

40 CFR Parts 792 and 793

(OPTS-42074; FRL-2885-4)

Cumene; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

**ACTION:** Proposed rule.

**SUMMARY:** EPA is proposing that manufacturers and processors of cumene (isopropyl benzene, CAS No. 98-82-8) be required, under section 4 of the Toxic Substances Control Act (TSCA), to perform testing for pharmacokinetics, subchronic toxicity, oncogenicity, mutagenicity, neurotoxicity, developmental toxicity and reproductive toxicity, if triggered, acute and chronic aquatic toxicity in saltwater and freshwater fish and invertebrates, and biodegradation and volatilization from water. This proposed rule is in response to the Interagency Testing Committee's (ITC's) designation of cumene for priority consideration for health and environmental effects testing.

**DATES:** Submit written comments on or before January 8, 1986. If persons request an opportunity to submit oral comments by December 23, 1985, EPA will hold a public meeting on this rule in Washington, D.C. For further information on arranging to speak at the meeting see Unit VIII of this preamble.

**ADDRESS:** Submit written comments, identified by the document control number (OPTS-42075), in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-108, 401 M St., SW., Washington, DC 20460.

A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

**FOR FURTHER INFORMATION CONTACT:** Edward A. Klein, Director, TSCA Assistance Office (TS-793), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460. Toll free: (800-424-9065). In Washington, DC: (554-1404). Outside the USA: (Operator-202-554-1404).

**SUPPLEMENTARY INFORMATION:** EPA is issuing a proposed test rule under section 4(a) of TSCA in response to the ITC's designation of cumene for health and environmental effects testing consideration.

**I. Introduction**

**A. ITC Recommendation**

Section 4(e) of TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.*) established the ITC to recommend to EPA a list of chemicals to be considered for testing under section 4(a) of the Act.

The ITC designated cumene (CAS No. 98-82-8) for priority consideration in its 15th report submitted to EPA on November 6, 1984. The report was published in the Federal Register of November 29, 1984 (49 FR 46939). The ITC recommended that cumene be considered for health effects testing for short-term genotoxicity, chronic toxicity including oncogenicity, teratogenicity, and reproductive effects; and environmental effects testing for acute and chronic toxicity to saltwater and freshwater fish and invertebrates. The bases for these recommendations were as follows: annual production capacity of 4 to 5 billion pounds, potential for occupational and environmental exposure, and insufficient data to assess the risk of cumene exposure to human health and the environment.

#### B. Test Rule Development Under TSCA

Under section 4(a) of TSCA, EPA shall by rule require testing of a chemical substance or mixture to develop appropriate test data if the Administrator finds that:

(A)(i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.

(ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture.

(ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight-of-evidence approach in making a section 4(a)(1) (A)(i) finding; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the finding under section 4(a)(1) (B)(i), EPA considers only production, exposure, and release information to determine

whether there is or may be substantial production and significant or substantial human exposure or substantial release to the environment. For the findings under sections 4(a)(1) (A)(ii) and (B)(ii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to, or environmental release of, the chemical. In making the finding under section 4(a)(1) (A)(iii) or (B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's process for determining when these findings apply is described in detail in EPA's first and second proposed test rules as published in the Federal Register of July 18, 1980 (45 FR 48524) and June 5, 1981 (46 FR 30300). The section 4(a)(1) (A) findings are discussed at 45 FR 48524 and 46 FR 30300, and the section 4(a)(1) (B) findings are discussed at 46 FR 30300.

In evaluating the ITC's testing recommendations concerning cumene, EPA considered all available relevant information including the following: information presented in the ITC's report recommending testing consideration and any public comments on the ITC's recommendation; production volume, use, exposure, and release information reported by manufacturers of cumene under the TSCA section 6(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 6(d) Health and Safety Data Reporting Rule (40 CFR Part 716) concerning cumene; and published and unpublished data available to the Agency. Based on its evaluation, as described in this proposed rule, EPA is proposing health and environmental effects testing requirements for cumene under sections

4(a)(1) (A) and (B). By these actions, EPA is responding to the ITC's designation of cumene for priority testing consideration.

## II. Review of Available Data

### A. Profile

Cumene is a colorless liquid with a sharp, penetrating odor; the air odor threshold is 0.88 ppm (Ref. 1). At 20 °C cumene has a water solubility of 50 mg/l (Ref. 2), a vapor pressure of 3.2 mm Hg (Ref. 3), and a density of 0.86 g/cm<sup>3</sup> (Ref. 4). The log octanol/water partition coefficient ( $K_{ow}$ ) is reported as 3.51 (Ref. 2) and 3.66 (Ref. 5). A log soil/sorption coefficient ( $K_{oc}$ ) of 3.45 was estimated by EPA, and a bioconcentration factor (BCF) of 340 was estimated from the log  $K_{ow}$  (Ref. 80).

### B. Production

Cumene is commercially produced by alkylating benzene under elevated temperature and pressure with propylene by a Friedel-Crafts reaction using a solid phosphoric acid catalyst (Ref. 4). Cumene is separated from the propylene and benzene reactants by distillation. Cumene is also present in crude oil and may be found as a minor component of finished petroleum products.

Cumene is produced domestically by 10 corporations with a combined annual production capacity of 4 to 5 billion pounds (Refs. 7 and 8). An additional 900 million pounds per year capacity on reserve. Approximately 339 million pounds were imported during 1984 (Ref. 7). The demand for cumene was 3.3 billion pounds and 3.4 billion pounds for 1983 and 1984, respectively. This level is expected to increase to 4.7 billion pounds in 1988 with an average growth rate of 4 percent per year through 1988 (Ref. 7).

Cumene domestic producers, production sites and capacities, and use are summarized in Table 1.

TABLE 1.—U.S. CUMENE PRODUCTION CAPACITY

Producer	Location	Capacity <sup>1</sup>	Use
Amoco Chemical Corp.	Texas City, TX	30	Alphamethylstyrene.
Apex Oil Co. <sup>2</sup>	Blue Island, IL	120	Phenol <sup>3</sup> .
Ashland Oil, Inc.	Cadetsbury, KY	400	Sold.
Chevron Corp. <sup>4</sup>	Philadelphia, PA	450	Do.
	Port Arthur, TX	450	Do.
Georgia-Gulf Corp.	Passadena, TX	800	Phenol.
Koch Industries, Inc.	Corpus Christi, TX	400	Sold.
Shell Oil Co.	Deer Park, TX	700	Phenol.
Tessco, Inc.	Westville, NJ <sup>5</sup>	150	Do.
	El Dorado, KS	135	Do.
Union Pacific Co. <sup>6</sup>	Corpus Christi, TX	400	Sold.

<sup>1</sup> Millions of pounds per year for 1984.

<sup>2</sup> Subsidiary of Clark Chemical Co.

<sup>3</sup> Acetone also produced.

<sup>4</sup> Subsidiary of Gulf Oil Corp.

<sup>5</sup> Under accusation by Coastal Refining & Marketing, Inc. (Ref. 81)

<sup>6</sup> Subsidiary of Champlin Petroleum Co.

### C. Use

More than 98 percent of the cumene produced in the United States is used to manufacture phenol by the cumene hydroperoxidation process (Refs. 7 and 8). Acetone is also produced by this process. Cumene is first oxidized to cumene hydroperoxide and then subjected to acid cleavage yielding a crude reaction mixture of phenol and acetone. Neutralization and distillation of the mixture removes impurities such as acetophenone, cumyl phenols, dimethyl-phenylcarbinol, and alpha-methylstyrene.

Cumene is also used to manufacture alpha-methylstyrene and as a chain inhibitor in the polymer industry (Ref. 7). It has been used to produce sulfonated cumene and used in the manufacture of liquid detergents and surfactants. Cumene has also been used as a high-octane aviation fuel additive (Ref. 4). Additionally, cumene is used as a solvent in perfumes and pharmaceuticals (Ref. 7).

### D. Exposure and Release

From the occupational data reported by industry, it appears that cumene production plant, maintenance, marine dock, and shipboard workers are exposed to cumene. The National Occupational Hazard Survey (NOHS) estimated that 863 workers were exposed to cumene in the workplace during 1972-1973 (Ref. 9). Cumene levels measured in the breathing zone of workers at the manufacturing sites are reported to be less than 20 ppm. Air samples taken at two refineries showed a time-weighted average (TWA) ranging from below the detection limit (limit not specified) to 2.4 ppm cumene with a mean TWA of <0.1 ppm. On oil tankers cumene levels as high as 30 ppm were detected (Ref. 10) Koch Refining Co. (Ref. 11) reported that samples from an unspecified area of the production plant showed no more than 0.5 ppm cumene in the air. Twenty workers in a Texaco refinery were reportedly exposed to 3 ppm cumene or less (Ref. 12). The American Petroleum Institute (API) (Ref. 13) reported that gasoline truck drivers were exposed during a 12-hour period to less than 0.1 ppm TWA cumene. Air samples taken in manufacturing and market distribution points (marine docks) involving cumene had an average TWA of 0.65 ppm with a maximum of 78 ppm (Ref. 18).

Approximately one half of the cumene manufacturing plants are located in a 2 major metropolitan areas increasing the potential human exposure to 15 to 18 million people. Estimated cumene concentrations in the ambient air from

these areas within a 1 and 5 km radius range between 17 and 289  $\mu\text{g}/\text{m}^3$  and 2.9 and 15.2  $\mu\text{g}/\text{m}^3$ , respectively, for a worst case model (Ref. 18).

Synthetic organic chemical plants (SOCP) which produce cumene release about 1.1 million pounds per year in fugitive emissions as estimated from leaks in fittings for valves, flanges, and pumps (Ref. 18).

Cumene may also be released during the production of phenol and acetone by the cumene hydroperoxidation process. For every kilogram of phenol produced, approximately 1 gram of cumene is released to the atmosphere (Ref. 18). A reported 2.05 billion pounds of phenol were produced from cumene in the United States in 1983 (Ref. 17). Therefore, it was estimated that 2 million pounds of cumene were released into the air in 1983 from the production of phenol (Ref. 18).

As a natural component of crude oil and the resultant petroleum products, cumene can be detected in the exhausts of automobile, jet engines, and outboard motors (Refs. 19 through 21). Land transportation vehicles alone were estimated to contribute 15 million pounds of cumene to the atmosphere in 1983 (Ref. 18).

Evidence suggests widespread release of cumene to aquatic environments. Cumene was detected in 204 of 4,000 samples of wastewater taken from a variety of industrial processes throughout the United States. Levels as high as 17.9 ppm were found in wastewaters from organic and plastics industries. Other industries whose wastewaters contained cumene include timber products, fruit and vegetable processing plants, paving and roofing, pesticides and pharmaceuticals, manufacturing, shipbuilding. It has also been found in the effluents from publicly owned treatment works (Ref. 22).

Several monitoring studies have shown cumene contamination of groundwater and other drinking water supplies (Refs. 23 through 30). Cumene was detected in groundwater supplies in the State of New York at a level of 290 ppb (Ref. 23). Cumene was also detected in Wyoming groundwater samples collected in wells near a coal gasification site 15 months after the completion of gasification. Cumene levels ranged from 19 to 59 ppb in the 3 wells which were sampled (Ref. 26). The presence of cumene in the well samples could also be attributed to shale oil deposits in the area.

Keith et al., Coleman et al., and Kingsley et al. (Refs. 28 through 30) reported the presence of cumene in finished drinking water samples.

Cumene levels of 0.01 ppb were measured in drinking water from Terrebonne Parish, LA (Ref. 28). The drinking water for Cincinnati, OH was reported to contain 0.01 to 0.5 ppb (Refs. 29 and 30). Terrebonne Parish receives its drinking water from sources generally contaminated by municipal waste; Cincinnati water is contaminated predominantly by industrial waste. Both of these areas acquire their water supplies from rivers. This would suggest cumene contamination of surface water. Surface water monitoring data in the United States were not found in the literature searched.

### E. Health Effects

#### 1. Absorption and distribution.

Senczuk and Litewka (Ref. 31) exposed 10 human volunteers (5 men and 5 women between 20 and 35 yrs old) to atmospheres of 240, 480 and 720  $\text{mg}/\text{m}^3$  (50, 100, and 150 ppm) cumene for 8-hour sessions. Each volunteer was exposed to one of the three concentrations every 10 days. The average retention of cumene vapors in the respiratory tract was about 50 percent. The total dose of cumene absorbed by the lungs during an 8-hour exposure to 240, 480, or 720  $\text{mg}/\text{m}^3$  was 270, 528, or 788 mg, respectively, in women and 466, 934, or 1,400 mg, respectively, in men. The difference in absorption between the sexes was not explained.

Evidence of dermal absorption of cumene is provided in a study by Valette and Cavier Cavier (Ref. 32). Cumene (0.2 ml) was applied to a shaved area of rat epidermis. The rate of absorption was assessed by measuring the sciatic nerve response to electrical stimulation. Significant differences in nerve conduction were noted 20 minutes after cumene administration. Toxicity studies which administer cumene orally suggest that absorption of cumene in the gastrointestinal tract occurs but the level of absorption has not been quantified (Refs. 33 and 34).

