular discharge and yellow anogenital discharge and decreased food consumption during the first week. The clinical observations generally disappeared overnight. No signs of toxicity were noted at 250 ppm. The study authors considered 250 ppm a NOAEL.

In a 13-week study, Fischer 344 rats (21/sex/dose) were exposed whole-body to 0, 100, 500, or 1200 ppm cumene vapor 6 hours/day, 5 days/week for 13 weeks, and were sacrificed at the beginning of the 14th week (Bushy Run 1989; Cushman et al. 1995). Separate groups of 10 rats/sex/dose received only one exposure and were used for neurobehavioral evaluation (study is described in the following paragraph). GC analysis of chamber air during exposure found mean

analytical concentrations of 1202, 496, and 100 ppm. No treatment-related deaths occurred. FOB analysis showed no changes compared to pre-exposure but motor activity was decreased in 500 and 1200 ppm males. Group observations during exposure showed that the 1200 and 500 ppm rats appeared hypoactive, and that 1200 ppm rats had blepharospasm and a delayed or absent startle reflex. Individual observations after exposure found ataxia at 1200 ppm in both sexes for days 14-17, and an increased incidence of periocular tissue swelling (indicative of irritation) and urine stains and/or urogenital wetness at 500 and 1200 ppm. No consistent alterations to body weights and weight gains were noted. Water consumption was increased for 500 and 1200 ppm males for weeks 2-13 (overall increase of 40%), and for 500 and 1200 ppm females during weeks 7, 8, and 10. Indirect ophthalmoscopy during week 13 revealed an increased incidence of cataracts (largely focal and nuclear): the fraction of affected males at 0, 100, 500, and 1200 ppm was 14, 38, 24, and 55%, and of females was 24, 24, 48, and 48%. However, eye lesions were not found microscopically although only a single section of the eye was examined. Blood analysis at week 14 showed small alterations in several hematology and clinical chemistry parameters at 500 and/or 1200 ppm that were not biologically significant. Light microscopy of peripheral or central nervous system nervous system tissues that were either perfusion-fixed (6 rats/sex/dose) or immersion-fixed (15 rats/sex/dose) found no treatment-related lesions. Necropsy showed periocular swelling as the only treatment-related effect. Both sexes had increased liver weight (500 and 1200 ppm) and adrenal weight (1200 ppm), and slightly increased kidney weight (500 and 1200 ppm females;1200 ppm males), but brain, lung, and gonad weights were unaffected. Microscopic lesions were found in only kidneys, consisting of proximal tubule epithelial cell hypertrophy, hyperplasia, interstitial nephritis, and increased hyaline droplet formation at 500 and 1200 ppm, and increased tubular proteinosis at 1200 ppm. Examination of epididymides and testes in males did not detect differences from controls for sperm count or morphology, spermatid count, or spermatogenesis. The study authors speculated that the hyaline droplet formation is rat-specific and not relevant to humans, that increased liver weight without correlating histopathology may not be toxicologically relevant, and that the increased adrenal weight may be a secondary effect of mild subclinical dehydration as evidenced by the clinical chemistry changes and increased water consumption.

Separate groups of rats (10/sex/dose) in the Bushy Run (1989) study received only a single whole-body exposure to 0, 100, 500, or 1200 ppm cumene vapor for 6 hours and were used only for FOB evaluations. The FOB was performed pre-exposure and 1, 6, and 24 hours post-exposure, after which the rats were sacrificed but not necropsied. At the 1-hour analysis, observations included "increases in the incidence and severity of gait abnormalities" in 1200 ppm males, "increases in mean activity counts" in 1200 ppm males and 500 and 1200 ppm females, increased horizontal activity for 500 ppm females and 1200 ppm males and females, and decreased rectal temperature in 1200 ppm males and females. These observations were not seen at the 6 or 24-hour post-exposure analyses, although after 6 hours 500 and 1200 ppm males had decreased toe-pinch withdrawal reflexes.

Bushy Run Research Center (1991; Cushman et al. 1995) conducted a follow-up 13-week inhalation study to clarify the findings of motor activity changes in males and cataracts in both sexes in their previous subchronic study (Bushy Run 1989; Cushman et al. 1995). Fischer 344 rats (15/sex/dose; 7 weeks old) were exposed whole-body 6 hours/day, 5 days/week for 13 weeks to 0, 50, 100, 500, or 1200 ppm cumene, followed by a 4-week recovery period. Cumene

air concentration was measured every 30 minutes during exposure by GC. Necropsy was conducted on all animals but histopathology only on the eyes, which were also examined by indirect ophthalmoscopy by two independent veterinary ophthalmologists. The animals' auditory brain stem responses were evaluated in an adjunct study conducted a week after treatment ended (Dow 1991; described in Section 3.3.1.). No animals died on study. The most notable clinical observation was an increased incidence of swollen periocular tissue, which occurred in both sexes (≥500 ppm males; ≥50 ppm females) after ≥18 days of treatment. Organ weight changes consisted of increased absolute and relative (to body and brain) weight of the liver in males (8-9% at 500 ppm; 11-14% at 1200 ppm) and females (11-14% at 1200 ppm), and of the lungs (5-8%) and adrenals (8-12%) in 1200 ppm females. The significance of these small changes, with no microscopic evaluation, was uncertain. There was no change in the incidence of cataracts, altered motor activity, auditory brain stem response, body weights, or gross pathology, except that 1200 ppm females had significantly lowered body weight gain during treatment week one.

A comparison of control data from 10 subchronic (≥90 days exposure) studies by Bushy Run Research Center (1992) indicated that the 19% control incidence of cataracts in Fischer 344 rats in the Bushy Run (1989; Cushman et al. 1995) 14-week study was spurious and invalidated this study's finding of cataracts in the treated animals. The highest control incidence in the other 9 studies was 4%, which was consistent with the Bushy Run (1991; Cushman et al. 1995) 13-week study in which a detailed analysis by two pathologists did not find an increased incidence of cataracts.

3.2.3. Mice

Lazarew (1929) determined that the lowest concentration of cumene that caused white mice to lie prostrate on their side was 20 mg/L (4065 ppm), and that caused loss of reflexive response to tapping on the ~10-liter glass exposure chambers was 25 mg/L (5081 ppm) for a two-hour exposure. The number and sex of animals tested and whether other concentrations of cumene were tested was not specified, only that 550 animals were used to test 35 different hydrocarbons.

In a very brief report, it was stated that exposure to 2337 ppm cumene for two hours produced narcosis in 50% of tested mice (Izmerov 1982). Concentrations of 1047-5203 ppm were tested, but no other study details were provided.

Nielsen and Alarie (1982) determined that the RD_{50}, i.e., the concentration of cumene that depresses the respiratory rate by 50% due to sensory irritation of the upper respiratory tract, was 2490 ppm in male Swiss-Webster mice. [Multiplying the RD_{50} by 0.03, which was previously shown to yield values that correlate well with sensory irritants' TLVs (Alarie 1981), yields 75 ppm, which is close to the TLV-TWA of 50 ppm for cumene.] Mice (4/dose) were exposed head-only in a body plethysmograph to 320, 700, 1210, 2650, or 4450 ppm cumene for 30 minutes followed by a 20-minute recovery period, during which time their tidal volume and respiratory rate were measured. Cumene air concentrations were monitored continuously with a Miran I infrared analyzer. The respiratory rate decreased quickly (≤ 1 minute) and in most cases did not return to normal during the recovery period. The maximum percent decreases in

respiratory rate over the 30 minute exposure period were 19%, 16%, 34%, 54%, and 61%, respectively, at 320, 700, 1210, 2650, and 4450 ppm (estimated by the AEGL author from the figure in the report). Tracheally cannulated mice (4/dose) were exposed to 2200, 2900, or 3700 ppm for 30 minutes in a similar experiment. Cumene did not cause significant pulmonary irritation, as 2200 ppm did not decrease the respiratory rate (estimated by the AEGL author from the figure in the report, the respiratory rate decreased 9%) and 2900 and 3700 ppm caused only about a 35% decrease in the respiratory rate and an RD_{50} for the cannulated mice was not attained.

An RD_{50} value of 2058 ppm was obtained by Kristiansen et al. (1986) using CF-1 male mice (4/dose) exposed head-only for 30 minutes to 556, 1321, 1812, 2863, or 4120 ppm cumene. The experimental protocol was the same as for the RD_{50} study by Nielsen and Alarie (1982). Respiratory inhibition occurred immediately after exposure started, and was maximal within two minutes for $\leq$1812 ppm, and within 10 minutes for $\geq$2863 ppm, after which the responses started to fade somewhat. As estimated from the figure in the report by the AEGL author, the percent inhibition in the respiratory rates was 20%, 35%, 58%, 58%, and 72% at 556, 1321, 1812, 2863, and 4120 ppm, respectively. Tracheally cannulated mice were exposed to 2200, 2770, 3224, 3969, or 5867 ppm cumene for the same duration. Respiratory inhibition was more slow to develop in the cannulated mice, being maximal after ~25 minutes of exposure. No inhibition occurred at 2200 ppm. As estimated from the figure in the report by the AEGL author, the percent inhibition in the respiratory rate was 24%, 30%, 40%, and 45% at 2770, 3224, 3969, or 5867 ppm cumene, and an RD_{50} was not achieved. Neither anaesthesia nor asphyxia were present in normal or cannulated mice since they moved in the plethysmograph during exposure.