Following absorption cumene generally tends to localize in tissues with a high-lipid content (Ref. 35). In two rats exposed to 500 ppm cumene vapor 8 hrs/day for 10 days, the highest levels of cumene were found in the spleen, bone marrow, and liver. Lesser amounts were detected in the brain, cerebellum (presumed to be analyzed separately from the brain), kidneys, and blood (Ref. 36).

#### 2. Metabolism and elimination.

In humans exposed to cumene vapors (240, 480 and 720  $\text{mg}/\text{m}^3$ ) for 8-hour sessions, the urinary excretion rate of the metabolite, 2-phenyl-2-propanol, rapidly increased during the exposure period.

Following cessation of exposure, the rate of the metabolite excretion approached zero. The total amount of excreted 2-phenyl-2-propanol was found to be directly proportional to the exposure concentration and the amount of absorbed cumene. No other metabolites were identified (Ref. 31).

Smith et al. (Ref. 37) observed at least 3 metabolites in the urine of rabbits administered an oral dose of 450 mg cumene/kg body weight. Robinson et al. (Ref. 33) further characterized these urinary metabolites as 40 percent 2-phenyl-2-propanol, 25 percent 2-phenyl-1-propanol, and 25 percent 2-phenylpropanoic acid. Each metabolite was excreted on the glucuronide conjugate. Rats given an oral dose of 100 mg cumene/kg body weight excreted conjugates of 2-phenyl-1-propanol. The glucuronide of 2-phenyl-2-propanol was detected in only 1 of 6 animals; no other phenolic compounds were detected (Ref. 34).

Cumene, administered intraperitoneally to rats, increased the urinary excretion of thio (SH) compounds. A mean value of 73 mmol SH per mol creatinine was measured in the urine of rats following a 1 mmol cumene/kg body weight dose. Three percent of the dose was excreted as mercapturic acid. Values for other aralkyl compounds tested ranged from 6 to 312 mmol SH per mol creatinine. These results indicated to the investigators that the positioning of the methyl groups would affect the metabolism of the aromatic hydrocarbon (Ref. 38).

The Agency has determined that the pharmacokinetic testing reported herein does not adequately assess the pharmacokinetic behavior of cumene following oral or inhalation exposures. The reported studies do not contain sufficient information concerning study design, analytical methods, or use of a radiolabel for determining cumene distribution or metabolites.

3. *Acute toxicity.* Gerarde (Ref. 35) reported that 6 of 10 rats died following an oral dose of 4.3 g cumene/kg body weight. The principal cause of death was hemorrhage of the lungs accompanied by adrenal, thymus, and bladder hemorrhaging. Other effects included enlarged, fatty livers; enlarged and congested spleens; hyperemia in the brain, spinal cord, stomach and intestines; and leukocytosis. Oral LD<sub>50</sub>s of 2.7 g and 1.4 g/kg cumene in rats also have been reported (Refs. 39 and 40). Signs of intoxication included weakness, ocular discharge, collapse and death.

A 4-hour exposure to 8,000 ppm cumene resulted in the death of 4 of 6 rats (Ref. 41). In a separate study, an

LD<sub>50</sub> of 800 ppm cumene was observed in rats exposed for 16 hrs. Symptoms which preceded death were nervousness, intoxication, incoordination, and somnolence (Ref. 39). No histopathology was reported for these experiments. In mice exposed to atmospheres of 1,200 to 1,400 ppm cumene for 7 hours, an LD<sub>50</sub> of 2,000 ppm was determined (Ref. 42). Dermal LC<sub>50</sub>s of 3,150 mg/kg and 10,000 mg/kg have been reported in rabbits (Refs. 39 and 41). These data are sufficient to assess the acute toxicity of cumene following oral, dermal, and inhalation exposure.

Non-lethal acute effects resulting from cumene exposure include narcosis in mice exposed to 4,000 or 5,000 ppm cumene vapor for 2 hours and bradypnea in mice exposed to 1,210 ppm cumene for 30 minutes (Refs. 43 and 44). Concentrations of 2,490 ppm adversely affected the respiration rate of 50 percent of an unspecified number of mice exposed for 30 minutes (Ref. 44).

4. *Subchronic toxicity.* Fabre et al. (Ref. 36) exposed rabbits (number not specified) to atmospheres of 6.5 mg cumene/l for 130 to 180 days. The animals showed no abnormal behavior patterns. Weight gain was also normal. No other information was provided.

In a subsequent study, an undetermined number of rats were exposed to 6.5, 4.0, or 2.5 mg cumene/l air. Three of the rats in the 6.5 mg/l group exhibited "some nervousness" along with intoxication, impaired locomotion, incoordination, and somnolence following exposure for a few hours. After 6 to 16 hours all the exposed animals died. Animals exposed to atmospheres of 4 mg/l for up to 16 hours also died. Thirty-six animals in the 2.5 mg/l group showed no "external signs of poisoning." Following an initial weight loss, animals in the 2.5 mg/l group gained weight regularly throughout the 180-day exposure period.

Histopathological examination of animals revealed no significant lesions in brain, cerebellum (presumed to be analyzed separately from the rest of the brain), liver heart, stomach, intestine, bone marrow, spleen, kidney, or reproductive organs. Passive congestion was seen in the lung, liver, spleen, kidney, and adenals (Ref. 36).

This study (Ref. 36) was considered inadequate with regard to characterizing the health effects of cumene exposure because of poor study design and statistics. While the report stated that 36 animals were exposed to 2.5 mg/l, no sample size was given for the higher concentrations. The animals used for histopathological analysis were selected according to different conditions of "poisoning." The number of animals

examined per concentration level was not stated, nor was the species (rat, rabbit, or both) examined specifically. There was no mention of the use of control animals in the study.

Another subchronic study was also considered inadequate owing to lack of information in the report. Jenkins et al. (Ref. 45) exposed rats and guinea pigs (15/species/concentration), dogs (2/concentration), and monkeys (3/concentration) to atmospheres of 1,195 mg/m<sup>3</sup> cumene vapor 8 hours/day, 5 days/week for 30 exposures; or 148 mg/m<sup>3</sup> or 18 mg/m<sup>3</sup> cumene vapor continuously for 90 or 130 days. A similar or greater number of animals of each species served as controls. Sex of the animals was not given. Results showed normal weight gain throughout the exposure period. Necropsy and histopathological examinations of the brain and spinal cord from the monkeys and dogs were conducted. Heart, lung, liver, spleen, and kidney were taken from all species. Hematological analyses of the rats, guinea pigs and dogs were also performed. Results from all of these analyses were considered "essentially negative." No mention of statistical analysis was made. No other information was given in the report.

Wolf et al. (Ref. 40) investigated the subchronic effects of cumene administered orally. Cumene in olive oil was administered by stomach tube to rats (10 females/dose) at doses of 462, or 769 mg/kg/day for a total of 3 doses over a 194-day period. A group of 20 rats served as controls and were fed doses of 2.5 ml olive oil on the same schedule as the treated group. Appearance, behavior, food consumption, and weight were monitored throughout the study. Hematological parameters were measured in "selected" animals in each dose group after 20, 40, 80, and 130 doses. Moribund animals and those animals surviving all 139 doses were sacrificed and examined for gross or histopathological effects. Results showed no treatment-related effects with the exception of increased kidney weight in the 462 and 769 mg/kg/day dose groups. Because there are flaws in the experimental design of this study, it cannot be considered adequate in determining the subchronic toxicity of cumene. The report lists only 2 organs as being examined, the liver and kidney. No other tissues or organs were discussed. The study also fails to explain how the animals were "selected" for hematology. In addition, only females were used in the study thus excluding the investigation of differential toxicity between the sexes.

5. *Chronic toxicity.* Pertinent data on the chronic toxicity of cumene were not found in the literature searched or submitted under the TSCA section 8(d) reporting requirement for this chemical.

6. *Mutagenicity.* Cumene has been tested for mutagenicity in the bacterium *Salmonella typhimurium* with and without metabolic activation. Most of these studies were found to be negative in tester strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 (Refs. 39, 46, and 47). Monsanto (Ref. 39) initially found a significantly higher number of revertants in test strains TA 100 and TA 1535, which were cultured with 0.17 µg cumene/plate. Upon retesting, the mutagenicity of cumene was considered negative.

A positive result for cumene mutagenesis in a spout test with *Salmonella* tester strain TA 100 was reported (Ref. 48). No further details regarding experimental design or results were provided in the conference proceedings of the 1975 Environmental Impact of Water Chlorination, where the study was reported.

Gulf Oil Products (Ref. 49) reported in a TSCA section 8(e) submission that cumene tested positive in a cell transformation study using mouse embryo BALB/3T3 cells. BALB/3T3 cells are reported to have a low incidence of spontaneous transformation and a high incidence of contact inhibition (Ref. 50). Cumene concentrations of 5, 20, 60, and 90 µg/ml were tested. Cumene was emulsified in a F68 polyol vehicle. Cells were incubated in cumene media (17 plates/dose) for 2 days and then transferred to fresh media for an additional 8-day incubation period. Two of the 17 plates per dose were then fixed and stained. The remaining cultures were allowed to incubate until day 29 of the study. These cultures were then fixed and stained for counting transformed foci. At a concentration of 60 µg/ml, cumene exhibited some cytotoxicity with only a 22-percent rate of colony formation. The test for transformation was considered positive if the increase in a population of highly polar, fibroblastic, criss-crossed array of cells exposed to the highest level of cumene was twice (2x) that of the control value or if the ratio of these cell types between 2 consecutive levels was greater than or equal to 2. Under these criteria cumene tested positive for transformation, showing more than a 2x increase over controls at 60 µg/ml. No colonies formed at the 90-µg/ml exposure level. Positive (1 µg/ml of 3-methylcholanthrene) and negative (media and 0.04 percent F68) control results indicated proper functioning of

the assay system. This study is considered adequate and suggests that cumene may produce oncogenic effects.

Another TSCA section 8(e) submission from Gulf Oil Products (Ref. 51) reported a position response for cumene in an unscheduled DNA synthesis (UDS) assay with rat hepatocytes. This test measures excision repair of DNA after damage by chemical or physical agents (Ref. 52). Primary hepatocytes were isolated from the liver of a rat. Cells were incubated in cumene concentrations of 8, 16, 32, 69, or 128 µg/ml with 3 cultures per concentration. Cumene was emulsified in a F68 polyol vehicle. Positive (0.05 µg/ml of 2-acetylaminofluorene) and negative (vehicle and media) controls were used for comparison. Using autoradiography UDS was determined by counting grains overlying nuclei and subtracting the background counts. Two criteria were considered in the evaluation of test results. A test was considered positive for UDS if the mean net nuclear grain count at any exposure level exceeded the media control by 6 grains (Ref. 53), or if the percentage of cells in repair at any exposure level was significantly ( $p < 0.01$ ) greater than the negative control. The first criterion did not indicate a positive finding for this study. The second criterion, however, did show a positive result. Cells cultured in 16 µg/ml cumene showed a significant increase in repair (28.7 percent) as compared to control cultures. Forty percent of the cells exposed to 32 µg/ml cumene were found to be in repair, thus this test was reported to be positive for cumene.

7. *Oncogenicity.* Pertinent data regarding the oncogenicity of cumene were not found in the literature searched or submitted under the TSCA section 8(d) reporting requirement for this chemical. As a result of the positive findings in the cell transformation and UDS assays, the Agency has determined a need for oncogenicity testing.

8. *Developmental and reproductive toxicity.* It was reported in a Russian abstract (Ref. 54) that a 4-month inhalation exposure to cumene at an unspecified maximum permissible concentration increased fetal mortality in pregnant rats from 7.5 to 39.3 percent. An increase in the frequency of developmental abnormalities from 3 to 11 percent was also reported. The type of developmental effects was not specified, and no further details, such as whether the developmental abnormalities were accompanied by maternal toxicity were given. As a result of the lack of information in this study, it is not considered adequate to assess the

potential toxicity of cumene to developmental and reproductive processes.

No other information on the developmental or reproductive toxicity of cumene was found in the literature searched or submitted under the TSCA section 8(d) reporting requirement for this chemical.

With the exception of the acute inhalation studies, data from the reported health effects studies do not adequately determine or predict the toxicity of cumene to human health.

#### F. Environmental Effects

1. *Microorganism.* Erben (Ref. 55) investigated the effects of cumene on the survival of a rotatoria, *Dicranophorus forcipatus*, under a closed laboratory rearing system. The organisms were exposed to cumene concentrations (v/v) of 0.02, 0.2, and 2.0 percent. Test populations were housed under dark conditions, without running water or aeration. The greatest level of mortality was observed during the first 48 hours of the study. Complete mortality was not obtained after 144 hours of exposure. It is not possible to quantify the toxic response to cumene based on the data provided. The results are questionable, as the data are based upon test solutions of cumene that are 1 to 3 orders of magnitude greater than the 50 mg/l solubility of cumene in water.

The effects of cumene on the photosynthetic rate of two algal species *Chlorella vulgaris* and *Chlamydomonas angulosa* have been studied (Ref. 2). The algal cultures were incubated in glass-stoppered flasks at 19 °C for 3 hours. Cumene concentrations of 1, 12.5, 25, 37.5, and 50 ppm were tested. The extrapolated median effective concentrations (EC<sub>50</sub>) for *C. vulgaris* and *C. angulosa* were 8.78 and 21.24 ppm, respectively.

The toxicity of cumene to two species of protozoans was investigated in open and closed systems (Ref. 56). In the open test system, an inoculum of approximately 20 cells of *Colpidium colpoda* was exposed to solutions of 2.5, 5, 10, 15, increasing at increments of 5 up to 45 ppm cumene in a cerophyl medium for 18 hours. A median lethal concentration (LC<sub>50</sub>) of 0.012 ppm was reported; however, this result was negated by a bacterial contamination in the culture.

In a closed system, where the organisms survived solely on dissolved oxygen, a morphologically similar protozoan to *C. colpoda*, *Tetrahymena ellioti*, was used as the test organism (Ref. 56). Test concentrations and incubation conditions were not reported.

Using cessation of ciliary movement as the criterion for cell death, a 24-hour  $LC_{50}$  was reported as 3.01 ppm cumene in a cerophyl medium. The organisms were reported to survive at lower concentrations; complete mortality reportedly occurred at levels higher than 3 ppm.

2. *Plants.* Data on the toxicity of cumene to plants were not found in the literature searched.

3. *Birds.* An 18-hour median lethal dose ( $LD_{50}$ ) of 98 mg cumene/kg was determined in wild-trapped red-wing black birds. A cumene/propylene glycol solution was administered by gavage to the red-wing black birds preconditioned to captivity for 2 to 8 weeks (Ref. 57).

4. *Freshwater fish and invertebrates.* Juhnke and Luedemann (Ref. 58) compared  $LC_{50}$  values for cumene determined in the golden orfe in two independent laboratories. Juhnke reported an  $LC_{50}$  of 47 mg/l for cumene; Luedemann reported a value of 207 mg/l which substantially exceeds the water solubility of cumene. The tests were reportedly conducted under comparable conditions. Length of exposure was not indicated. An  $LC_{50}$  of 20 to 30 mg/l has been reported for the fathead minnow. No other details of the study were provided (Ref. 59).

The acute toxicity of cumene to *Daphnia magna* has also been determined in closed and open systems (Refs. 60 and 61). In the closed system, 10 animals per vial were exposed to various concentrations of cumene for 48 hours. Death was defined as immobility. The 48-hour  $LC_{50}$  for cumene was determined to be 0.6 ppm. Adverse effects, which were not described, were reported to be evident in animals exposed to sublethal concentrations (Ref. 60). The specific range of cumene concentrations tested was not provided. The vials had no air spaces and were not aerated. The temperature was maintained at 23 °C. The pH, however, was not held constant and dropped from 7 to 5 units. The animals were not fed during the 48-hour exposure period.

Bringmann and Kuehn (Ref. 61) established a 24-hour  $EC_{50}$  of 91 ppm cumene in *D. magna*. Animals were exposed using an open test system. The  $EC_{50}$  was extrapolated graphically or established as the geometric mean of the  $EC_0$  and  $EC_{100}$ . The tests were run with ten 24-hour-old animals per concentration; the pH was maintained at  $8.0 \pm 0.2$ . It is unclear whether the reported  $EC_{50}$  cumene level represents an initial, final or average concentration. However, it is roughly twice the reported water solubility of cumene (Ref. 2). No mention is made of analytically determining the cumene

concentration during the study period. Therefore, this study does not adequately assess cumene toxicity to freshwater invertebrates.

5. *Marine vertebrates and invertebrates.* No information on the toxicity of cumene to marine vertebrates was found in the literature searched.

Le Roux (Ref. 62) investigated the effect of cumene on the growth rate of mussel larvae (*Mytilus edulis*). The larvae were exposed to cumene concentrations of 0, 1, 10, and 50 ppm in seawater. No consistent statistical relationship between change in growth rate and cumene concentration could be established. It was reported that the growth rate of cumene-exposed larvae was generally greater than that of control larvae.

In a brine shrimp bioassay, shrimp eggs were placed in a hatching apparatus 48 hours prior to toxicity testing. Upon hatching, a suspension of 30 to 50 shrimp/ml was introduced into bottles containing cumene concentrations of 1 to 10,000 mg/l. After 24 hours the number of live and dead shrimp was compared. The 24-hour tolerance limit for brine shrimp to cumene was extrapolated graphically from the screening data to equal 110 mg/l (Ref. 63). The solubility of cumene in synthetic saltwater was measured in this study to be 500 mg/l. A more realistic solubility of cumene in seawater is 42.5 mg/l (Ref. 18).

As a result of the varying data and flawed study designs, these environmental effects studies were not considered adequate for assessing the acute toxicity of cumene to aquatic organisms.

No information on the chronic toxicity of cumene to aquatic organisms was found in the literature searched or submitted under the TSCA section 8(d) reporting requirement for this chemical.

#### G. Chemical Fate

Cumene enters the environment as a vapor or in wastewaters. In air, the dominant degradation pathway for cumene is expected to be hydroxyl radical attack; nitrate radical reaction may also occur, especially at night. Transport mechanisms of cumene out of air may include precipitation scavenging and dry deposition. In water, biodegradation appears to be the dominant degradation mechanism. Oxidation and photolysis appear to be unimportant. The dominant transport mechanism from water is volatilization (Ref. 64). In soil, the major degradation mechanism also appears to be biodegradation, with volatilization and leaching the major transport mechanisms from soil to air and water.

Assuming uniform initial environmental distribution the subsequent partitioning of cumene in the environment is estimated to be 50 percent in air, 40.2 percent in water and 0.1 percent in soil. The deposition of cumene from air to water was estimated to be 0.09 parts per trillion. Cumene will react with hydroxyl (HO) and nitrate ( $NO_3$ ) radicals during the daytime and nighttime, respectively. Using a HO radical concentration of  $1 \times 10^6$  molecules  $cm^{-3}$  (polluted atmospheres) and  $0.5 \times 10^6$  molecules  $cm^{-3}$  (unpolluted atmospheres) and the Revishankara et al. (Ref. 6) rate constant ( $7.79 \pm 0.4 \times 10^{-12}$   $cm^3$  molec $^{-1}$  s $^{-1}$ ), the half-life of cumene in the troposphere was estimated to be 25 hours in a polluted atmosphere and 49 hours in an unpolluted atmosphere (Ref. 18).

Biodegradation and volatilization are the major removal processes from water. The cumene volatilization half-life in water was estimated to be 5 to 14 days depending on the type of ecosystem, (i.e. pond, lake, river), and various aquatic parameters (Ref. 18). Actual monitoring data of cumene's volatilization rate in water were not found in the literature searched.

Cumene degradation has been studied in groundwater and seawater. Although cumene degradation occurs in groundwater, the process may be hindered by insufficient nitrogen in the groundwater, thus limiting the growth of microbes which could degrade cumene. A typical groundwater supply may also contain a lower dissolved oxygen concentration which will, therefore, inhibit cumene biodegradation (Ref. 65).

Marine environments, which contain low concentrations of available nitrogen, may also hinder cumene biodegradation. Cumene degradation in synthetic seawater containing ammonium nitrate was slightly higher than that measured in ordinary seawater (Ref. 66). Price et al. (Ref. 63) also studied the biodegradation of cumene in seawater. They failed to detect any significant oxygen uptake. It should be noted, however, that the reported solubility of cumene in the synthetic seawater the investigators used was 500 mg/l, which differs from a previously reported value of 42 mg/l (Ref. 18). Whether this difference would affect the biodegradation rate is unclear.

A variety of microorganisms found in soil, freshwater, and marine environments are capable of degrading cumene. These include *Pseudomonas*, *Nocardia*, *Cladosporium*, *Penicillium*, *Aspergillus*, *Candida*, *Sporobolomyces*.

*Aureobasidium*, and *Coryneform* species (Ref. 18).

Degradation pathways were studied by Gibson (Ref. 69) and Jigami et al. (Refs. 70 and 71). Cumene was converted into an orthodihydroxy compound without alteration of the isopropyl side chain. Degradation then proceeded to (+)-2-hydroxy-7-methyl-6-oxo-octanoic acid. Thus it appears that the benzene ring is attacked before the isopropyl side chain is altered.

Marion and Malaney (Ref. 67) showed that activated sludge from 3 different communities was able to biodegrade 50 mg/l cumene as evidenced by oxygen uptake. In another study, activated sludge, which had previously been acclimated to 250 mg/l benzene as the sole carbon and energy source, was used to degrade cumene. The oxygen demand due to cumene biodegradation was 37.8 percent of the theoretical after 192 hours of incubation (Ref. 68). Activated sludge, acclimated to 500 mg/l aniline as the carbon and energy source, was able to degrade cumene after 30 hours (Ref. 69).

Price et al. (Ref. 63) discovered that 62 percent of the theoretical oxygen demand due to cumene biodegradation occurred by 10 days with unacclimated, settled, domestic wastewater as the inoculum. By 20 days only an additional 8 percent had been used.

The chemical reactions of cumene in water are slow compared to microbial biodegradation. The two most important chemical processes in water are oxidation by alkylperoxy ( $RO_2$ ) and HO radicals (Refs. 72 and 73). The rate constants for the reaction of  $RO_2$  radical and HO radical in pure water systems were determined experimentally to be  $10 M^{-1} s^{-1}$  and  $3 \times 10^9 M^{-1} s^{-1}$ , respectively. These rate constants and the type of products produced from each reaction were used to determine steady-state concentrations for the  $RO_2$  radical and HO radical of  $10^{-9}$  and  $10^{-17}$ , respectively. From these concentrations, the half-life for cumene in water was estimated as 2.2 years from  $RO_2$  radical oxidation, and 0.7 year from HO radical oxidation (Refs. 72, 74, and 75). Because biodegradation probably occurs in less than 1 month, oxidation is not expected to be an important process in water.

The estimated ( $K_{oc}$ ) is 2,800 (Refs. 18 and 64). Generally,  $K_{oc}$  values greater than 1,000 indicate that the compound will be tightly bound to the soil particles (Ref. 76); however, it was shown that microorganisms found in sediment (estuarine) could rapidly degrade cumene (Ref. 77). Therefore, a portion of the cumene adsorbed onto the soil is expected to biodegrade. Nonetheless, since cumene has been detected in

groundwater, this would indicate that detectable concentrations can leach to the groundwater.

EPA's review of the information on the chemical fate of cumene in air and soil indicates that the available data are adequate to characterize the fate of cumene in these media. The data on cumene's fate in water, however, are not sufficient. Data on the biodegradation of cumene in water suggest that biodegradation will occur, but are not adequate to quantitatively determine biodegradation rates in natural waters. In addition, there are no data on the actual volatilization rate of cumene from water. Quantitative estimates or, alternatively, actual monitoring of environmental (aquatic) concentrations, are needed in order to assess the results of the aquatic toxicity tests. Testing is necessary to develop such data.

### III. Findings

EPA is basing the proposed testing requirements for cumene on sections 4(a)(1)(A) and (B) of TSCA.

1. Under section 4(a)(1)(B), EPA finds that cumene is produced in substantial quantities and that there is substantial environmental release with the potential for substantial human exposure from manufacturing, processing, use, and disposal. Approximately 3.5 billion pounds of cumene were produced in the U.S. in 1984. A 900-million pound capacity was on reserve, while an additional 300 million pounds of cumene were imported. More than 98 percent of the cumene manufactured or imported was used in the production of phenol, and to a lesser extent acetone. Cumene may also be used as a solvent or as a precursor in the manufacture of alpha-methylstyrene. Workers potentially exposed to cumene range between 700 to 800. During manufacturing, processing, and use an estimated 3 million pounds of cumene are lost to the atmosphere per year in fugitive emissions. Although this amount is only approximately one fifth the estimated atmospheric release of cumene from land transportation vehicles, the industrial releases are localized and may result in more significant exposures to the general population living near these facilities than the more ubiquitous vehicle emissions. Over half of the cumene manufacturing and processing plants are located in two major metropolitan areas, thus increasing the potential human exposure to 15 to 16 million people. Airborne releases of cumene are not expected to substantially affect aquatic concentrations of the chemical; however, there is evidence of

widespread release of cumene to the environment in industrial effluents.

EPA finds that there are insufficient data to reasonably determine or predict the pharmacokinetic, neurotoxic, developmental, reproductive, mutagenic and oncogenic effects of human exposure to cumene resulting from the manufacturing, processing, use, and disposal of the chemical. Furthermore, EPA finds that there are insufficient data to reasonably determine or predict the biodegradation and volatilization in aquatic systems and the acute and chronic toxicity to saltwater and freshwater fish and invertebrates resulting from the the manufacture, processing, use, and disposal of the chemical. EPA finds that testing is necessary to develop such data.