Male CFW (Charles River Swiss) albino mice (8/group) were exposed to 2000, 4000, or 8000 ppm (more likely 6100 ppm; 8000 ppm exceeds the cumene saturated vapor concentration of ~6100 ppm at 25°C) cumene for 20 minutes and their neurological response (i.e., FOB) was evaluated during and immediately after exposure (Tegeris and Balster 1994). This study is described in detail in Section 3.3.2. No observations were reported other than those that were part of the FOB. Neurobehavioral findings at 2000, 4000, and/or 8000 ppm during and/or after exposure were consistent with CNS depression and included changes in posture, decreased arousal and rearing, palpebral closure, greater ease of removal, lacrimation, abnormal gait and righting reflex, decreased mobility, motor coordination, forelimb grip strength, and response to sensory stimuli, and increased landing foot splay. The effects were reversible and were generally more pronounced during than after exposure.

3.2.4. Dogs

Beagle dogs (2 males/group) were exposed 8 hours/day, 5 days/week for 6 weeks to 244 ppm cumene, or continuously for 90 days to 3.7 or 30 ppm cumene (Jenkins et al. 1970). Chamber cumene concentrations were monitored by GC, infrared analysis, and/or total hydrocarbon analysis (method for particular concentration not specified). No animals died on study, or had treatment-related effects on body weight gain, hematological parameters (leukocytes, hemoglobin, hematocrit), necropsy results, or for the histopathology of the brain, spinal cord, heart, lungs, liver, spleen, or kidneys.

3.2.5. Guinea Pigs

Jenkins et al. (1970) subjected MNRI:(ASH) Princeton derived guinea pigs 8 hours/day, 5 days/week for 30 exposures to 244 ppm cumene, or continuously for 90 days to 3.7 or 30 ppm cumene (3 males/group). A total of 15 males and females were tested at each concentration, but the number of each sex was not specified. Chamber cumene concentrations were monitored by GC, infrared analysis, and/or total hydrocarbon analysis (not specified). No animals died on study, or had treatment-related effects on body weight gain, hematological parameters (leukocytes, hemoglobin, hematocrit), necropsy results, or for the histopathology of the heart, lungs, liver, spleen, or kidneys.

3.2.6. Rabbits

Rabbits exposed to 2439 ppm cumene 8 hours/day, 6 days/week for one week had no signs of toxicity, only their urine output was decreased slightly (Fabre et al. 1955). No toxic effects were noted on rabbits similarly exposed up to 6 months to 1321 ppm cumene (Fabre et al. 1955).

3.3. Neurotoxicity

Neurotoxicity, characterized by CNS depression (narcosis, decreased motor activity, incoordination, prostration, impaired gait and reflexes to stimuli), occurred in the vast majority of the single and multiple-exposure studies conducted on rats and mice (see Tables 2, 3, and 4). From a single exposure, the lowest exposure that resulted in CNS depression was 500 ppm for 6 hours in rats (Bushy Run 1989). In multiple-exposure studies, CNS effects were seen starting the first week of exposure to 300 ppm 6 hours/day, 5 days/week for 4 weeks (Monsanto 1985). Rabbit data was very limited and conflicting: Izmerov (1982) reported that at 2337 ppm, narcosis occurred in 50% of tested rabbits, whereas Fabre et al. (1955) reported no CNS depression from exposure to 2439 ppm 8 hours/day for 5 days. Studies with monkeys, dogs and guinea pigs were performed only at low concentrations ($\leq$244 ppm for 8 hours), and no neurotoxic effects were seen.

An electrophysiological screen for auditory dysfunction was conducted on rats that had participated in a 13-week inhalation study (Bushy Run 1991; Cushman et al. 1995) because several compounds related structurally to cumene (toluene, xylene, styrene) were shown to cause ototoxicity. Three to six days following the last exposure to 0, 50, 100, 500, or 1200 ppm, 10 rats/sex/group were put under light anaesthesia with inhaled isoflurane. Stainless steel electrodes inserted in the scalp were used to measure auditory brain stem responses (ABRs) to 4.2 msec tone-pips at 4, 8, 16, and 30 kHz frequencies and at 70-80 dB (~50 dB above the ABR threshold). Automated computer techniques and statistical analysis found no treatment-related differences from controls for ABR at any test frequency for any dose group, even after analysis with body temperature and weight as covariates.

A functional observational battery (FOB) was developed for mice and used to evaluate responses to exposure to 2000, 4000, and 8000 ppm (likely 6100 ppm; see section 3.2.3.) cumene for 20 minutes (Tegeris and Balster 1994). [Five other alkylbenzenes and pentobarbital

were also tested and produced similar effects, as described in Section 4.3.] Male CFW (Charles River Swiss) albino mice (8/group) were exposed in plastic cages with steel wire tops that were sealed with a plastic lid during exposure. Static vapor exposures were generated by vaporizing cumene from filter paper with a fan, and chamber atmospheres were monitored with infrared spectrometry. The FOB was a modification of the FOB used for rats, and evaluated posture, arousal, rearing, clonic and tonic movements, palpebral closure, gait, and gait abnormalities during the last two minutes of exposure. Following exposure, mice were immediately removed from the chambers and within ~2 minutes the above parameters were re-tested on an open field, along with ease of removal, handling reactivity, urination, defecation, lacrimation, piloerection, mobility, righting reflex, forelimb grip strength, inverted screen test, landing foot splay, and responses to sensory stimuli (approach, click noise, touch, and tail pinch). Neurobehavioral findings during and/or after exposure were consistent with CNS depression and included changes in posture (≥4000 ppm), decreased arousal (≥4000 ppm) and rearing (≥2000 ppm), palpebral closure (≥4000 ppm), greater ease of removal (8000 ppm), lacrimation (≥4000 ppm), gait abnormalities (≥4000 ppm), and righting reflex abnormalities (≥2000 ppm), decreases in mobility (≥4000 ppm), motor coordination (8000 ppm), forelimb grip strength (≥4000 ppm), and response to sensory stimuli (≥4000 ppm), and increased landing foot splay (≥2000 ppm). The effects were generally more pronounced during than after exposure, and were quickly reversible after treatment ended.

3.4. Developmental/Reproductive Toxicity

Mated female CD Sprague-Dawley rats (25 plug-positive/group; ≥88% pregnant/group) were exposed 6 hours/day to 0, 100, 500, or 1200 ppm cumene during gestation days (GD) 6-15, and New Zealand White rabbits (15/group; all pregnant) were exposed 6 hours/day to 0, 500, 1200, or 2300 ppm cumene during GD 6-18 (Darmer et al. 1997). The cumene used in this GLP study was 99.9% pure. The test atmosphere was generated by vaporizing liquid cumene, and the cumene air concentration was measured every 30 minutes by GC (4320L glass and steel exposure chamber; 14 air changes/hour). Treatment did not affect any evaluated developmental parameters, including the number of viable implantations per litter, sex ratio, fetal body weights, external, visceral, or skeletal malformations, or the incidence of variations. Maternal toxicity in rats consisted of decreased food consumption at ≥500 ppm, and of decreased body weight gain during exposure, and an increase in relative liver weight and perioral wetness at 1200 ppm. Rabbit dams had lowered food consumption at ≥500 ppm, and the 2300 ppm group had decreased body weight gain during exposure, increased relative liver weight and incidence of perioral wetness, and two dams died. The cause of death was not stated, only that one animal was found dead and the other was killed moribund.

3.5. Genotoxicity

The vast majority of the mutagenicity tests conducted using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and/or TA1538 with or without metabolic activation, yielded negative results when cumene was tested at up to cytotoxic concentrations (Florin et al. 1980; Monsanto Co. 1982; Microbiological Associates 1987a; Simmon and Kauhanen 1978). Mutations were also not induced by 0.0005-0.05% w/v cumene, with or without metabolic activation, in *Saccharomyces cerevisiae* D3 (Simmon and Kauhanen 1978). Cumene emulsified

in 0.04 or 0.05% Pluronic F127 did not induce mutations in the CHO/HGPRT assay when tested at up to 225 μg/mL, although one of the two sets of assays had a high background mutation frequency (Gulf Oil Co. 1985c).

Cumene tested without metabolic activation was negative in the BALB/3T3 mouse embryo cell transformation assay (Microbiological Associates 1987b). Cells were incubated for 3 days with 50-500 μg/mL cumene, and severe to complete cytotoxicity occurred at ≥150 μg/mL. Another laboratory, however, obtained a positive response in this assay using 60 μg/mL cumene; other test concentrations were 5, 20, and 90 μg/mL (Gulf Oil Co. 1984). Partial cytotoxicity occurred at 60 μg/mL (44% relative colony forming efficiency), and complete cytotoxicity at 90 μg/mL (no attached cells).

Chromosome aberrations were not induced in Chinese hamster ovary (CHO) cells treated with 24-225 μg/mL cumene with S-9 activation, or treated with 19-200 μg/mL cumene without activation (Microbiological Associates 1987c). Toxicity occurred at the highest doses with and without activation.

Micronuclei were not induced in mouse bone marrow polychromatic erythrocytes of Crl:CDR-1 (ICR) mice gavaged with 250-1000 mg/kg cumene for one or two consecutive days (Gulf Oil Co. 1985d). No alteration occurred for the ratio of polychromatic to normochromatic erythrocytes.