2. Under section 4(a)(1)(A), EPA finds that cumene may present an unreasonable risk of mutagenic and oncogenic effects. TSCA section 8(e) submissions reported positive results in a cell transformation test and in a hepatocyte primary culture/unscheduled DNA synthesis assay. These positive results suggest that cumene may be mutagenic and/or oncogenic. EPA finds that there are insufficient data to reasonably determine or predict the mutagenic and oncogenic effects of cumene and that testing is necessary to develop such data.

### IV. Proposed Rule

#### A. Proposed Testing and Test Standards

The Agency is proposing that health effects, chemical fate, and environmental effects testing be conducted on cumene in accordance with specific guidelines set forth in Title 40 of the Code of Federal Regulations as enumerated below. Test methods under new Parts 796, 797, and 798 were published in the Federal Register of September 27, 1985 (50 FR 39252). The health effects tests to be conducted are: (1) pharmacokinetics, comparing oral and inhalation routes of exposure as specified in § 798.7475; (2) inhalation subchronic toxicity as specified in § 798.2450, and as modified in § 799.1285(c)(2)(i)(B); (3) oral subchronic toxicity as specified in § 798.2650 and as modified in § 799.1285(c)(3)(i)(B); (4) neurotoxicity as specified in § 798.6050, § 798.6200, and § 798.6400, and to be conducted in conjunction with the subchronic exposure tests; (5) oncogenicity as specified in § 798.3300 and (6) developmental toxicity as specified in § 798.4350.

The Agency is proposing that both oral and inhalation subchronic tests be conducted on cumene. The inhalation

route will address the concern that the Agency has with occupational exposure to cumene. Data obtained from the oral subchronic test will enable the Agency to assess the potential toxicity of cumene to the general population resulting from groundwater and drinking water exposures.

The inhalation and oral subchronic toxicity tests will serve as (1) an exposure range-finding test for the oncogenicity test, (2) an exposure paradigm for the neurotoxicity tests, and (3) a screen for determining the need for a reproductive toxicity test.

The Agency is proposing that a two-generation reproduction and fertility effects test be conducted if the results of gross or histopathological evaluation of the reproductive tissues in male or female exposed animals from the subchronic exposure tests show adverse effects. Tissues to be evaluated include testes, ovaries, epididymis, vas deferens, prostate, seminal vesicles, vagina, cervix, fallopian tubes, and pituitary. Absolute reproductive tissue/organ weights and reproductive organ-to-body weight ratios shall also be evaluated. An effect is considered adverse if there is a statistically significant ( $p < 0.05$ ) difference in the incidence of lesions or in the mean organ/tissue or weight ratios between any exposed group and a control group of animals. Where one of the above parameters is adversely affected, a two-generation reproductive study shall be conducted using the test method specified in § 798.4700 with inhalation as the route of exposure. EPA is proposing that if no adverse effects are observed in the reproductive tissues from the subchronic exposure test no further reproductive effects testing shall be required at this time.

To assess the potential for cumene to cause gene mutations, the Agency is proposing that mutagenicity testing be conducted on subclones of CHO cells for gene mutations in cells in culture as specified in § 798.5300 and as modified in § 799.1285(c)(9)(i)(A)(2). If the results of cells in culture test are positive a *Drosophila* sex-linked recessive lethal assay (SLRL) shall be conducted using the method specified in § 798.5275 and as modified in § 799.1285(c)(9)(i)(B)(2). A positive result in the SLRL assay will trigger a mouse specific locus test specified in § 798.5200 and as modified in § 799.1285(c)(9)(i)(C)(2). If the cells in culture test is negative no further testing will be required. If the SLRL assay is negative then the mouse specific locus test will not be required.

To assess the potential for cumene to cause chromosomal aberrations, the Agency is proposing that an *in vitro*

cytogenetic assays be conducted on cumene as specified in § 798.5375 and as modified in § 799.1285(c)(8)(i)(A)(2). If the results of the *in vitro* test are positive then a dominant-lethal assay will be required as specified in § 798.5450 and as modified in § 799.1285(c)(8)(i)(C)(2). A positive result in the dominant-lethal assay will trigger a heritable translocation assay specified in § 798.5460 and as modified in § 799.1285(c)(8)(i)(D)(2). If the *in vitro* cytogenetics assay is negative, the *in vivo* bone marrow assay specified in § 798.5385 and as modified in § 799.1285(c)(8)(i)(B)(2) will be required. Should be *in vivo* bone marrow test results prove negative, then no further chromosomal aberrations testing would be required. A positive result in the *in vivo* bone marrow test would trigger the dominant-lethal assay. Again, if the dominant-lethal test is positive a heritable translocation assay shall be conducted.

If the results from the dominant-lethal assay and/or the SLRL are positive, EPA will hold a public program review prior to initiating the heritable translocation and/or mouse-specific locus testing. Public participation in this program review will be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting will be published in the Federal Register. Should the Agency determine, based on the weight of the evidence then available, that proceeding to the heritable translocation test and/or mouse specific locus assay is no longer warranted, the Agency would propose to repeal that test requirement and, after public comment, issue a final amendment to rescind the requirement.

For a more detailed discussion concerning mutagenicity tiered testing and program review see the final test rule for the C9 aromatic hydrocarbon fraction (50 FR 20662).

Acute and chronic toxicity testing is also being proposed for cumene in freshwater and saltwater fish and invertebrates. The aquatic toxicity tests are to be conducted using flow-through aquatic environments, with cumene concentrations at the end of test no less than 80 percent of the initial concentrations. The specific tests to be conducted are (1) Daphnid acute toxicity test specified in § 797.1300 using *Daphnia magna*, (2) a Mysid shrimp acute toxicity test as specified in § 797.1930 using *Mysidopsis bahia*, (3) fish acute freshwater toxicity tests as specified in § 797.1400 using *Pimephales promelas*, *Salmo gairdneri*, and *Lepomis macrochirus*; (4) the saltwater acute toxicity tests shall be conducted on

*Menidia* and *Cyprinodon variegatus* using the method specified in § 797.1400 and the modification proposed for § 797.1400; the proposed modification for saltwater testing appear in the proposed rule for octamethylcyclotetrasiloxane, a copy of which is in the docket of this proposed rule for cumene (5) The freshwater and saltwater invertebrate chronic toxicity test shall be conducted using the *Daphnia* chronic toxicity test and Mysid shrimp chronic toxicity test specified in § 797.1330 and § 797.1950, respectively; (6) vertebrate chronic toxicity tests shall be conducted on the most sensitive freshwater and saltwater species (i.e., having the lowest LC<sub>50</sub>) in accordance with the test specified in § 797.1600.

The biodegradation test for cumene shall be conducted using the eco-core method described by Bourquin et al. (Ref. 83). The volatilization test shall be conducted with cumene using the method described by Smith et al. (Ref. 84). The Agency believes that these chemical fate methodologies specify the minimal conditions for acceptable investigation of cumene's chemical behavior in an aquatic system.

The Agency is proposing that the above-referenced health and environmental effects tests be considered the test standards for the purposes of the proposed tests for cumene. The health and environmental effects-tests specify generally acceptable minimal conditions for characterizing the potential toxicity of cumene. The Agency reviews its standards every year according to the process described in the Federal Register of September 22, 1982 (47 FR 41857).

EPA intends to propose shortly in a separate Federal Register notice certain revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study. In addition, these revisions will avoid repetitive chemical-by-chemical changes to the guidelines in their adoption as test standards for chemical-specific test rules. EPA is proposing that these modifications be adopted in the test standards for cumene.

The proposed chemical fate tests specify generally accepted minimal conditions for determining the biodegradation and volatilization rates of cumene from an aquatic system. The Agency believes that these tests reflect current state-of-the-art methods for such testing and are being proposed as acceptable methods for testing the fate of cumene in aquatic systems.

With the exception of the oral subchronic test, the Agency is proposing that inhalation be the initial route of

exposure for the health effects testing of cumene. Inhalation is the route to which the greatest number of people are likely to be exposed to cumene (in light of about 3 million pounds per year in fugitive air emissions). Although administration of cumene by the oral route is more convenient and economical, conducting the test by inhalation would provide a more accurate assessment of the potential toxicity of cumene. Extrapolating toxicity data resulting from an oral study to depict an inhalation exposure, and vice versa, would introduce additional variability into the assessment of cumene's toxicity to human health. Should pharmacokinetic data, or the results of the subchronic toxicity studies, become available which shows that there are no differences in the absorption efficiency of cumene or in the type of metabolites produced between the two routes of exposure, then the Agency would consider changing the proposed inhalation exposure requirement or amending the final rule to the use of an oral route.

Certain modifications and clarifications of the subchronic oral inhalation test standards have been included in the proposed testing for cumene. The modifications include a requirement of histopathological examination of reproductive organs. The Agency believes that if there are certain effects (described in Unit IV. A) seen in the subchronic studies, then there would be cause for concern of possible reproductive effects resulting from exposure to cumene. While a detailed histopathological analysis may not show all potential reproductive effects, it will serve as a minimal indicator of reproductive toxicity. If certain effects are seen in the reproductive tissues, a 2 generation study will automatically be required without promulgating an additional test rule for cumene.

The modifications to the mutagenicity tests include the incorporation of cumene's chemical properties into the test procedures. The Agency believes that these modifications are necessary to ensure that resulting data will be reliable and adequate for assessing the mutagenic potential of cumene.

#### B. Test Substance

EPA is proposing that cumene of at least 99 percent purity be used as the test substance. Commercial cumene is generally greater than 99 percent pure.

#### C. Persons Required to Test

Section 4(b)(3)(B) of TSCA specifies that the activities for which EPA makes section 4(a) findings (manufacture, processing, distribution, use and/or

disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. Both manufacturers and processors are required to test if the findings are based on distribution, use, or disposal.

Because EPA has found that there are insufficient data and experience to reasonably determine or predict the effects of the manufacture, processing, and use of cumene on human health and the environment, EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process, cumene at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements contained in this proposed rule. The end of the reimbursement period will be 5 years after the last final report is submitted or an amount of time after the submission of the last final report required under the test rule equal to that which was required to develop data, if more than 5 years.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement. EPA promulgated procedures for applying for TSCA section 4(c) exemptions in 40 CFR Part 790.

When both manufacturers and processors are subject to a test rule, EPA expects that manufacturers will conduct the testing and that processors will ordinarily be exempted from testing. As described in 40 CFR Part 790, processors will be granted an exemption automatically without filing applications if manufacturers perform all of the required testing. Manufacturers are required to submit either a letter of intent to perform testing or an exemption application within 30 days after the effective date of the final test rule.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for cumene. EPA is interested in evaluating the effects attributable to cumene itself and as

noted in Unit IV.B above, has specified a relatively pure substance for testing.

Manufacturers and processors subject to this test rule must comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

#### D. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practice (GLP) standards, which appear in 40 CFR Part 792.

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors are required to submit individual study plans at least 30 days prior to the initiation of each study.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. The Agency is proposing specific reporting requirements for each of the proposed test standards as follows:

1. The pharmacokinetic test and the neurotoxicity, developmental toxicity, and first-tier mutagenicity studies shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final test rule. The second- and third-tier mutagenicity test shall be completed and final results submitted within 3 to 4 years of the final rule, respectively. Progress reports on all studies will be required quarterly.

2. The subchronic toxicity test shall be completed and final results submitted to the Agency within 12 months of the effective date of the final rule. Progress reports shall be submitted quarterly.

3. The reproductive effects test shall be completed and final results submitted to the Agency within 41 months of the effective date of the final rule if those criteria necessary to trigger reproductive effects testing are met. Progress reports shall be submitted quarterly.

4. The oncogenicity test shall be completed and the final results submitted to the Agency within 53 months of the effective date of the final rule. Progress reports shall be submitted quarterly.

5. The aquatic vertebrate and invertebrate acute toxicity tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final test rule. Progress reports shall be required quarterly.

6. The aquatic vertebrate and invertebrate chronic toxicity tests shall be completed and final results submitted to the Agency within 2 years of the effective date of the final rule. Progress reports shall be required quarterly.

7. The biodegradation and volatilization tests shall be completed and final results submitted to the Agency within 1 year of the effective date of the final rule. Progress reports shall be required quarterly.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the *Federal Register* as required by section 4(d) of TSCA.

Persons who export a chemical substance or mixture which is subject to a section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) are in 40 CFR Part 707 (45 FR 82844; December 18, 1980). In brief, as of the effective date of the final test rule, an exporter of cumene must report to EPA the first annual export or intended export to cumene to any one country. EPA will notify the foreign country concerning the test rule for the chemical.