Unscheduled DNA synthesis (UDS), characterized as a statistically significant ($p \leq 0.01$) increase in the percentage of cells in repair, occurred in rat liver primary cultures incubated for 19 hours with 16 or 32 μg/mL cumene (Gulf Oil Co. 1984). UDS was not induced at 8 or 64 μg/mL, and nearly all cells died at ≥128 μg/mL. The cumene was emulsified in 4% pluronic F68 polyol, which had a final culture concentration of 0.04%. A subsequent evaluation concluded that the study results were invalid because the control UDS levels were ~10-fold greater than the historical range, which was not stated (CMA 1986).

3.6. Chronic Toxicity/Carcinogenicity

Cumene chronic toxicity or carcinogenicity animal studies were not found. As of 11/26/04, the conducted NTP 2-year inhalation study with rats and mice was not publicly available and had the status: "Pathology Quality Assessment in Progress." The U.S. EPA places cumene in Classification D; not classifiable as to human carcinogenicity due to absence of adequate data (further details in Section 2.6.).

3.7. Summary

CNS depression (narcosis, decreased motor activity, incoordination, prostration, impaired gait and reflexes to stimuli, etc.) was the most commonly reported effect in single or multiple exposure animal studies. Rats and mice were the most sensitive species, as neurotoxicity was seen at ≥500 ppm from a single 6-hour exposure. The limited data indicated that rabbits were less sensitive to neurotoxic effects than rats and mice; monkeys, dogs, and guinea pigs were not tested at sufficiently high doses to produce neurotoxicity. CNS depression was typically seen

during or within 6 hours after exposure; examination at ≥24 hours showed no effects. This finding is consistent with the rapid absorption, metabolism, and excretion of cumene, as discussed in Section 4.1. None of the studies demonstrated histopathological changes in CNS tissues, however.

Cumene also caused eye and respiratory irritation. Eye irritation from a single exposure, consisting of clear or red discharge, lacrimation, and/or swollen periocular tissue) occurred at ≥2000 ppm (rat 6-hour exposure). Cumene was not a potent respiratory irritant in animals, as 30- minute exposure RD_{50} values of 2058 and 2490 ppm were obtained using mice. Eye and respiratory irritation were found frequently in multiple-exposure studies, and at lower concentrations than in single-exposure studies. In rats, exposure to ≥300 ppm 6 hours/day caused red discharge around the nose and eyes starting the first exposure week, and swollen periocular tissue was observed after ≥18 exposures to ≥50 ppm. More serious respiratory effects (lung congestion, hemorrhage, periocular tissue swelling at necropsy) occurred from repeated exposure for at least 90 days to ≥500 ppm. The lowest concentration at which death occurred from a singe exposure, likely due to CNS depression, was 1321 ppm in rats.

Other common treatment-related effects seen in single-exposure studies included congestion in multiple organs and liver, kidney, and spleen lesions. Findings in only multiple-exposure studies included decreased body weight gain and food consumption, and increased absolute and/or relative weight of the liver, kidneys, and adrenals and decreased thymus weight in one or both sexes. The kidney, liver, and thymus weight increases were in some cases accompanied by microscopic changes, but histopathological evaluations were not always conducted.

No developmental toxicity was seen in either rats or rabbits exposed during GD 6-15 and 6-18, respectively, and dams had relatively mild effects (decreased food consumption and body weight gain, increased liver weight, and perioral wetness) at ≥500 ppm. However, two rabbit dams exposed to 2300 ppm died and the cause of death, and whether it was treatment-related, were not addressed in the study.

A wide spectrum of genotoxicity tests were conducted, and the majority of the results were negative. No chronic or carcinogenesis animal studies were located other than the "in progress" report of the NTP 2-year inhalation study with rats and mice. The U.S. EPA places cumene in Classification D; not classifiable as to human carcinogenicity due to lack of adequate data.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

In both animals and humans, cumene was shown to be metabolized and excreted primarily in the urine as the 2-phenylpropan-2-ol conjugate [= dimethylphenylcarbinol (DMPC)].

Tissue distribution and excretion were examined in several groups of rats repeatedly exposed to 508 ppm cumene for 8 hours/day (Fabre et al. 1955). The results of these studies are summarized in Table 6. Overall, the results show that blood and lipophilic organs including the endocrine glands, CNS, spleen, and liver retained a relatively large proportion of cumene. Cumene tissue levels decreased significantly by 48 hours after treatment, more noticeably in low-lipid organs (e.g. kidney, stomach) than in the blood and in lipid-rich organs. Cumene blood and tissue levels were generally greater after 60 days than after 10 days exposure. The study did not address the seeming inconsistency in finding lower blood levels 3 days after an 180-day exposure than 10 days after a 10 (or 60)-day exposure.

TABLE 6. Cumene Distribution Studies in Rats
[Exposed to 508 ppm cumene, 8 hr/day, 5 days/wk; (Fabre et al. 1955)]

Tissue or organ	10 days exp.; immediate sacrifice (n=2)	10 days exp.; sacrifice after 48 hrs (n=2)	10 of 60 days[1] exp.; sacrifice after 10 days (n=1)	60 days exp.; sacrifice after 24 hrs (n=6)	60 days exp.; sacrifice after 24 hrs [2] (n=4)	180 days exp.; sacrifice after 3 days (n=4)
	Tissue concentration of cumene (μg/g)					
Blood	–	29	16.5	29	Plasma: 8 Globulins: 43	<5
Spleen	29	<5	–	10	–	11.5
Bone marrow	25	<5	–	–	–	–
Liver	20	8	–	7.5	–	6.5
Cerebellum	15	20-30	–	53	–	5
Brain	8	10	–	18	–	<5
Spinal cord	–	–	–	7.5	–	–
Kidney	12	–	–	<5	–	<5
Stomach	6	–	–	<5	–	–
Lung	<5	–	–	<5	–	<5
Heart	<5	<5	–	<5	–	<5
Bladder	<5	–	–	–	–	–
Thyroid	–	–	–	83	–	>100
Pituitary gland	–	–	–	–	–	>100
Pancreas	–	–	–	–	–	<5
Ovaries	–	–	–	–	–	35
Testicles	–	–	–	–	–	30
Adrenals	–	–	–	70	–	43

" – " Signifies that this parameter was not reported in the study; exp. = exposure.
[1] It was unclear from the study text if the rat was treated for 10 or 60 days.
[2] Blood was collected on sodium fluoride, centrifuged, and cumene measured in the plasma and globulins.

To compare tissue levels in species, Fabre et al. (1955) treated one rabbit 8 hours/day for 150 days with 1321 ppm cumene and allowed it to rest for 10 days prior to blood collection.

Detectable levels of cumene were found only in the adrenals (not quantifiable) and in the blood (8 μg/g). Therefore the rabbit appears to metabolize cumene (and remove it from the blood) faster than the rat, as blood of similarly treated rats contained 16.5 μg/g cumene.

Senczuk and Litewka (1976) measured the absorption of inhaled cumene and the associated excretion of its metabolite dimethylphenylcarbinol (DMPC) in 10 healthy volunteers (5/sex) 20-35 years old. Exposure was head-only to 240, 480, or 720 mg/m^3 (49, 98, or 146 ppm) for 7 hours over an 8-hour period: two 2.5-hour periods each followed by a 30-minute break, ending with a 2-hour period. Each individual was exposed to one of the concentrations every 10 days. Cumene vapor in the exposure chamber, and its concentration in the inhaled and exhaled air, was determined by GC. The exhaled air was collected by having subjects exhale into a pipe in the front wall of the exposure chamber at approximately 30 minutes, 2.5-3 hours, 5.5-6 hours, and 8 hours after exposure began. Urine was collected before exposure and 2.5, 5.5, 8, 10, 12, 14, 24, 32, 40, and 48 hours after the beginning of exposure. The urine content of DMPC was measured by GC following urine acid hydrolysis in boiling water, cooling, and extraction in ether for 4 hours. A mean of 50% (45-64%) of inhaled cumene was "retained in the respiratory tract" (this was likely the difference in cumene content of inhaled and exhaled air; not stated), the fraction "retained" decreasing slightly over the 8-hour period. The total amount of cumene absorbed over the 8-hour period, based on retained inhaled cumene and unspecified ventilation rates at 240, 480, or 720 mg/m^3 was, respectively 271, 526, and 789 mg for women and 466, 934, and 1400 mg for men. The majority of DMPC urinary excretion occurred within 8 hours of exposure, the rate being the greatest during the last two hours, and decreasing after exposure ended, approaching 0 after 48 hours. The elimination kinetics appeared to follow a 2-compartment model, in which the half-life of the first phase was 2 hours and of the second phase was 10 hours. Over 48 hours, ~ 35% of the absorbed cumene was metabolized to DMPC for each dose. The study showed a direct correlation between the exposure chamber air concentration, the amount of absorbed cumene, and the amount of excreted cumene metabolite. The utility of this study is limited because it left out methods details and appeared to contain several inconsistencies and/or typographic errors.