#### E. Enforcement Provisions

The Agency considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to: (1) Establish or maintain records; (2) submit reports, notices, or other information; or (3) permit access to or copying of records required by the Act or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce \* \* \*". The Agency considers a testing facility to be a place where the chemical is held or stored and, therefore, subject to inspection. Laboratory inspections and data audits will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11 by duly designated representatives of the EPA for the purpose of determining compliance with any final rule for cumene. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, and that reports accurately reflect the underlying raw data and interpretations and

evaluations, and to determine compliance with TSCA GLP standards and the test standards established in the rule.

EPA's authority to inspect a testing facility is also derived from section 4(b)(1) of TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and to include such other requirements as are necessary to provide such assurance. The Agency maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to \$25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers or processors that fail to submit a letter of intent or an exemption request and that continue manufacturing or processing after the deadlines for such submissions. Knowing or willful violations could lead to the imposition of criminal penalties of up to \$25,000 for each day of violation and imprisonment for up to 1 year. In determining the amount of penalty, EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Section 15 and 16 of TSCA apply to "any person" who violates various provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular, this includes individuals who report false information or who cause it to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

#### V. Issues for Comment

This proposed rule specifies TSCA test guidelines and independent, published test methods as the test standards for health, environmental effects and chemical fate testing of

cumene. The Agency is soliciting comments as to whether the OTS health and environmental effects test guidelines and the independent methods are appropriate and applicable for testing of cumene. Also regarding the testing of cumene, the Agency requests comments on:

1. The adequacy of the proposed testing.
2. The route of administration for the health effects testing. Specifically, should any other test besides the pharmacokinetic and subchronic tests include oral in addition to or instead of the inhalation route of exposure?
3. Should dermal exposure be included in any or all of the health effects testing.
4. The proposed subchronic testing with oral and inhalation routes of exposure.
5. The adequacy of requiring a two-generation reproductive toxicity test if the criteria given in Unit IV.A above are met; or should a two-generation reproductive toxicity test be required immediately without using the subchronic exposure test as a screen.
6. The reporting times for the identified health and environmental effects and chemical fate tests.
7. Whether there are any other testing approaches which should be considered.

#### VI. Economic Analysis of Proposed Rule

To evaluate the potential economic impact of test rules, EPA has adopted a two-stage approach. All candidates for test rules go through a Level I analysis. This consists of evaluating each chemical or chemical group on four principal market characteristics: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis, along with the consideration of the costs of the required tests, indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for the chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted. This Level II analysis attempts to predict more precisely the magnitude of the expected impact.

Total testing costs of the maximum set of tests in this proposed rule for cumene are estimated to range from \$1,117,828 to \$1,864,960. The annualized test costs (using a cost of capital of 25 percent over a period of 15 years) range from

\$289,648 to \$483,243. Based on the 1984 production volume of 3.4 billion pounds, the annualized unit test costs range from 0.009 to 0.014 cents per pound. In relation to the current list price of 23 cents per pound for cumene, these costs are equivalent to 0.04 to 0.06 percent of price.

Based on the economic analysis conducted for cumene, the potential for a significant economic impact as a result of the testing required in this proposed rule is low. This conclusion is suggested by the following observations.

(a) Cumene is a major commodity chemical produced in large volumes. Consequently, the test costs on an annualized, unit basis are extremely small.

(b) Cumene is a broadly based chemical intermediate whose cost represents a very small portion of the cost of final products. This situation leads to insensitivity of final demand with respect to cumene price. Demand sensitivity combined with very low unit testing costs makes the potential for economic impact appear insignificant.

For a more detailed discussion of cumene market test costs and potential economic impacts, see the economic analysis (Ref. 82).

#### VII. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules. Copies of the study, *Chemical Testing Industry: Profile of Toxicological Testing*, can be obtained through the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22161.

(PB 82-140773). On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing in this proposed rule.

#### VIII. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, D.C. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); In Washington, D.C.:

(554-1404); outside the U.S.A. (Operator—202-554-1404), by December 23, 1985. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, the Agency will transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

#### IX. Public Record

EPA has established a record for this rulemaking (docket number OPTS-42075). This record contains the basic information considered by the Agency in developing this proposal and appropriate Federal Register notices. The Agency will supplement the record with additional relevant information as it is received.

This record includes the following information:

##### A. Supporting Documentation

(1) Federal Register notices pertaining to this rule consisting of:

- (a) Notice containing the ITC designation of cumene to the Priority List.
- (b) Rules requiring TSCA section 8 (a) and (d) reporting on cumene.
- (c) Notice containing TSCA test guidelines cited as test standards for this rule.
- (d) Notice containing revision of TSCA test guidelines cited as test standards for this rule.

(2) Communications before proposal consisting of:

- (a) Written public comments and letters.
- (b) Contact reports of telephone conversations.
- (c) Meeting summaries.
- (3) Reports—published and unpublished factual materials.

##### B. References

- (1) Amore, J.E., Hautala, E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J. Appl. Toxicol.* 3(8): 272-90, 1983.
- (2) Hutchinson, T.A., Heldebus, J.A., Tum, D., Mackay, D., Mascarenhas, R.A., Shin, W.Y. The correlation of the toxicity to algae of hydrocarbons and halogenated

hydrocarbons with their physical-chemical properties. *Environ. Sci. Res.* 18: 577-586, 1980.

(3) Verschuren, K. Handbook of Environmental Data on Organic Chemicals. NY: Van Nostrand Reinhold Co. 1977.

(4) Kirk-Othmer. Kirk-Othmer Encyclopedia of Chemical Technology Vol. 1, 3rd ed. Grayson, M., Eckroth, D. eds. New York: Wiley, 1978.

(5) Yalkowsky, S.H., Valvani, S.C. Partition coefficients and surface areas of some alkylbenzenes. *J. Med. Chem.* 19(5): 727-728, 1978.

(6) Ravishankara, A.R., Wagner, S., Fischer, S., Smith, G., Schiff, R., Watson, R.T., Tsai, G., Davis, D.D. A kinetics study of the reaction of OH with several aromatic and olefinic compounds. *Int. J. Chem. Kinetics* 16: 783-804, 1984.

(7) Chemical Marketing Reporter. Chemical Profile: Cumene. July 23, 1984.

(8) SRI International, Stanford Research Institute International. Cumene. In: Chemical Economics Handbook. Menlo Park, CA, 1984.

(9) NIOSH. National Occupational Hazard Survey. Cincinnati, OH: National Institute for Occupational Safety and Health, 1984.

(10) Gulf Oil Products Co. Letter from J.P. Dey to M. Grief of TSCA Interagency Testing Committee concerning unpublished information on the production, use, occupational exposure, and release of cumene. July 2, 1984.

(11) Koch Refining Co. Material Safety Data Sheet: Cumene. PO Box 2808, Corpus Christi, TX 78403.

(12) Texaco. Letter from R.T. Richards to M. Grief of TSCA Interagency Testing Committee concerning unpublished information on the production, use, occupational exposure, and release cumene. May 14, 1984.

(13) API American Petroleum Institute. Attachment to letter by W.F. O'Keefe to M. Grief of TSCA Interagency Testing Committee, 1984.

(14) No reference.

(15) No reference.

(16) Deane, J.L., Hughes, T.W. Source Assessment Manufacture of Acetone and Phenol from Cumene. U.S. EPA, Washington, D.C. EPA 600/2-79-019D, 1979.

(17) USITC. U.S. International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1982. USITC Publication 1422, 1983.

(18) Jackson, J., Gray, D.A., Bush, C., Jacobson, R., Howard, P.A., Santodonato, J. Test Rule Support Document: Cumene. Syracuse Research Corporation. Contract No. 88-02-4209. U.S. EPA, Office of Toxic Substances, 1985.

(19) Nelson, P.F., Quigley, S.M. The hydrocarbon composition of exhaust emitted from gasoline fueled vehicles. *Atmos. Environ.* 8(1): 79-87, 1984.

(20) Katzman, H., Libby, W.F. Hydrocarbon emissions from jet engines operated at simulated high-altitude supersonic flight conditions. *Atmos. Environ.* 9(9): 639-642, 1975.

(21) Montz, W.E., Puyser, R.L., Brammer, J.D. Identification and quantification of water soluble hydrocarbons generated by two-cycle