The pharmacokinetics (PK), excretion, and tissue distribution of cumene were examined in F-344 rats (7-9 weeks old; 4-5 rats/sex/dose) exposed nose-only for 6 hours with ~100, 500, or 1200 ppm cumene (RTI 1989; oral and iv exposures also performed). Indwelling jugular cannulae were surgically implanted for blood collection. One set of rats received unlabeled cumene (102, 525, or 1328 ppm analytical by GC), their blood was collected 0, 5, 10, 15, 30 min, and 1, 2, 4, 8, 16, 24, and 48 hours after the start of exposure, and its cumene content measured by GC. The second set of rats received [^{14}C-phenyl]-cumene (104, 494, or 1194 ppm analytical by GC) and was used to evaluate excretion and tissue distribution. Radiolabeled blood samples were collected 4, 6, 8, 16, 24, 48, 72 hours after start of exposure. PK modeling of the radioactive blood samples was used to estimate the area under the curve (AUC), the coefficients and exponents of the model exponential phase, and the half-life for each animal, sex, and all animals combined. Excretion was rapid and efficient: after 72 hours 96.0-98.9% of the radioactivity was recovered for all groups. Urine was the major route of excretion (77-93% of radioactivity), although with increasing test concentration radioactivity in the urine decreased and in the volatile breath and feces increased, more in females than males. After 72 hours, at 100, 500, and 1200 ppm, the percent radioactivity in volatile breath (which was shown to be

cumene) was 2.3, 3.4, and 8.4% for males, 2.8, 7.0, and 17.3% for females; in CO_2 breath was 0.2% for all exposures; and in feces was 1.5, 2.0, 2.5% for males, 2.0, 3.2, 4.8% for females. Adipose generally had the highest concentration of radiolabel for both sexes, followed by (in no consistent order) kidney, liver, muscle, bone, and ovaries in females. No tissue contained >0.15% of the dose.

In the RTI (1989) inhalation study, radiolabel appeared in the blood within 4 hours of the start of exposure, peaked at 6 hours (total duration of exposure), and declined rapidly thereafter in a manner similar for the three doses. As shown in Figure 1 for males, the concentration of radioactivity in blood increased with dose and time, and did not reach steady-state during the 6-hour exposure period. Data for females (not shown) were similar to males. PK modeling of the radioactive blood samples using a one-compartment model predicted blood cumene concentrations well except at the peak concentration due to collection of too few blood samples. The AUC at all doses was 31-38% greater in males than females, indicating that males absorbed more of the administered dose (i.e., cumene plus its metabolites) than females, which was also seen in the human absorption/excretion study of Senczuk and Litewka (1976). The half-lives for disappearance of radiolabel from blood at 100, 500, and 1200 ppm were, respectively, 4.3, 4.8, and 7.3 hours for males and 3.4, 4.5, and 5.8 hours for females. In non-radioactive blood samples, cumene was absorbed and eliminated rapidly. Blood cumene levels increased with time and dose, similarly for both sexes, and are shown in Figure 2 for males. Steady-state cumene levels were not achieved. PK modeling of the data using a two-compartment model estimated similar AUCs for males and females, which increased with dose. The model also estimated a terminal half-life for excretion at 500 ppm of 19 hours for males and 15 hours for females, and at 1200 ppm of 21 hours for males and 37 hours for females (could not be calculated at 100 ppm). The greater half-life at 1200 ppm, also seen when following blood radioactivity, indicates that the excretion system for cumene and its metabolites is saturated to some degree at 1200 ppm.

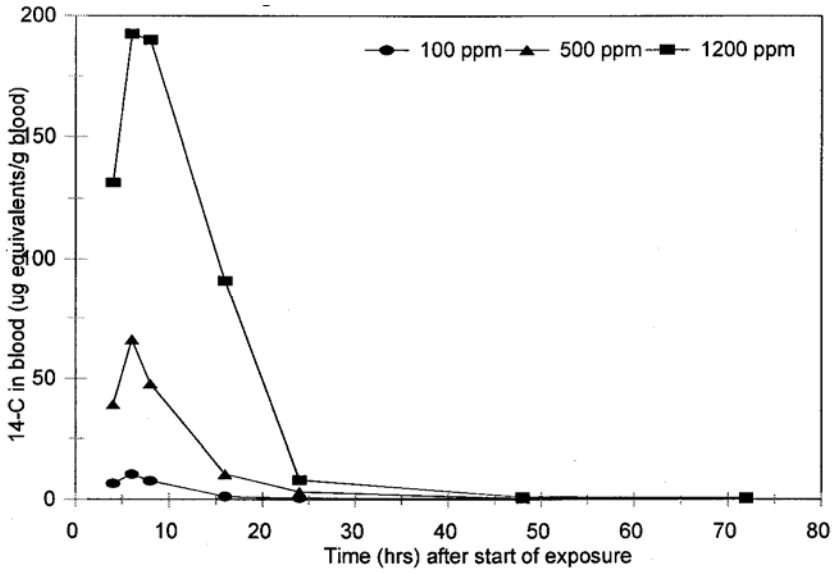

Figure 1. Blood ^{14}C levels in male rats exposed for 6 hours

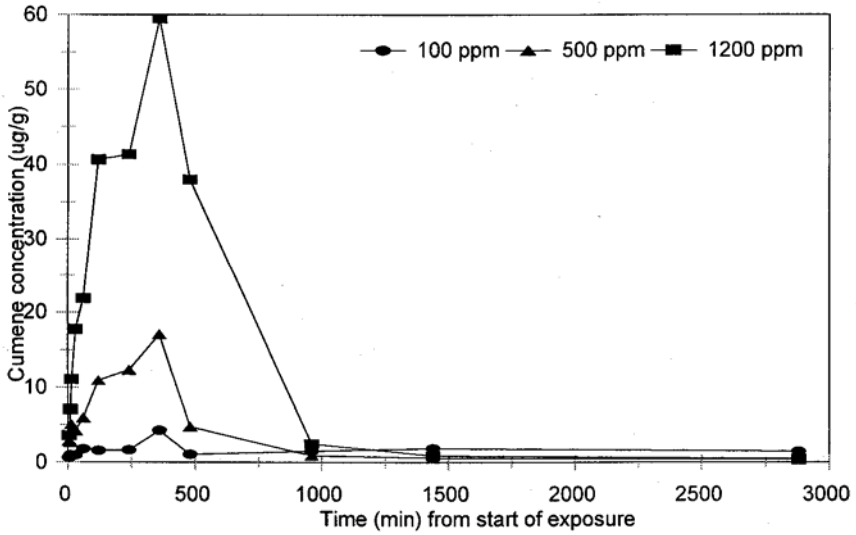

Figure 2. Blood cumene levels in male rats exposed for 6 hours

Metabolites present in urine composite samples (0-24 and 24-48 hour) were characterized and identified using known standards by C8 reverse-phase HPLC. In the urine at all exposure levels, small (≤2% each) amounts of 2-phenyl-1,2-propandiol, 2-phenyl-2-propanol, and 2-phenylpropionic acid were found. Also found were six unknowns, which were the same urinary metabolites found following iv or oral dosing based on HPLC retention times in the RTI (1898) study. For the 100 and 500 ppm groups, the six unknowns represented, respectively (1)<1-3%, (2) 6-13%, (3) 5-7%, (4) 15–23%, (5) 3-8%, and (6) 47-63% of the radioactivity. At 1200 ppm, the proportion of metabolite 2 increased (14-31%) and of metabolite 6 decreased (30-52%). The six metabolites were isolated as discrete HPLC peaks using urine samples from rats treated orally, because these samples contained the highest concentration of the metabolites among the three exposure routes tested. The six unknowns were treated with a 10-fold excess of deconjugating enzyme preparation containing β-glucoronidase and sulfatase activity. HPLC of the resulting samples showed that metabolites 1, 4, and 5 were conjugates of 2-phenyl-1,2-propandiol, and metabolite 6 was a conjugate of 2-phenyl-2-propanol.

A comparison of the RTI (1989) results using the three different exposure routes showed that cumene was absorbed well by all routes, after which it was extensively metabolized and excreted. The rates and routes of excretion were similar for the three doses and both sexes. Urine was the major route of elimination, containing ~70% of the dose. There was no evidence for accumulation of cumene in tissues. The metabolic profile was the same by all exposure routes. For all doses and routes, ≥50% of the urinary radioactivity was represented by 2-phenyl-2-propanol and its glucuronide and/or sulfate conjugates.

Due to unacceptably low total recovery of radioactivity in the RTI (1989) iv bolus injection study (<90% TRR), a RTI (1991) conducted a repeat iv study quantitating cumene disposition. Male and female Fischer 344 rats (4/sex; 9 weeks old) were given a single bolus tail lateral vein injection of ~33 mg/kg [^{14}C]cumene (2-5 μCi; 2 mL/kg) and placed in glass metabolism cages. Indwelling jugular cannulae were surgically implanted in the rats for the

collection of blood to mimic the previous study, although blood was not collected. Exhaled breath was collected both during and immediately following injection ("dose breath", 5-10 minute period) and after transfer to the metabolism cages ("volatile breath"). Urine was collected at 8, 16, and 24 hours after dosing, and feces 24 hours after dosing. Rats were sacrificed 24 hours after dosing. The TRR was 90.2% for males and 86.9% for females, of which the majority was in the urine (58% TRR for males; 64% TRR for females). A substantial fraction of the TRR was exhaled by both males (13.1% as volatile breath, 2.3% as dose breath) and females (9.8% as volatile breath, 4.0% as dose breath), and contained cumene and its (unidentified) radiolabeled metabolites, but ≤0.1% TRR was $^{14}CO_2$. The feces represented a small fraction of the TRR (mean of ≤1.1% for males; 0.3% for females). The carcass contained 12.9% TRR for males and 4.9% TRR for females. The study authors concluded that radioactivity was lost in the earlier study primarily in the exhaled "dose breath" and during cage opening.

Ishida and Matsumoto (1992) examined the stereoselective metabolism of cumene in six rabbits given 30 g cumene by stomach tube (in 2.4-g aliquots). Urine was collected daily and incubated with β-glucuronidase/arylsulphatase for 48 hours at 37°C, and extracted with ether for 48 hours to yield 28.88 g metabolites in neutral, acidic, and phenolic fractions. The fractions were subjected to preparative analytical techniques (TLC, HPLC, GC, and IR and ^{1}H-NMR spectroscopy) and were in some cases chemically derivatized prior to analysis. Four metabolites were identified using known reference standards: (1) 2-phenyl-2-propanol (not optically active), (2) 2-phenyl-1-propanol [90.3% R(+)], (3) 2-phenylpropanoic acid [99.0% S(+)], and (4) 2-hydroxy-2-phenyl propanoic acid [81.0% R(+)]. The relative amounts of metabolites I, II, III, and IV, as a fraction of the recovered metabolites were 29%, 4.0, 19%, and 2.7%, respectively. The study authors concluded that the data suggest that ω-hydroxylation occurs first at the pro-S methyl group, followed by stereochemical inversion of 2-phenylpropanol from the R(-) to the S(+) acid.

4.2. Mechanism of Toxicity

The most commonly reported toxic effect and sensitive endpoint of cumene exposure is CNS depression, characterized in animals by narcosis, decreased motor activity, incoordination, prostration, impaired gait and reflexes to stimuli, etc. The exact mechanism by which this occurs is unknown, but is believed to involve the affinity of cumene, which is lipid-soluble and not water-soluble, for nerve tissue due to its high lipid content. Signs of CNS depression occurred in most of the available acute and subchronic cumene inhalation studies with rats and mice and in one study with rabbits. In the available animal studies, the CNS depressant effects occurred during exposure and shortly thereafter, but by 24 hours effects generally disappeared (Bushy Run 1989). This is consistent with the rapid absorption and excretion of cumene shown in pharmacokinetic studies (RTI 1989, Senczuk and Litewka 1976).

Cumene also causes sensory irritation (at neurotoxic concentrations). Based on studies of respiratory rate inhibition (RD_{50}) caused by cumene and other related alkylbenzenes (listed in Section 4.3.), Nielsen and Alarie (1982) concluded that the sensory irritation of these compounds is caused by a physical interaction with a receptor protein in a lipid layer, rather than by a chemical interaction. This conclusion is based on the finding that the ratio of the RD_{50} to the

saturated vapor pressure (i.e. the thermodynamic activity) was relatively constant for the series of tested alkylbenzenes.

4.3. Structure Activity Relationships

A number of related alkylbenzenes including cumene were compared with respect to their odor perception levels, metabolism, and toxicity (Gerarde 1960). The study author draws a number of conclusions, although often only qualitative statements were made with no numeric data. Conclusions by Gerarde (1960) for mono-substituted alkyl benzenes included:
(1) Branching and unsaturation of the benzene side chain enhances odor whereas longer side chains have less odor since vapor pressure decreased with increasing molecular weight. For example, n-propylbenzene has a sweet, bland odor whereas isopropylbenzene (i.e., cumene) has a sharp penetrating odor.
(2) Branching of the side chain generally increases the rate of percutaneous absorption, as cumene is absorbed better than p-cymene, toluene, p-xylene, and ethylbenzene.
(3) The alkylbenzenes, but not benzene, cause CNS depression manifest as sluggishness, anesthesia, narcosis, and coma due to their affinity for lipid-containing nerve tissue. The narcotic potency decreases as chain length increases, beginning to decline at four carbons.
(4) The duration of CNS depression increases with length and branching of the side chain, cumene and n-butylbenzene being "long-acting" and toluene and ethylbenzene "short-acting."
(5) The aromatic hydrocarbons are metabolized by conjugation with sulfuric acid, glycine, or glucuronic acid, producing in water-soluble products that can be excreted in the urine.
The CNS effects (and toxicity) are dependent on the rate of biotransformation into water-soluble metabolites, which occurs more quickly for straight-chain than branched side chains.
(6) A comparison of rat 4-hr LC_{50} values shows that inhaled cumene (8000 ppm) is more toxic than benzene (16000 ppm) but less toxic than *p-tert*-butyltoluene (248 ppm).
(7) In mice, 7-hr LC_{50} values were lower for cumene (2000 ppm) than for toluene (5000 ppm) or benzene (10,000 ppm). Narcosis from cumene developed more slowly and lasted longer than from toluene or benzene.
(8) Normal neurological function usually returns after the alkylbenzenes are eliminated from tissues, unless the administered dose was sufficient to cause profound narcosis, coma, or endothelial injury (causing hemorrhage).
(9) Pulmonary elimination of systemic hydrocarbons in rabbits was directly related to the compounds'vapor pressure. The percent of an oral dose eliminated as hydrocarbon in three days (and the vapor pressure at 40°C) was 43% for benzene (181 mm Hg), 18% for toluene (59 mm Hg), >5% for cumene (10 mm Hg), >5% for n-propylbenzene (>10 mm Hg), and >2% for *p-tert*-butyltoluene (>5 mm Hg).

Nielsen and Alarie (1982) determined RD_{50} values, i.e., the concentration that depresses the respiration rate by 50%, in male Swiss-Webster mice for a number of alkylbenzenes (benzene itself actually increased the respiratory rate due to action on the CNS). The compounds and their RD_{50} values in ppm were toluene (5300), ethylbenzene (4060), n-propylbenzene (1530), cumene (2490), n-butylbenzene (710), tert-butylbenzene (760), n-amylbenzene (230), n-hexylbenzene (125), and p-tert-butyltoluene (360). The data indicated that the potency for respiratory inhibition i.e., upper respiratory irritation, increased with chain length. Exposure of tracheally cannulated mice to these compounds resulted in only slight or no pulmonary irritation.

Tegeris and Balster (1994) conducted a neurological evaluation (FOB) of mice exposed for 20 minutes to 2000, 4000, or 8000 ppm benzene (likely 6100 ppm; see section 3.2.3.) and 5 alkylbenzenes including cumene, toluene, ethylbenzene, propylbenzene, and m-xylene (study and cumene results are detailed in Section 3.2.2.). Pentobarbital (5-40 mg/kg) was also tested, but was administered intraperitoneally. The mice were evaluated during and immediately after exposure, but no observations were reported other than those that were part of the FOB. The six compounds and pentobarbital produced a very similar profile of effects, which were consistent with CNS depression. Findings included changes in posture, decreased arousal and rearing, palpebral closure, greater ease of removal, abnormal gait and righting reflex, decreased mobility, motor coordination, forelimb grip strength, and response to sensory stimuli, and increased landing foot splay. Pentobarbital and benzene differed from the other compounds in that they caused an increase in clonic movement but did not cause lacrimation [per the study report Table 1, cumene and toluene are listed as causing increased clonic movement, but this appears to be a typographic error because the study text stated that only benzene caused clonic movements]. The effects were reversible and were generally more pronounced during than after exposure.

4.4. Other Relevant Information

4.4.1. Species Variability

The data indicated that rats and mice were more sensitive to cumene neurotoxicity than rabbits. This may be due to the rabbits' more rapid elimination of cumene from the blood (Gerarde 1960). Comparisons with other species (squirrel monkeys, dogs, guinea pigs) could not be made because the latter were not exposed to sufficiently high concentrations to elicit toxicity.

Single-exposure acute lethality studies were not available to compare rats and mice directly, as an LC_{50} was located only for mice in an older study (~2000 ppm for 7 hours; Werner et al. 1944). The other available single and multiple-exposure studies did not clearly define if rats or mice were more sensitive. Thus, in the NTP (2004) 14-day rat and mouse study, 4/10 mice but 0/10 rats died from three or four 6-hour exposures to 1000 ppm, most animals of both species died after 2 exposures to 2000 ppm, and all died after one exposure to 4000 ppm. Earlier studies with few details provided conflicting data. For example, exposure to ~5000-6000 ppm for 2 hours caused 1/6 rats to die (Union Carbide 1985), 50% of mice to die (Izmerov 1982), or no mouse deaths (Lazarew 1929). Therefore, the data overall indicated that rats and mice are similarly sensitive to cumene toxicity.

4.4.2. Susceptible Populations

Many lipophilic organic vapors, including cumene, produce an anesthetic effect in exposed humans, prompting numerous studies of the susceptibility of individuals of different ages to anesthesia (Gregory et al. 1969; Stevens et al. 1975; Lerman et al. 1983; LeDez and Lerman 1987; Katoh and Ikeda 1992; Chan et al. 1996). Concentrations of various anesthetic gases that induce "anesthesia" (i.e. lack of movement) were typically reported as the minimum alveolar concentration (MAC) that produces lack of movement in 50% of persons exposed to that concentration. The results indicated that newborns, particularly those that are premature, pregnant women, and the elderly were the most sensitive, then normal adults, and older infants, toddlers and children were the least sensitive. The total range of sensitivity was 2-3 fold. CNS

effects of these agents are thought to be additive if mixtures are involved. Cumene produces CNS dysfunctions that are similar to those produced by other anesthetics; therefore, it is reasonable to assume that the same 2-3 fold difference in sensitivity among infants and adults applies to cumene.