- outboard motors. *Arch. Environ. Contam. Toxicol.* 11(5): 561-565. 1982.
- (22) Shackelford, W.M., Cline, D.M., Faas, L., Kurth, G. An evaluation of automated spectrum matching for survey identification of wastewater components by gas chromatography-mass spectrometry. *Analytica Chimica Acta*, 146: 15-27. 1983.
- (23) Burmaster, D.E. The new pollution groundwater contamination. *Environment* 24(2): 6-36. 1982.
- (24) Stepan, S., Smith, J.F., Riha, M. Movement and chemical change of organic pollutants in an aquifer. *Aust. Water Res. Coun. Conf. Ser.* 1:415-424. 1981.
- (25) Tester, D.J., Harker, R.J. Groundwater pollution investigations in the Great Ouse Basin. *Water Pollution Control*: 80: 614-631. 1981.
- (26) Stuermer, D.H., Ng, D.J., Morris, C.J. Chemical characteristics of organic constituents in groundwater near a coal gasification site. Pac. Northwest Lab. Dept. of Energy DEB3-015528. 1983.
- (27) Burnham, A.K., Calder, G.V., Fritz, J.S., Junk, G.A., Svec, H.J., Willis, R. Identification and estimation of neutral organic contaminants in potable water. *Anal. Chem.* 44(1): 139-142. 1971.
- (28) Keith, L.H., Garrison, A.W., Allen, F.R., Carter, M.H., Floyd, T.L., Pope, J.D., Thruston, A.D. Identification of organic compounds in drinking water from thirteen U.S. cities. In: Identification and Analysis of Organic Pollutants in Water. Keith, L.H. ed. Ann Arbor Science, Ann Arbor, MI. 1976.
- (29) Coleman, W.E., Munch, J.W., Streicher, R.P., Ringhand, H.P., Kopfler, F.C. The identification and measurement of components in gasoline, kerosene, and No. 2 fuel oil that partition into the aqueous phase, after mixing. *Arch. Environ. Contam. Tox.* 13: 171-178. 1984.
- (30) Kingsley, F.A., Gin, C., Coulson, D.M., Thomas, R.F. Gas chromatographic analysis of purgable halocarbon and aromatic compounds in drinking water using two detectors in series. In: Water Chlorination: Environmental Impact and Health Effects. Vol. 4. Book 1. Chemistry and Water Treatment. Jolley R.L., Brungs, W.A., Cotruvo, J.A., Cumming, R.B., Mattice, J.S., and Jacobs V.A., eds. Ann Arbor Science, 1983.
- (31) Senczuk, W., Litewka, B. Determination of dimethylphenylcarbinol in the urine to evaluate the degree of isopropylbenzene poisoning. *Bromatol. Chem. Toksykal.* 7(1) 93-97. 1974.
- (32) Valette, G., Cavier, R. Absorption percutanée at constitution chimique; cas des hydrocarbures des alcools et des esters. *Arch. Int. Pharmacodyn.* ICVII, No. 2 1954.
- (33) Robinson, D., Smith, J.N., Williams, R.T. Studies in detoxification. The metabolism of alkylbenzenes, isopropyl benzenes (cumene) and derivatives of hydratropic acid. *Biochem. J.* 59: 153-159. 1955.
- (34) Bakke, O.M., Scheline, R.R. Hydroxylation of aromatic hydrocarbons in the rat. *Toxicology and Applied Pharmacology*, 16: 681-700. 1970.
- (35) Corarde, H.W. The biochemorphology of the phenylalkanes and phenylalkenes. *A.M.A. Arch. Ind. Health*, 19: 403-418. 1959.
- (36) Fabre, R., Truhaut, R., Bernuchan, T., Loissilier, F. Toxicology studies of solvents to replace benzene. III. Study of Isopropylbenzene or cumene. *Arch. Mal. Prof.* 16(4): 285-299. 1955.
- (37) Smith, S.N., Smithies, R.H., Williams, R.T. The metabolism of alkylbenzenes. a. Glucuronic acid excretion following the administration of alkylbenzenes. b. Elimination of toluene in the expired air of rabbits. *Biochem. J.* 56: 317. 1954.
- (38) Van Doorn, R., Leijdekkers, Ch. M., Bos, R.P., Brouns, R.M.E., Henderson, P.T. Alcohol and sulphate intermediates in the metabolism of toluenes and xylenes to mercapturic acids. *J. Appl. Tox.* 1(4) 236-242. 1981.
- (39) Monsanto Co. TSCA section 8(d) submission Cumene Health Studies. Y-78-213 Acute Toxicity, eye and skin irritation, ML-81-107 Ames/Salmonella Mutagenicity Assay. 1978.
- (40) Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L., Oyen, F. Toxicological studies of certain alkylated benzenes and benzene. *A.M.A. Arch. Ind. Health* 14: 337-398. 1956.
- (41) Smyth, H.F., Carpenter, C.P., Weil, C.S. Range finding toxicity data: List IV. *A.M.A. Arch. Ind. Hyg. Occup. Med.* 4: 119. 1951.
- (42) Werner, H.W., Dunn, R.C., von Oettingen. The acute effects of cumene vapors in mice. *J. Ind. Hyg. and Toxicol.* 26(8) 284-288. 1944.
- (43) Lazarow, N.W. Urber die giftigkeit verschiedener kohlenwasserstoffdämpfe. *Arch. Eptl. Path. Pharmacol.* 143: 233. 1929.
- (44) Nielson, G.D., Alarie, Y. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodynamic properties. *Toxicol. Appl. Pharmacol.* 65(3): 459-477. 1982.
- (45) Jenkins, L.J., Jones, R.A., Siegel, J. Longterm inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. *Toxicol. Appl. Pharmacol.* 18: 818-823. 1970.
- (46) Florin, I., Ruthberg, L., Curvall, M., Enzell, C.R. Screening of tobacco smoke constituents for mutagenicity using the Ames test. *Toxicology*, 15(3): 219-232. 1980.
- (47) Simmon, V.F., Kayhanan, K., Tardiff, R.G. Mutagenic activity of chemicals identified in drinking water. *Dev. Toxicol Environ. Sci. Iss. Prog. Genet. Toxicol.* 2: 249-258. 1977.
- (48) Tardiff, R.G., Carlson, G.P., Simmon, V. Halogenated Compounds in Tap Water: A Toxicological Evaluation. Environmental Impact of Water Chlorination. Proc. Conf. 1975: 213-227. 1976.
- (49) Gulf Oil Products Co. TSCA section 8(e) submission. 8EHQ-1184-0536 Project No. 84-2131 Cell Transformation Test of Cumene. 1984.
- (50) DiPaolo, T.A., Talano, K., Popesco, N.C. Quantitation of chemically induced neoplastic transformation of BALB/3T3 closed cell lines. *Cancer Res.* 32: 2686-2695. 1972.
- (51) Gulf Oil Products Co. TSCA section 8(e) submission 8EHQ-1184-0336 Project No. 84-2130 Hepatocyte Primary Culture/DNA Repair Test of Cumene. 1984.
- (52) Williams, G.M., Laspia, M.F., Dunkel, V.C. Reliability of the Hepatocyte Primary Culture DNA repair test in testing of coded carcinogens and non-carcinogens. *Mut. Res.* 97: 359-370. 1982.
- (53) Williams G.M. Detection of carcinogens by unscheduled DNA synthesis in rat liver primary cell cultures. *Cancer Res.* 37: 1845-1851. 1977.
- (54) Serebrennikov, O.A., Ogleznev, G.A. Developmental anomalies in the mother-fetus system following exposure to petrochemical products. Deposited Doc/ISS VINITI (2667-26678): 151-152. 1978.
- (55) Erben, R. Effects of some petrochemical products on the survival of *Dicranophorus forcipatus* O.F. Mueller (Rotatoria) under laboratory conditions. *Verh.-Int. Ver. Theor. Angew. Limnol.* 20(3): 1981-1988. 1978.
- (56) Rogerson, A., Shiu, W.Y., Htuang, G.C., Mackay, D., Berger, J. Determination and interpretation of Hydrocarbon toxicity to ciliate protozoa. *Aquatic Toxicol.* 3(3): 215-228. 1983.
- (57) Schafer, E.W., Bowles, W.A., Hurlburt, J. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. *Arch. Environ. Contam. Toxicol.* 12(3): 355-382. 1983.
- (58) Junhke, L., Luedemann, D. Results of the study of 200 chemical compounds on acute fish toxicity using the golden orfe test. *Z. Wasser Abwasser-Forschung*, 11: 161-164. 1978.
- (59) Dow Chemical Co. Letter to the Document Control Officer, L. Hampton, U.S. EPA. Dow Item No. D-1594, Feb. 6, 1985.
- (60) Bobra, A.M., Shin, W.Y., Mackey, D. A predictive correlation for the acute toxicity of hydrocarbons and chlorinated hydrocarbons to the water flea (*Daphnia magna*). *Chemosphere* 12(9, 10): 1121-1124. 1983.
- (61) Bringmann, G., Kuehn, R. Results of toxic action of water pollutants on *Daphnia magna* strains tested by an improved standardized procedure. *Z. Wasser Abwasser Forsch.* 15(1): 1-6. 1982.
- (62) Le Roux, S. The toxicity of pure hydrocarbons to mussel larvae. *Rapp P-V Reun Cons. Int. Explor. Mer.* 171: 189-190. 1977.
- (63) Price, K.S., Waggy, G.T., Conway, R.A. Brine shrimp bioassay and seawater BOC of petrochemicals. *J. Water Pollut. Control Fed.* 46(1): 63-77. 1974.
- (64) Lyman, W.J., Reehl, W.F., Rosenblatt, D.H. Handbook of Chemical Property Estimation Methods. McGraw Hill Book Co. New York. 1982.
- (65) Kappeler, T., Wuhrman, K. Microbial degradation of the water-soluble fraction of gas oil-I. *Water Res.* 12: 327-333. 1978.
- (66) Walker, J.D., Calomiris, J.J., Herbert, T.L., Colwell, R.R. Petroleum hydrocarbons: degradation and growth potential for Atlantic Ocean sediment bacteria. *Mar. Biol.* 34(1): 1-9. 1978.
- (67) Marion, C.V., Malaney, G.W. Ability of activated sludged microorganisms to oxidize aromatic organic compounds. Proceedings of the Industrial Waste Corp. 18: 297-308. 1964.
- (68) Malaney, G.W., McKinney, R.E. Oxidative abilities of benzeneacclimated

activated sludge. *Water and Sewage Works*. 113(8): 302-308. 1986.

(69) Gibson, D.T. Microbial degradation of aromatic compounds. *Science* 161: 1083-1097. 1968.

(70) Jigami, Y., Omori, T., Minoda, Y. The degradation of isopropylbenzene and isobutylbenzene by *Pseudomonas* sp. *Agricul. Bio. Chem.* 39(9): 1781-1788. 1975.

(71) Jigami, Y., Omori, T., Minoda, Y. A new metabolic divergence in the degradation of isopropylbenzene and isobutylbenzene by *Pseudomonas* sp. *Agric. Biol. Chem.* 43(a): 2001-2003. 1979.

(72) Mill, T. Structure reactivity Correlations for Environmental Reactions. EPA-560/71-79-012. 1979.

(73) Hendry, D.G., Mill, T., Piszkiwicz, L., Howard, J.A., Eigenmann, H.K. Critical review of H-atom transfer in the liquid phase: chlorine atom, alkyltrichloromethyl, alkoxy, and alkylperoxy radicals. *J. Phys. Chem. Ref. Data*. 3: 937-978. 1974.

(74) Mill, T., Richardson, H., Hendry, D.G. Oxidation of organic compounds in aquatic systems: The free radical oxidation of cumene. In: *Aquatic Pollutants: Transformation and Biological Effects*. Proceedings of the 2nd International Symposium on Aquatic Pollutants. Noordwijkerhout (Amsterdam), The Netherlands, Sept. 26-28, 1977. Hutzinger, O., Van Lelyveld, L.H., Zoeteman, B.C. J., eda. Pergamon Press. 1978.

(75) Mill, T., Hendry, D.G., Richardson, H. Free-radical oxidants in natural waters. *Science* 207: 898-887. 1980.

(76) Kanaga, E.E. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. *Ecotox. Environ. Safety*. 4: 29-38. 1980.

(77) Walker, J.D., Colwell, R.R. Degradation of hydrocarbons and mixed hydrocarbon substrate by microorganisms from Chesapeake Bay. *Prog. Water Technol.* 7: 783-791. 1975.

(78) Sutton, C., Calder, J.A. Solubility of alkylbenzenes in distilled water and seawater at 25 °C. *J. Chem. Eng. Data*. 20: 320-322. 1975.

(79) No reference.

(80) USEPA. U.S. Environmental Protection Agency. Chemical property and environmental behavior estimates for chemicals on the 15th ITC list. Intra-agency memorandum to J. Davidson, Existing Chemical Assessment Division from the Designed Development Branch. 1984.

(81) Chemical Manufacturers Association. Cuene program panel: industrial hygiene survey. 2561 M St. N.W. Washington, D.C. 20037. 1985.

(82) Economic Analysis for Cumene.

(83) Bourquin, A.W., Hood, M.A., Garnas, R.I. An artificial microbial ecosystem for determining effects and fact of toxicants in a salt-marsh environment. *Development in Industrial Microbiology* 18. 1977.

(84) Smith, J.H., Bomberger, D.C., Haynes, D.L. Prediction of the volatilization of high volatility chemicals from natural water bodies. *Env. Sci. and Tech.* 14(11): 1332-1337. 1980.

Confidential Business Information (CBI), while part of the record, is not available for public review. A public

version of the record, from which CBI has been deleted, is available for inspection in the OPTS Reading Rm. E-107, 401 M St., SW., Washington, DC from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

## X. Other Regulatory Requirements

### A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "Major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that this test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order, i.e., it will not have an annual effect on the economy of at least \$100-million, will not cause a major increase in prices, and will not have a significant adverse effect on competition or the ability of U.S. enterprises to compete with foreign enterprises.

This proposed regulation was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

### B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses because: (1) There are no known small manufacturers; (2) any small processors are not likely to perform testing or participate in the organization of the testing effort; (3) they will experience only very minor costs in securing exemption from testing requirements; and (4) they are unlikely to be affected by reimbursement requirements.

### C. Paperwork Reduction Act

The information collection requirements contained in this rule have been approved by OMB under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and have been assigned OMB number 2070-0033. Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs of OMB marked "Attention: Desk Officer for EPA." The final rule package will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Parts 796 and 799

Testing, Environmental protection, Hazardous substances, Chemicals.

Recordkeeping and reporting requirements.

Dated: October 28, 1985.

John A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that Subchapter R of Chapter I of Title 40 of the Code of Federal Regulations be amended as follows:

## PART 798—[AMENDED]

1. Part 798 is amended as follows:

a. The authority citation continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. New § 798.7475 is added, to read as follows:

### § 798.7475 Oral and inhalation pharmacokinetic test.

(a) *Purpose.* The purpose of these studies is to determine:

(1) Bioavailability of the test substance after oral and inhalation exposure;

(2) Whether or not the biotransformation of the test substance is qualitatively and quantitatively the same after oral and inhalation exposure and;

(3) Whether or not the biotransformation of the test substance is changed qualitatively or quantitatively by repeated dosing.

(b) *Definitions.* Bioavailability refers to the rate and extent to which an administered compound is absorbed, i.e., reaches the systemic circulation.

(c) *Test procedures.*—(1) *Animal selection.*—(i) *Species.* The preferred species is the rat for which extensive data on the toxicity and carcinogenicity of numerous compounds are available.

(ii) *Animals.* Adult male and female Fischer 344 rats are the animals of choice. The rats shall be 7 to 9 weeks old weighing 100 to 145 grams for females and 125 to 175 grams for males. Prior to testing the animals are selected at random for each group. Animals showing signs of ill health are not used.

(iii) *Animal care.* Animals shall be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms shall be maintained at a temperature of 25 ± 2 °C and humidity 50 ± 10 percent with a 12-hour light/dark cycle per day. The rats shall be kept in a quarantine facility for at least 7 days prior to use. The animals shall be acclimated to the experimental environment for a minimum of 48 hours prior to treatment. Certified feed and water are provided *ad libitum*.

(iv) *Numbers*—(A) At least 8 animals (4 males and 4 females) shall be used at each dose level.

(B) Females shall be nulliparous and nonpregnant.

(2) *Administration of test substance*—

(i) *Test compounds*. The studies require the use of both nonradioactive test substance and <sup>14</sup>C-labeled test substance. Both preparations are needed to investigate the provisions of paragraph (a)(2) of this section. The use of <sup>14</sup>C-test substance is recommended for the provisions of paragraph (a) (1) and (3) of this section because it would facilitate the work, improve the reliability of quantitative determinations, and increase the probability of observing previously unidentified metabolites.

(ii) *Dosage and treatment*—(A) *Oral studies*. At least two doses shall be used in the study, a "low" and "high" dose. When administered orally, the "high" dose should induce some overt toxicity such as weight loss. The "low" dose shall not induce observable effects attributable to the test substances. Oral dosing shall be performed by gavage using an appropriate vehicle.

(B) *Inhalation studies*. Three concentrations shall be used in the study. Upon exposure, the two higher concentrations should ideally induce some overt symptoms of toxicity, although the intermediate concentration may be excluded from this condition. The lowest concentration shall not induce observable effects attributable to the test substance.

(iii) *Determination of bioavailability*—(A) *Oral studies*. (1) Group A (8 animals, 4 of each sex) shall be dosed once orally with the low dose of <sup>14</sup>C-test substance.

(2) Group B (8 animals, 4 of each sex) shall be dosed once orally with the high dose of <sup>14</sup>C-test substance.