4.4.3. Concentration-Exposure Duration Relationship

Scaling across time was not performed for AEGL-1, as using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time. For AEGL-2 and AEGL-3 values for 10, 30, 60, 240, and 480 minutes, scaling across time was performed using the ten Berge et al. (1986) equation, $C^n \times t = k$. This equation describes the concentration-time relationship for many irritant and systemically acting vapors and gases, where the exponent n ranges from 0.8 to 3.5, and n ranged from 1 to 3 for 90% of the chemicals. Because no data were available from which to determine the concentration-time relationship for cumene inhalation toxicity, i.e. n in the ten Berge equation, default values of n=3 and n=1 were used to extrapolate to shorter and longer exposure times, respectively, than tested in the key study, to obtain protective values.

Unlike in most studies where the key study exposure duration is ≥4 hours, the cumene 10-minute AEGL-2 and AEGL-3 values were not set equal to the 30-minute values, but were scaled from 6 hours (key study exposure duration) using $C^n \times t = k$ and the default n=3. The reasoning is as follows. For AEGL-3, the POD was exposure of rats for 6 hours to 1200 ppm (Bushy Run 1989). Scaling to 10 minutes using $C^3 \times t = k$ yields 3953 ppm, a concentration that was tolerated by mice for 20 minutes (4000 ppm; Tegeris and Balster 1994) and by rats for 1 hour (4400 ppm; Ciba-Geigy 1985) with marked neurotoxic signs but no mortality. For the AEGL-2, the POD was exposure of rats to 500 ppm for 6 hours (Bushy Run 1989). Scaling to 10 minutes using $C^3 \times t = k$ yields 1650 ppm, which is below a concentration that mice were exposed to for 20 minutes with minor neurological effects (2000 ppm; NOEL for gait abnormalities) (Tegeris and Balster 1994). Therefore, scaling from 6 hours to 10 minutes using $C^3 \times t = k$ provided values at 10 minutes that in other studies caused effects within the scope of the respective AEGL level, and lowering the 10-minute values further to be protective was not necessary.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Two human reports provided quantitative exposure data. In an anecdotal report by a chemical company, it was stated that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers, although some could tolerate “considerably” greater concentrations (Dow 1948). How this information was obtained was not described. In a human metabolism study, healthy volunteers inhaled 49, 98, or 146 ppm cumene for 7 hours over an 8-hour period, after which the urinary level of a cumene metabolite was evaluated (Senczuk and Litewka 1976). The responses of the individuals to the exposure were not reported. A number of workplace monitoring studies were available, in which concentrations generally stayed below 1 ppm and the effect on workers was not discussed.

5.2. Summary of Animal Data Relevant to AEGL-1

The following three animal studies were considered potentially useful for developing AEGL-1 values: (1) Bushy Run 1989 FOB study, in which 100 ppm for 6 hours had no effects and 500 ppm caused mild motor changes, (2) Tegeris and Balster 1994, in which exposure of mice to 2000 ppm for 20 minutes caused mild motor skill impairment, and (3) the NTP 2004 14-day study in which exposure for 6 hours to 250 ppm caused no visible effects in rats or mice but greater concentrations caused neurological toxicity.

5.3. Derivation of AEGL-1

AEGL-1 values were based on a brief chemical company report that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers (Dow 1948). A modifying factor of 2 was applied to 300 ppm to obtain a concentration (150 ppm) that would cause effects within the scope of AEGL-1, i.e., mild eye and respiratory irritation. An uncertainty factor of 3 was applied for intraspecies variability, because mild eye and respiratory irritation is not expected to vary greatly among humans. The resulting AEGL value (i.e., 50 ppm) was adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. The AEGL-1 is supported by human data (volunteers willingly tolerated exposure to 49-146 ppm cumene for an 8-hour period with two 30-minute breaks, but observations were not recorded; Senczuk and Litewka 1976), and several rat studies (a single or multiple exposures for 6 hours to 100 ppm caused no toxic effects; Bushy Run 1989; Darmer et al. 1997). AEGL-1 values are shown in Table 7 and calculations are detailed in Appendix A.

TABLE 7. AEGL-1 Values for Cumene

10-minute	30-minute	1-hour	4-hour	8-hour
50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No quantitative human data with an AEGL-2 endpoint were located.

6.2. Summary of Animal Data Relevant to AEGL-2

AEGL-2 values can be derived from (1) RTI 1989, in which rats exposed for 6 hours to 580 ppm had no effect on respiratory rate or clinical signs but severe effects were seen at 1480 ppm, (2) exposure of rats to 500 ppm in the FOB study (Bushy Run 1989), which caused mild neurological effects (3) exposure of mice to 4000 ppm for 20 minutes(Tegeris and Balster 1994), which caused moderate motor impairment, and (4) exposure to 500 ppm for 6 hours in the NTP (2004) study, which was considered a NOEL for ataxia seen at 1000 ppm (ataxia reported at 500 ppm in rats on day 1 only was considered an anomaly).

6.3. Derivation of AEGL-2

AEGL-2 values were based on the neurotoxicity FOB study in which rats were exposed to 100, 500, or 1200 ppm cumene for 6 hours (Bushy Run 1989). No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused gait abnormalities and decreased rectal temperature. The AEGL-2 was based on exposure to 500 ppm, which caused mild reversible neurological changes and was a NOEL for ataxia and an impaired ability to escape. Data were not available to determine the cumene toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using n=3 to extrapolate to exposure times < 6 hours (exposure duration in the key study), and n=1 to extrapolate to exposure times >6 hours. An interspecies UF of 1 was used because the key study tested the most sensitive species (rat), and the critical endpoint was mild and not seen at similar exposure concentrations (~500 ppm) in several non-FOB rat studies from one 6-hour exposure. Additionally, an interspecies UF of 3 would yield all AEGL-2 values below 244 ppm, which had no effect on body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans. The AEGL-2 values are shown in Table 8 and calculations are detailed in Appendix A.

TABLE 8. AEGL-2 Values for Cumene

10-minute	30-minute	1-hour	4-hour	8-hour
550 ppm (2700 mg/m^3)	380 ppm (1900 mg/m^3)	300 ppm (1300 mg/m^3)	190 ppm (930 mg/m^3)	130 ppm (640 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No quantitative human information on lethal cumene exposure was located.

7.2. Summary of Animal Data Relevant to AEGL-3

Animal studies potentially useful for AEGL-3 derivation included: (1) the Smyth et al. (1951) study in which rats exposed for 4 hours to 4000 ppm all survived for 14 days, whereas 4/6 of rats exposed to 8000 ppm (more likely 6100 ppm; see Section 3.1.1.) died, and narcosis occurred at both doses, (2) the Werner et al. (1944) mouse lethality studies in which three similar 7-hour LC_{50} values were provided, which were calculated without using all the data, the observation period was unclear (possibly 3 days), and individual test concentrations and effects were not stated, (3) the Chevron (1989) 2-week repeat exposure study in which one rat exposed to 2000 ppm for 2 days died, (4) the Gulf Oil Co. (1985b) 5-day repeat exposure study in which rats exposed to 2000 ppm 6 hours/day for 5 days had neurotoxicity but all survived to day 8, and

all rats exposed to 5000 ppm died on day 2, (5) the Bushy Run 1989 FOB study, in which 1200 ppm for 6 hours caused consistent motor disturbances, and (6) the NTP 2004 14-day study in which two 6-hour exposures to 2000 ppm caused 100% mortality and neurological effects, using a single 6-hour exposure.

7.3. Derivation of AEGL-3

AEGL-3 values were based on the same FOB study as the AEGL-2 values (Bushy Run 1989), and one 6-hour exposure to 1200 ppm was considered an estimate of the lethality threshold because (1) inhalation of 2000 ppm for 6 hours/day for 2 days caused severe CNS depression and 100% mortality in rats and mice (NTP 2004), and (2) up to 90 days of exposure to 1200 ppm for 6 hours/day, 5 days/week caused some toxicity but no lethality in several rat studies (Bushy Run 1989, 1991; Darmer 1997). Scaling to different exposure times was performed using $C^n \times t = k$ (ten Berge et al. 1986) and n=3 or n=1, as was done to derive AEGL-2 values. A total uncertainty factor of 3 was used: 1 for interspecies and 3 for intraspecies uncertainty. An interspecies UF of 1 was used because the animal data clearly showed that inhalation of 1200 ppm for 6 hours was not lethal for the most sensitive species; additionally, use of a UF of 3 would yield AEGL-3 values below AEGL-2 values, and would yield 4 and 8-hour AEGL-3 values that humans were willing to tolerate over an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans. The resulting AEGL-3 values are shown in Table 9 and calculations are detailed in Appendix A. The 10-minute and 30-minute AEGL-3 values exceed 10% of the LEL (lower explosive limit) of cumene, which is 0.9% or 9000 ppm.

TABLE 9. AEGL-3 Values for Cumene

10-minute	30-minute	1-hour	4-hour	8-hour
1300 ppm* (6400 mg/m^3)	920 ppm* (4500 mg/m^3)	730 ppm (3600 mg/m^3)	460 ppm (2300 mg/m^3)	300 ppm (1500 mg/m^3)

*These values exceed 10% of the LEL of 9000 ppm.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values were based on a brief chemical company report that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers (Dow 1948). A modifying factor of 2 was applied to 300 ppm to obtain a concentration that would cause effects within the scope of AEGL-1, i.e. 150 ppm. An uncertainty factor of 3 was applied for intraspecies variability, because the critical effect (mild eye and respiratory irritation) is not expected to vary greatly among humans. The resulting AEGL value (i.e., 50 ppm) was adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. The AEGL-1 is supported by human data (volunteers willingly tolerated exposure to 49-146 ppm cumene for an 8-hour period with two 30-minute breaks, but observations were not recorded; Senczuk and

Litewka 1976), and several rat studies (a single or multiple exposures for 6 hours to 100 ppm caused no toxic effects; Bushy Run 1989; Darmer et al. 1997).