(B) *Inhalation studies*. (1) Group C (4 males and 4 females) is to be exposed (6 hours) to a mixture of nonradioactive test substance in air at the prescribed low hydrocarbon concentration.

(2) Group D (4 males and 4 females) shall be exposed (6 hours) to nonradioactive test substance in air at the intermediate hydrocarbon concentration.

(3) Group E (4 males and 4 females) shall be exposed (6 hours) to nonradioactive test substance in air at the high hydrocarbon concentration.

(4) Group F is identical to paragraph (c)(2)(iii)(B)(2) of this section but using <sup>14</sup>C-labeled test substance.

(5) Group G is identical to paragraph (c)(2)(iii)(B)(2) of this section but using <sup>14</sup>C-labeled test substance.

(6) Group H is identical to paragraph (c)(2)(iii)(B)(2) of this section but using <sup>14</sup>C-labeled test substance.

(C) *Collection of excreta*. After oral administration (Groups A–B) and inhalation exposure (Groups F–H) the rats shall be placed in individual metabolic cages for collection of excreta (urine, feces and expired air) at 8, 24, 48, 72, and 96 hours posttreatment.

(D) *Kinetic studies*. Groups C–E shall be used to determine the kinetics of absorption of the test substance through the lungs. The concentration of the hydrocarbon in inspired and expired air, and blood shall be measured at 0, 3, 6, 12, 24, 48, 72, and 96 hours during and after inhalation exposure. Values for percentage of test substances retention, body burden and saturability shall be calculated from these experiments.

(E) *Repeated dosing study*. Rats (4 animals from each sex) shall receive a series of single daily oral doses of nonradioactive test substance over a period of at least 14 days, followed at 24 hours after the last dose by a single oral dose of <sup>14</sup>C-labeled test substance. Each dose shall be at the low-dose level.

(3) *Observation of animals*—(i) *Bioavailability*—(A) *Blood levels*. The levels of total <sup>14</sup>C-label shall be determined in whole blood and blood plasma or blood serum at 8, 24, 48, 72, and 96 hours after dosing rats in groups A–B and F–H.

(B) *Expired air, urinary and fecal excretion*. The quantities of total <sup>14</sup>C-label excreted in expired air, urine and feces by rat groups A–B and F–H shall be determined at 8, 24, 48, 72 and 96 hours after dosing and, if necessary, daily thereafter until at least 90 percent of the dose has been excreted or until 7 days after dosing, whichever occurs first.

(C) *Tissue distribution*. Determine the concentration and quantity of <sup>14</sup>C-label in tissues and organs at the time of sacrifice for rat groups A–B and F–H and the repeated-dosing group.

(ii) *Biotransformation after oral and inhalation exposure*. Appropriate qualitative and quantitative methods shall be used to assay urine specimens collected from rat groups A–B and F–H. Suitable enzymatic steps shall be used to distinguish, characterize and quantitate conjugated and nonconjugated test substance metabolites.

(iii) *Change(s) in biotransformation*. Appropriate qualitative and quantitative assay methodologies shall be used to compare the composition of <sup>14</sup>C-labeled components of urine collected at 24 and 48 hours after dosing rate group A with those in the urine collected at similar times in the repeated-dosing study.

(d) *Data and reporting*—(1) *Treatment of results*. Data should be summarized in tabular form.

(2) *Evaluation of results*. All observed results, quantitative or incidental, shall be evaluated by an appropriate statistical method.

(3) *Test report*. In addition to the reporting requirements as specified in the EPA Good Laboratory Practice Standards (Subpart J, Part 792 of this chapter) the following specific information should be reported:

(i) Labeling site of the test substance;

(ii) A full description of the sensitivity and precision of all procedures used to produce the data;

(iii) Percentage retention and saturation concentration for the inhalation studies;

(iv) Quantity of isotope, together with percent recovery of the administered dose in feces, urine, expired air and blood for both routes of administration;

(v) Quantity and distribution of <sup>14</sup>C-test substance in bone, brain, fat, gonada, heart, kidney, liver, lung, muscles, spleen, tissue which displayed pathology and residual carcass;

(vi) Biotransformation pathways and quantities of the test substance and its metabolites in urine collected after oral administration (single low and high doses) and inhalation exposure (low, intermediate and high concentrations);

(vii) Biotransformation pathways and quantities of the test substance and its metabolites in urine collected after repeated administration of the test substance to rats.

(4) *Counting efficiency*. Data should be made available to the Agency upon request.

**PART 799—[AMENDED]**

2. Part 799 is amended as follows:

a. The authority citation continues to read as follows:

Authority: 15 U.S.C. 2603; 2611, 2625.

b. New § 799.1285 is added, to read as follows:

**§ 799.1285 Cumene.**

(a) *Identification of test substance*. (1) Cumene (CAS No. 98–82–3) shall be tested in accordance with this section.

(2) Cumene of at least 99-percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data*. All persons who manufacture or process cumene other than as an impurity after the effective date of this rule (44 days after the publication date of the final rule in the Federal Register) to the end of the reimbursement period shall

submit letters of intent to conduct testing or exemption applications, submit study plans, conduct tests in accordance with Part 792 of this chapter, and submit data as specified in this section. Subpart A of this part, and Part 790 of this chapter for single-phase rulemaking.

(c) *Health effects testing*—(1) *Pharmacokinetics*—(i) *Required testing.* Metabolism studies using the oral and inhalation routes of exposure shall be conducted with cumene in accordance with § 798.7475 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetics testing shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final rule.

(B) Progress reports shall be submitted quarterly beginning 90 days after the effective date of the final rule.

(2) *Inhalation subchronic toxicity*—(i) *Required testing.* (A) Inhalation subchronic toxicity testing shall be conducted with cumene in accordance with § 798.2450 of this chapter and modifications specified in paragraph (c)(2)(i)(B) of this section.

(B) *Modifications.* The following modifications to § 798.2450 of this chapter for testing cumene are required.

(1) *Animal selection—Numbers.* The requirement under § 798.2450(d)(1)(iv) of this chapter is modified so that at least 30 animals (15 males and 15 females) shall be used for each test group.

(2) *Control groups.* The requirement under § 798.2450(d)(2) of this chapter is modified to require a concurrent control.

(3) *Exposure conditions.* The requirement under § 798.2450(d)(5) of this chapter is modified so that the animals shall be exposed to the test substance 6 hours per day, 5 days per week for 13 weeks (65 days of exposure).

(4) *Observation of animals.* The requirement under § 798.2450(d)(8) of this chapter is modified so that animals shall be weighed weekly, and the requirement under § 798.2450(d)(9) of this chapter is modified so that food and water consumption shall also be measured weekly.

(5) *Gross pathology.* The requirement under § 798.2450(d)(12)(iii) of this chapter is modified so that the following organs and tissues or representative samples thereof shall also be preserved in a suitable medium for histopathological evaluation: vas deferens, vagina, cervix, and fallopian tubes.

(6) *Test report—Individual animal data.* The requirement under § 798.2450(e)(3)(iv)(D) of this chapter is modified to read "Food and water consumption data."

(ii) *Reporting requirements.* (A) The required subchronic toxicity test shall be completed and final results submitted to the Agency within 12 months of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(3) *Oral subchronic toxicity*—(i) *Required testing.* (A) Oral subchronic tests shall be conducted with cumene in accordance with § 798.2650 of this chapter and as modified in paragraph (c)(3)(B)(i) of this section.

(B) *Modifications.* The following modifications to § 798.2650 of this chapter for testing cumene are required.

(1) *Animal selection—Numbers.* The requirement under § 798.2650(e)(1)(iv)(A) of this chapter is modified so that at least 30 rodents (15 per sex) shall be used at each dose level.

(2) *Control groups.* The requirement under § 798.2650(e)(2) of this chapter is modified to require a concurrent control group.

(3) *Administration of test substance.* The requirement under § 798.2650(e)(7)(i) of this chapter is modified to require that cumene be administered by gavage.

(4) *Observation of animals.* The requirement under § 798.2650(e)(8)(v) of this chapter is modified to require weekly measurements of food and water consumption.

(5) *Gross necropsy.* The requirement under § 798.2650(e)(10)(iii) of this chapter is modified so that the following organs and tissues or representative samples thereof are also preserved in a suitable medium for histopathological evaluation: Vas deferens, vagina, cervix, and fallopian tubes.

(ii) *Reporting requirements.* (A) The required subchronic toxicity test shall be completed and final results submitted to the Agency within 12 months of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(4) *Neurotoxicity*—(1) *Required testing.* Neurotoxicity tests shall be conducted with cumene by inhalation in accordance with §§ 798.6050, 798.6200, and 798.6400 of the chapter.

(ii) *Reporting requirements.* (A) The neurotoxicity tests shall be completed and final results submitted to the Agency within 1 year of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(5) *Reproductive toxicity*—(i) *Required testing.* A reproductive toxicity test shall be conducted with cumene by inhalation in accordance with § 798.4700 of this chapter if the gross or histopathological evaluation of the testes, ovaries, pituitary, epididymus, vas deferens, prostate, seminal vesicles, vagina, cervix, or fallopian tubes, or the absolute reproductive tissue/organ weight, or the reproductive organ-to-body weight ratios from any exposed group of animals from the subchronic inhalation toxicity test conducted in accordance with paragraph (c)(2) of this section or subchronic oral toxicity test conducted in accordance with (c)(3) of this section are significantly different ( $p < 0.05$ ) from control animals.

(ii) *Reporting requirements.* (A) Reproductive toxicity tests shall be completed and final results submitted to the Agency within 41 months of the effective date of the final test rule if those criteria necessary to trigger reproductive effects testing are met.

(B) Progress reports shall be submitted to the Agency on a quarterly basis beginning 21 months after the effective date of the final rule.

(6) *Developmental toxicity*—(i) *Required testing.* Developmental toxicity tests shall be conducted with cumene by inhalation in accordance with § 798.4350 of this chapter.

(ii) *Reporting requirements.* (A) The developmental toxicity test shall be completed and final results submitted to the Agency within 1 year of the effective date of the final test rule.

(B) Progress reports shall be submitted to the Agency on a quarterly basis beginning 90 days after the effective date of the final rule.

(7) *Oncogenicity*—(i) *Required testing.* An oncogenicity test shall be conducted with cumene by inhalation in accordance with § 798.3300 of this chapter.

(ii) *Reporting requirements.* (A) The oncogenicity test shall be completed and final results submitted to the Agency within 53 months of the effective date of the final rule.

(B) Progress reports shall be submitted quarterly beginning 90 days after the effective date of the final rule.

(8) *Mutagenicity—Chromosomal aberrations*—(i) *Required testing.* (A)(1) An *in vitro* cytogenetics test shall be conducted with cumene in accordance with § 798.5375 of this chapter.

(2) *Modifications.* The following modifications to § 798.5375 of this chapter for testing cumene are required.

(i) *Cells—Type of cells used in the assay.* The requirement under

§ 798.5375(d)(3)(i) of the chapter is modified so that cumene shall be tested in Chinese hamster ovary (CHO) cells.

(ii) *Metabolic activation.* The requirement under § 798.5375(d)(4) of this chapter is modified so that the metabolic activation system shall be derived from the postmitochondrial fraction (S9) of livers from rats pretreated with Aroclor 1254.

(iii) *Control groups.* The requirement under § 798.5375(d)(5) of this chapter is modified so that the word "vehicle" is deleted.

(iv) *Test chemicals.* The requirement under § 798.5375(d)(6) of this chapter is modified to read as follows:

Cumene, in varying amounts (for example 1-1000  $\mu$ l), shall be added directly to the treatment flasks. Multiple concentrations of the test substance over a range adequate to define the response shall be tested. The highest test concentration tested with and without metabolic activation shall be that dose which shows cytotoxicity or reduced mitotic activity.

(v) *Test performance—Treatment with test substance.* The requirement under § 798.5375(e)(2) is modified to read as follows:

Cells in the exponential phase of growth shall be treated with the test substance in the presence and absence of a metabolic activation system. Cells shall be incubated on a rocker panel at 37°C to insure maximum contact between the cells and the test agent. Flasks shall be closed with a stopper with a rubber septum. Samples shall be removed with a glass-tight syringe at the beginning of the incubation period and analyzed to determine the concentration of cumene in the headspace. For experiments without activation, treatment shall continue for 10 hours (including treatment with spindle inhibitor). For experiments with activation, treatment shall be for 2 hours. At the end of the treatment period, cells shall be washed and refed with culture medium. Incubation shall continue for 8 hours (including treatment with spindle inhibitor). Alternative treatment schedules may be justified by the investigators.

(vi) *Culture harvest time.* The requirement under § 798.5375(e)(5)(i) of this chapter shall be modified to read as follows:

Multiple harvest times shall be used. If cell cycle length is changed by treatment, the fixation intervals shall be changed accordingly.

Additionally, the requirement under § 798.5375(e)(5)(ii) of this chapter shall be deleted.