AEGL-2 values were based on a neurotoxicity FOB study in which rats were exposed to 100, 500, or 1200 ppm cumene for 6 hours (Bushy Run 1989). No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused gait abnormalities and decreased rectal temperature. The AEGL-2 was based on exposure to 500 ppm, which caused mild reversible neurological changes and was a NOEL for ataxia and an impaired ability to escape. Data were not available to determine the cumene toxicity concentration-time relationship, which may be described by $C^n \times t = k$, so scaling across time was performed using n=3 or n=1 to extrapolate to exposure times <6 hours and >6 hours, respectively. An interspecies UF of 1 was used because the key study tested the most sensitive species (rat), and the critical endpoint was mild and not seen at similar exposure concentrations (~500 ppm) in several non-FOB rat studies from one 6-hour exposure. Additionally, a UF of 3 would yield all AEGL-2 values below 244 ppm, which had no effect on body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans.

AEGL-3 values were based on the same FOB study as the AEGL-2 values (Bushy Run 1989), where a 6-hour exposure to 1200 ppm was considered an estimate of the lethality threshold due to CNS depression. Scaling to different exposure times was performed using $C^n \times t = k$ (ten Berge et al. 1986) and n=3 or n=1, as was done to derive AEGL-2 values. A total uncertainty factor of 3 was used: 1 for interspecies and 3 for intraspecies uncertainty. An interspecies UF of 1 was used because the animal data clearly showed that inhalation of 1200 ppm for 6 hours was not lethal for the most sensitive species; additionally, use of a UF of 3 would yield AEGL-3 values below AEGL-2 values, and 4 and 8-hour AEGL-3 values that humans were willing to tolerate over an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976). An intraspecies UF of 3 was used because CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans. The resulting 10-minute and 30-minute AEGL-3 values exceed 10% of the LEL (lower explosive limit) of cumene, which is 0.9% or 9000 ppm. The AEGL values are summarized in Table 10.

TABLE 10. Summary of AEGL Values for Cumene

Classification	Exposure Duration				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)	50 ppm (250 mg/m^3)
AEGL-2 (Disabling)	550 ppm (2700 mg/m^3)	380 ppm (1900 mg/m^3)	300 ppm (1300 mg/m^3)	190 ppm (930 mg/m^3)	130 ppm (640 mg/m^3)
AEGL-3 (Lethal)	1300 ppm* (6400 mg/m^3)	920 ppm* (4500 mg/m^3)	730 ppm (3600 mg/m^3)	460 ppm (2300 mg/m^3)	300 ppm (1500 mg/m^3)

*These values exceed 10% of the LEL of 9000 ppm.

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for cumene are shown in Table 11. The NIOSH TWA-REL is intended to prevent symptoms including irritation of the eyes, skin, mucous membranes, dermatitis, headache, narcosis, and coma (NIOSH 2004). The ACGIH TLV-TWA is intended to prevent irritation and induction of narcosis (ACGIH 2003). The NIOSH IDLH was originally 8000 ppm, which is the concentration that caused 4/6 rats to die from a 4-hour exposure in the Smyth et al. (1951) study. This was revised to 900 ppm based on safety considerations, since 900 ppm is 10% of the lower explosive limit of 0.9%, although the IDLH document (NIOSH 2004) stated that 1500 ppm would have been appropriate based on the toxicity data.

German workplace guidelines list BAT values (biological tolerance values) of 2 mg cumene per liter blood, and 50 mg 2-phenyl-2-propanol (cumene metabolite) per g creatinine in the urine, when assayed in workers at the end of exposure or work shift (Deutsche Forschungsgemeinschaft 2002).

TABLE 11. Extant Standards and Guidelines for Cumene (ppm)

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	50	50	50	50	50
AEGL-2	550	380	300	190	130
AEGL-3	1300	920	730	460	300
PEL-TWA (OSHA)[a]					50 (skin)
REL-TWA (NIOSH)[b]					50 (skin)
IDLH (NIOSH)[c]		900			
TLV-TWA (ACGIH)[d]					50
MAK (German)[e]					50 (skin)
MAK Peak Limit (German)[f]	200 (15 min)				
MAC (Dutch)[g]					20 ppm
MAC – STEL (Dutch)[h]	50 (15 min)				
LLV (Swedish)[I]					25 ppm
STV (Swedish)[j]	35 (15 min)				

[a]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1989) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[b]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2004) is defined analogous to the ACGIH-TLV-TWA.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2004) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. Based strictly on safety considerations, since 900 ppm is 10% of the lower explosive limit of 0.9%.

[d]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

[f]**MAK Spitzenbegrenzung (Peak Limit Category II, excursion factor of 4])** (Deutsche Forschungsgemeinschaft [German Research Association] 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift, with at least 1 hour between exposures; total exposure may not exceed 8-hour MAK.

[g]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC– STEL (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration – Short-Term /Excursion Limits)** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH TLV-STEL (i.e., the maximum average concentration to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift, with at least 1 hour between exposures; total exposure may not exceed 8-hour MAC).

[i]**LLV (Level Limit Value)** Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 23rd March, 2000. Defined analogous to the ACGIH-TLV-TWA.

[j]**STV (Short-Term Value)** Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health, Adopted 23rd March, 2000. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 minutes.

8.3. Data Adequacy and Research Needs

The cumene database contained very few single-exposure studies within the scope of AEGL-1, AEGL-2, or AEGL-3, and no human studies useful for derivation of AEGL-2 or AEGL-3 values. Only one LC_{50} study was available, that of Werner et al. (1944). Additional studies with different exposure durations are also needed to determine empirically the value of n in the ten Berge equation, to allow extrapolation to alternate exposure durations.

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APPENDIX A: Derivation of AEGL Values for Cumene

Derivation of AEGL-1

Key Study: Dow 1948. A brief chemical company report that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers.

Toxicity endpoint: Mild eye and respiratory irritation at 150 ppm (apply MF=2 to 300 ppm).

Time scaling: None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time

Uncertainty factors: Total Uncertainty Factor: 3
Intraspecies: 3: the critical effect (mild eye and respiratory irritation) is not expected to vary greatly among humans.

Modifying factor: 2: Applied to 300 ppm to obtain a concentration (150 ppm) that would cause effects within the scope of AEGL-1, i.e. mild eye and respiratory irritation

Calculations:

10-minute AEGL-1	300 ppm / (3 x 2) = 50 ppm [250 mg/m^3]
30-minute AEGL-1	300 ppm / (3 x 2) = 50 ppm [250 mg/m^3]
1-hour AEGL-1	300 ppm / (3 x 2) = 50 ppm [250 mg/m^3]
4-hour AEGL-1	300 ppm / (3 x 2) = 50 ppm [250 mg/m^3]
8-hour AEGL-1	300 ppm / (3 x 2) = 50 ppm [250 mg/m^3]

Derivation of AEGL-2

Key Study: Bushy Run 1989. Rats were exposed to 100, 500, or 1200 ppm cumene for 6 hours in a neurotoxicity functional observational battery (FOB) study. No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused increased incidence or severity of gait abnormalities and decreased rectal temperature.

Toxicity endpoint: Mild reversible neurological changes and NOEL for ataxia and an impaired ability to escape at 500 ppm.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <6 hrs (key study exposure) and n=1 for >6 hrs to obtain protective AEGL values

Uncertainty factors: Total Uncertainty Factor: 3

Interspecies: 1: The key study tested the most sensitive species (rat), and the critical endpoint was mild and not seen at similar exposure concentrations (~500 ppm) in several non-FOB rat studies from one 6-hour exposure. Additionally, a UF of 3 would yield all AEGL-2 values below 244 ppm, which had no effect on body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970).

Intraspecies: 3: CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans

Modifying factor: None

Calculations for 10, 30, 60, and 240 min:

$$(500 \text{ ppm} / 3)^3 \times 6 \text{ hours} = k = 2.78 \times 10^7 \text{ ppm}^3\text{-hr}$$

$$C^3 \times 0.167 \text{ hr} = 2.78 \times 10^7 \text{ ppm}^3\text{-hrs}$$

$$\underline{\text{10-minute AEGL-2}} = C = 550 \text{ ppm } [2700 \text{ mg/m}^3]$$

$$C^3 \times 0.5 \text{ hr} = 2.78 \times 10^7 \text{ ppm}^3\text{-hrs}$$

$$\underline{\text{30-minute AEGL-2}} = C = 380 \text{ ppm } [1900 \text{ mg/m}^3]$$

$$C^3 \times 1 \text{ hr} = 2.78 \times 10^7 \text{ ppm}^3\text{-hrs}$$

$$\underline{\text{60-minute AEGL-2}} = C = 300 \text{ ppm } [1300 \text{ mg/m}^3]$$

$$C^3 \times 4 \text{ hr} = 2.78 \times 10^7 \text{ ppm-hrs}$$

$$\underline{\text{4-hour AEGL-2}} = C = 190 \text{ ppm } [930 \text{ mg/m}^3]$$

Calculation for 8 hrs: $(500 \text{ ppm} / 3)^1 \times 6 \text{ hours} = k = 1000 \text{ ppm-hr}$

$$C^1 \times 8 \text{ hr} = 1000 \text{ ppm-hrs}$$

$$\underline{\text{8-hour AEGL-2}} = C = 130 \text{ ppm } [640 \text{ mg/m}^3]$$

Derivation of AEGL-3

Key Study: Bushy Run 1989, as for AEGL-2. The AEGL-3 was based on one six-hour exposure to 1200 ppm, which was considered an estimate of the lethality threshold because (1) inhalation of 2000 ppm for 6 hours/day for 2 days caused severe CNS depression and 100% mortality in rats and mice (NTP 2004), and (2) up to 90 days of exposure to 1200 ppm for 6 hours/day, 5 days/week caused some toxicity but no lethality in several rat studies (Bushy Run 1989, 1991; Darmer 1997).