(vii) *Analysis.* The requirement under § 798.5375(e)(7) of this chapter is modified by deleting the phrase "human lymphocytes."

(B) (1) An *in vivo* cytogenetics test shall be conducted with cumene in accordance with § 798.5385 of this

chapter if cumene produces a negative result in the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(8)(i)(A) of this section:

(2) *Modifications.* The following modifications to § 798.5385 of this chapter for testing cumene are required.

(i) *Animal selection—(A) Species and strain.* The requirement under § 798.5385(d)(3)(i) of this chapter is modified such that mice shall be used in the study.

(B) *Number and sex.* The requirement under § 798.5385(d)(3)(iii) of this chapter is modified so that the sentence "The use of a single sex or different number of animals should be justified" is deleted.

(ii) *Control groups—Concurrent controls.* The requirement under § 798.5385(d)(4)(i) is modified by deleting the word "vehicle."

(iii) *Test chemicals—(A) Vehicle.* The requirement under § 798.5385(d)(5)(i) of this chapter is not applicable to cumene and is, therefore, omitted.

(B) *Dose levels.* The requirement under § 798.5385(d)(5)(ii) of this chapter is modified to read as follows:

Three dose levels shall be used. The highest dose tested shall be the maximum tolerated dose, that dose producing some indication of cytotoxicity (e.g., partial inhibition of mitosis), or the highest dose attainable.

(C) *Route of administration and treatment schedule.* The requirement under § 798.5385(d)(5)(iii) and (iv) of this chapter is modified to read as follows:

Animals shall be exposed by inhalation for 8 hours/day for 5 consecutive days.

(iv) *Test performance.* The requirements under § 798.5385(e) (1), (2), (3), and (4) of this chapter shall be modified to read as follows:

(1) *Treatment.* Animals shall be treated with the test substance for 5 consecutive days at the selected doses.

(2) *Sample collection.* Bone marrow samples shall be taken 8 and 24 hours after the termination of the last treatment.

(3) *Spindle inhibitor and slide preparation.* Prior to sacrifice animals shall be injected I.P. with an appropriate spindle inhibitor (e.g., colchicine or Colcemid®) to arrest cells in C-metaphase. Immediately after sacrifice, bone marrow shall be obtained, exposed to a hypotonic solution, and fixed. The cells shall then be spread on slides and stained. Chromosome preparations shall be made following standard procedures.

(4) *Analysis.* The number of cells to be analyzed per animal shall be based upon the number of animals used, the negative control frequency, the predetermined sensitivity, and the power chosen for the test slides shall be coded for microscopic analysis.

(C) (2) A dominant-lethal assay shall be conducted with cumene in

accordance with § 798.5450 of this chapter if cumene produces a positive result in the *in vitro* or *in vivo* cytogenetics test conducted pursuant to paragraph (c) (8) (i) (A) or (B) of this chapter.

(2) *Modifications.* The following modifications to § 798.5450 of this chapter for testing cumene are required.

(i) *Description.* The requirement under § 798.5450 (d)(2) of this chapter is modified so that cumene shall be administered by inhalation for 5 consecutive days at 8 hours per day.

(ii) *Animal selection—(A) Species.* The requirement under § 798.5450 (d)(3)(i) of this chapter is modified so that mice shall be used in the study.

(B) *Number.* The requirement under § 798.5450 (d)(3)(iii) of this chapter is modified such that the number of males in each group shall be sufficient to provide 30 to 50 pregnant females per mating interval and that each male shall be mated no more than 2, and preferably to only one, female per mating interval.

(iii) *Control groups—Concurrent controls.* The requirement under § 798.5450 (d)(4)(i) of this chapter is modified such that concurrent positive and negative controls shall be used in each experiment.

(iv) *Test chemical.* The requirement under § 798.5450 (d)(5) of this chapter is modified to read as follows:

Exposure shall be by inhalation for consecutive days at 8 hours per day, concentrations shall be used. The highest concentration shall produce signs of toxicity (e.g., slightly reduced fertility) or shall be the highest attainable.

(v) *Test performance.* The requirement under § 798.5450 (e) of this chapter is modified so that during mating, females shall be left with males no longer than 7 consecutive days and that the mating period shall continue for at least 6 weeks.

(D) (1) A heritable translocation assay shall be conducted with cumene in accordance with § 798.5460 of this chapter if the results from the dominant-lethal assay conducted pursuant to paragraph (c)(8)(i)(C) of this section are positive for cumene.

(2) *Modifications.* The following modifications to § 798.5460 of this chapter for testing cumene are required.

(i) *Animal selection—Species.* The requirement under § 798.5460 (d)(3) of this chapter is modified so that the mouse shall be the test species.

(ii) *Test chemical—A Vehicle.* The requirement under § 798.5460 (d)(5)(i) of this chapter is omitted.

(B) *Route of administration.* The requirement under § 798.5460 (d)(5)(iii)

of this chapter is modified so that animals shall be exposed by inhalation.

(ii) *Reporting requirements.* (A) *Mutagenic effects—chromosomal aberration tests with cumene* shall be completed and the final results submitted to the Agency after the effective date of the rule: *In vitro* cytogenetics, 12 months; *in vivo* cytogenetics (bone marrow cytogenetics), 16 months; dominant-lethal assay, 24 months; and heritable translocation assay, 48 months.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(9) *Mutagenic effects—Gene mutation—(1) Required testing.* (A) (1) A gene mutation test in mammalian cells shall be conducted with cumene in accordance with § 798.5300 of this chapter.

(2) *Modifications.* The following modifications to § 798.5300 of this chapter for testing cumene are required.

(i) *Reference substances.* The requirement under § 798.5300(c) of this chapter is not applicable to the testing of cumene.

(ii) *Cells—Type of cells used in the assay.* The requirement under § 798.5300(d)(3)(i) of this chapter is modified such that mutation induction at the HPRT locus shall be measured in Chinese hamster ovary (CHO) cells.

(iii) *Metabolic activation.* The requirement under § 798.5300(d)(4) of this chapter is modified such that the metabolic activation system shall be derived from the postmitochondrial fraction (S9) of livers from rats pretreated with Aroclor 1254.

(iv) *Test chemicals—(A) Vehicle.* The requirement under § 798.5300(d)(6)(i) of this chapter is omitted.

(B) *Exposure concentrations.* The requirement under § 798.5300(d)(6)(ii) of this chapter is modified so that cumene, in varying amounts, (for example 1–1000 ul) shall be added directly to the treatment flasks.

(v) *Test performance.* (A) The requirement under § 798.5300(e)(1) of this chapter is modified to read as follows:

Cells should be exposed to the test substance both with and without metabolic activation. Treatment flasks shall be incubated on a rocker panel to insure maximum contact between the cells and the test agent. Incubation shall be at 37 °C for 18 hours for experiments without metabolic activation and for 5 hours for experiments with activation. Each flask shall be closed with a cap with a rubber septum. Headspace samples shall be taken at the beginning and the end of exposure period and analyzed to determine the amount of cumene in each flask.

(B) The requirement under § 798.5300(e)(2) of this chapter shall be modified to include the following:

Cells treated with metabolic activation shall be washed and incubated in culture medium for 21–28 hours prior to subculturing for variability and expression of mutant phenotype. Approximate subculture schedules (generally twice during the expression period) shall be used.

(B)(1) A *Drosophila* sex-linked recessive lethal test shall be conducted with cumene in accordance with § 798.5275 of this chapter if the results from the gene mutation in mammalian cells assay conducted pursuant to paragraph (c)(9)(i)(A) of this section are positive for cumene.

(2) *Modifications.* The following modifications to § 798.5275 of this chapter for testing cumene are required.

(i) *Test chemical—(A) Vehicle.* The requirement under § 798.5275(d)(5)(i) of this chapter is omitted.

(B) *Dose levels.* The requirement under § 798.5275(d)(5)(ii) of this chapter is modified such that a single dose of the test substance is sufficient to test. The use of two additional exposure levels is not required.

(C) *Route of administration.* The requirement under § 798.5275(d)(5)(iii) of this chapter is modified to read as follows:

Route of administration shall be by exposure to cumene vapors.

(C)(1) A mouse specific locus assay shall be conducted with cumene in accordance with § 798.5200 of this chapter if cumene produces a positive result in the sex-linked recessive lethal assay conducted pursuant to paragraph (c)(9)(i)(B) of this section.

(2) *Modifications.* The following modifications to § 798.5200 of this chapter for testing cumene are required.

(i) *Test chemical—(A) Vehicle.* The requirement under § 798.5200(d)(5)(i) of this chapter is omitted.

(B) *Dose levels.* The requirement under § 798.5200(d)(5)(ii) of this chapter is modified to read as follows:

A minimum of 2 dose levels shall be tested. The highest dose tested shall be the maximum dose tolerated without toxic effects, provided that any temporary sterility induced due to elimination of spermatogonia is of only moderate duration, as determined by a return of males to fertility within 80 days after treatment, or shall be the highest dose attainable.

(C) *Route of administration.* The requirement under § 798.5200(d)(5)(iii) of this chapter is modified to read as follows:

Animals shall be exposed to the test substance by inhalation. Exposure shall be 6 hours per day. Duration of exposure shall be

dependent upon accumulated total dose desired for each group.

(ii) *Test performance—Treatment and mating.* The requirement under § 798.5200(e)(1) of this chapter is modified such that each male shall be mated to a fresh group of 2 to 4 virgin females each week for 7 weeks, after which he shall be returned to the first group of females and rotated through the 7 sets of females for as long as he lives or until the desired number of offspring are obtained.

(ii) *Reporting requirements—(A) Mutagenic effects.* Gene mutation tests shall be conducted and the final results submitted to the Agency within the specified times after the effective date of the final rule: mammalian cells in culture assay, 12 months; *Drosophila* sex-linked recessive lethal, 24 months; and mouse specific locus, 48 months.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(d) *Environmental effects testing—(1) Aquatic acute toxicity—(i) Required testing.* Freshwater and saltwater invertebrate and vertebrate tests shall be conducted with cumene concentrations at the end of test no less than 80 percent of the initial concentrations in a flow-through aquatic environment on the following organisms:

*Daphnia magna*, to be conducted in accordance with § 797.1300 of this chapter; *Mysidopsis bahia* to be conducted in accordance with § 797.1930 of this chapter; *Pimephales promelas*, *Salmo gairdneri*, *Lepomis macrochirus*, *Menidia* and *Cyprinodon variegatus* to be conducted in accordance with § 797.1400 of this chapter.

(ii) *Reporting requirements.* (A) The acute toxicity tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(2) *Aquatic chronic toxicity—(i) Required testing.* Aquatic chronic toxicity testing shall be conducted with cumene concentrations at the end of test no less than 80 percent of the initial concentrations in a flow-through aquatic environment on (A) the freshwater vertebrate test species with the lowest LC<sub>50</sub> as determined in accordance with paragraph (d)(1) of this section, and in accordance with § 797.1600 of this chapter, (B) the Daphnid in accordance with § 797.1350 of this chapter, (C) the saltwater vertebrate species with the lowest LC<sub>50</sub> as determined in

accordance with paragraph (d)(1) of this section, in accordance with § 797.1600 of this chapter, and (D) mysid in accordance with § 797.1950 of this chapter.

(ii) *Reporting requirements.* (A) Chronic testing shall be completed and final results submitted to the Agency within 2 years of the effective date of the final test rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(e) *Chemical fate testing—(1) Biodegradation—(i) Required testing.* Biodegradation testing in water shall be conducted with cumene in accordance with the method described by Bourquin et al., *Developments in Industrial Microbiology* 18: 185-191, 1977. The method is available from the Office of the Federal Register Information Center, 11th and L Streets, NW., Washington, DC., and the OPTS Reading Room (docket no. OPTS-42075, Environmental Protection Agency, 401 M Street Washington, DC.). This incorporation by reference was approved by the Director of the Federal Register on [date]. The method is incorporated as it exists on the effective date of this rule; a notice of any change will be published in the Federal Register.

(ii) *Reporting requirements.* (A) The biodegradation test shall be completed and final results submitted to the Agency within 1 year of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90 days after the effective date of the final rule.

(2) *Volatilization—(1) Required testing.* Volatilization tests shall be conducted with cumene in accordance with the method described by Smith et al., *Env. Sci. and Tech.* 14(11): 1332-1337, 1980. The method is available from the Office of the Federal Register Information Center, 11th and L Streets, Washington, DC., and the OPTS Reading Room (docket number OPTS-42075, Environmental Protection Agency, 401 M Street SW., Washington, DC.). This incorporation by reference was approved by the Director of the Federal Register on [date]. The method is incorporated as it exists on the effective date of this rule; a notice of any change will be published in the Federal Register.

(ii) *Reporting requirements.* (A) The volatilization test shall be completed and final results submitted to the Agency within 1 year of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency quarterly beginning 90

days after the effective date of the final rule.

(Information collection requirements have been approved by the Office of Management and Budget under control number 2070-0033)

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