Toxicity endpoint: Threshold for lethality due to CNS depression

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <6 hrs (key study exposure) and n=1 for >6 hrs to obtain protective AEGL values

Uncertainty factors: Total Uncertainty Factor: 3

Interspecies: 1: The animal data clearly showed that inhalation of 1200 ppm for 6 hours was not lethal for the most sensitive species; additionally, use of a UF of 3 would yield AEGL-3 values below AEGL-2 values, and 4 and 8-hour AEGL-3 concentrations that humans were willing to tolerate over an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976).

Intraspecies: 3: CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans

Modifying factor: None

Calculations for 10, 30, 60, and 240 min:

$$(1200 \text{ ppm}/3)^3 \times 6 \text{ hours} = k = 3.84 \times 10^8 \text{ ppm}^3\text{-hrs}$$

$$C^3 \times 0.167 \text{ hr} = 3.84 \times 10^8 \text{ ppm}^3\text{-hrs}$$

10-minute AEGL-3 = C = 1300 ppm [6400 mg/m^3]

$$C^3 \times 0.5 \text{ hr} = 3.84 \times 10^8 \text{ ppm}^3\text{-hrs}$$

30-minute AEGL-3 = C = 920 ppm [4500 mg/m^3]

$$C^3 \times 1 \text{ hr} = 3.84 \times 10^8 \text{ ppm}^3\text{-hrs}$$

60-minute AEGL-3 = C = 730 ppm [3600 mg/m^3]

$$C^3 \times 4 \text{ hr} = 3.84 \times 10^8 \text{ ppm-hrs}$$

4-hour AEGL-3 = C = 460 ppm [2300 mg/m^3]

Calculation for 8 hrs: $(1200 \text{ ppm}/3)^1 \times 6 \text{ hours} = k = 2400 \text{ ppm-hrs}$

$$C^1 \times 8 \text{ hr} = 2400 \text{ ppm-hrs}$$

8-hour AEGL-3 = C = 300 ppm [1500 mg/m^3]

APPENDIX B: Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT_{50}, i.e., concentration at which 50% of the odor panel observed an odor without necessarily recognizing it) of 0.008 ppm was obtained for cumene from Hellman and Small (1974). The same citation listed an OT_{50} of 0.30 for n-butanol, as compared to the reference value of 0.04 ppm as the odor threshold provided by van Doorn et al (2002). Based on the differences in n-butanol values from the two sources, an "inter-laboratory" correction factor is applied to cumene as follows:

$\frac{0.04 \text{ ppm n-butanol}}{0.3 \text{ ppm n-butanol}}$ X 0.008 ppm OT_{50} cumene = **0.00107 ppm "corrected" OT_{50} cumene**

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$$I = k_w \times \log (C / OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C / 0.00107) + 0.5$, which can be rearranged to
$\log (C / 0.00107) = (3 - 0.5) / 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 0.00107 = 0.0071$ ppm
$C = 11.8 \times 0.00107 = 0.0126$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33

LOA = C x 1.33 = 0.0126 ppm x 1.33 = 0.017 ppm

The LOA for cumene is 0.017 ppm.

APPENDIX C: Derivation Summary for Cumene AEGLs

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
50 ppm	50 ppm	50 ppm	50 ppm	50 ppm

Key Study: Dow (Dow Chemical Company). 1948. Toxicology and hygiene - isopropylbenzene. July 6, 1948. Study authors were E.M. Adams and V.K. Rowe. Previously released to NTIS/OTS #0206685, but since withdrawn. Provided 9/2004 courtesy of S. Ripple, Dow Corporation.

Test Species/Strain/Number: Humans; number not specified

Exposure Route/Concentrations/Durations: Inhalation of 300-400 ppm for unspecified duration

Effects: Exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of most workers

Endpoint/Concentration/Rationale: Mild eye and respiratory irritation at 150 ppm; exposure duration not specified.

Uncertainty Factors/Rationale:
Uncertainty factors: Total Uncertainty Factor: 3
Intraspecies: 3: The critical effect (mild eye and respiratory irritation) is not expected to vary greatly among humans.

Modifying Factor: 2: Applied to 300 ppm to obtain a concentration (150 ppm) that would cause effects within the scope of AEGL-1, i.e. mild eye and respiratory irritation

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time

Data Adequacy: The database was small, but the derived values for 10 minutes to 8 hours are supported by human data (volunteers willingly tolerated exposure to 49-146 ppm cumene for an 8-hour period with two 30-minute breaks, but observations were not recorded; Senczuk and Litewka 1976), and several rat studies (a single or multiple exposures for 6 hours to 100 ppm caused no toxic effects; Bushy Run 1989; Darmer et al. 1997).

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
550 ppm	380 ppm	300 ppm	190 ppm	130 ppm

Key Reference: Bushy Run (Bushy Run Research Center). 1989. Cumene fourteen-week vapor inhalation study in rats with neurotoxicity evaluation (Part 1-2) with attached studies and cover letter dated 120789. BRRC Report no. 52- 628, study authors D.E. Dodd and W.J. Kintigh. EPA/OTS; Doc #40-8992172 . [Data was also presented in Cushman et al. 1995]

Test Species/Strain/Number: Fischer F344 rats (10/sex/dose)

Exposure Route/Concentrations/Durations: Inhalation of 0, 100, 500, or 1200 ppm for 6 hours

Effects: FOB was performed pre-exposure and 1, 6, and 24 hours post-exposure, after which the rats were sacrificed but not necropsied. No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused increased incidence or severity of gait abnormalities and decreased rectal temperature.

Endpoint/Concentration/Rationale: Mild reversible neurological changes and NOEL for ataxia and an impaired ability to escape at 500 ppm.

Uncertainty Factors/Rationale:
Uncertainty factors: Total Uncertainty Factor: 3
Interspecies: 1: The key study tested the most sensitive species (rat), and the critical endpoint was mild and not seen at similar exposure concentrations (~500 ppm) in several non-FOB rat studies from one 6-hour exposure. Additionally, a UF of 3 would yield all AEGL-2 values below 244 ppm, which had no effect on body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970).
Intraspecies: 3: CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not performed.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <6 hrs (key study exposure) and n=1 for >6 hrs to obtain protective AEGL values

Data Adequacy: The database was adequate and the derived AEGL values are supported by other rat and mouse studies in which one 6-hour exposure to ~500 ppm caused no observed neurotoxicity, whereas ≥1000 ppm caused ataxia (RTI 1989; NTP 2004 preliminary results). The AEGL-2 values and use of an interspecies UF of 1 are also supported by the Jenkins (1970) study, in which inhalation of 244 ppm 8 hours/day for 30 days did not affect body weight gain, hematology, or tissue pathology in monkeys, rats, dogs, or guinea pigs; use of a UF of 3 would bring the AEGL-2 values all below 244 ppm.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1300	920	730	460	300

Key Reference: Bushy Run (Bushy Run Research Center). 1989. Cumene fourteen-week vapor inhalation study in rats with neurotoxicity evaluation (Part 1-2) with attached studies and cover letter dated 120789. BRRC Report no. 52- 628, study authors D.E. Dodd and W.J. Kintigh. EPA/OTS; Doc #40-8992172 . [Data was also presented in Cushman et al. 1995]

Test Species/Strain/Number: Fischer F344 rats (10/sex/dose)

Exposure Route/Concentrations/Durations: Inhalation of 0, 100, 500, or 1200 ppm for 6 hours

Effects: FOB was performed pre-exposure and 1, 6, and 24 hours post-exposure, after which the rats were sacrificed but not necropsied. No toxicity was seen at 100 ppm, 500 ppm caused mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex), and 1200 ppm additionally caused increased incidence or severity of gait abnormalities and decreased rectal temperature.

Endpoint/Concentration/Rationale: 1200 ppm is threshold for lethality from CNS depression.

Uncertainty factors: Total Uncertainty Factor: 3
Interspecies: 1: The animal data clearly showed that inhalation of 1200 ppm for 6 hours was not lethal for the most sensitive species; additionally, use of a UF of 3 would yield AEGL-3 values below AEGL-2 values, and 4 and 8-hour AEGL-3 concentrations that humans were willing to tolerate over an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976).
Intraspecies: 3: CNS depression from a lipid-soluble narcotic is not expected to vary by more than a factor of 3 among humans

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not performed.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <6 hrs (key study exposure) and n=1 for >6 hrs to obtain protective AEGL values

Data Adequacy: The database was adequate and the derived values are supported by data from two species, by both single and multiple-exposure studies.

1

APPENDIX D: Category Plot for Cumene