

201-15924A

**The Flavor and Fragrance High Production Volume  
Consortia**

**The Terpene Consortium**

**Test Plan for Aromatic Terpene Hydrocarbons**

*p*-Cymene

CAS No. 99-87-6

**FFHPVC Terpene Consortium Registration Number**

201-15924A

**Submitted to the EPA under the HPV Challenge Program by:  
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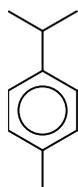
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# The Flavor and Fragrance High Production Volume Consortia

## Test Plan for Aromatic Terpene Hydrocarbons

### 1 Identity of Substances



***p*-Cymene**

**CAS No. 99-87-6**

**Synonyms:** *p*-Methylcumene  
4-Methylisopropylbenzene  
*p*-Methylisopropylbenzene  
*p*-Isopropyltoluene

## Summary of Key Hazard Data for Aromatic Terpene Hydrocarbons - *p*-Cymene

ENDPOINT	SUBSTANCE/SURROGATE /CHEMICAL CATEGORY <sup>1</sup>	VALUE/RANGE <sup>2</sup>	REFERENCE
<b>Physical Properties</b>			
<i>Vapor pressure</i>	<i>p</i> -Cymene	1.46 mm Hg (25°C)	Mackay,1992
<i>Partition Coefficient</i>	<i>p</i> -Cymene	4.1	Banerjee, 1980
<b>Environmental Fate</b>			
<i>Biodegradation</i> <sup>3</sup>	<i>p</i> -Cymene	+ (MITI)	Klopman, 1997
<b>Ecotoxicity</b>			
<i>Fish</i>	<i>p</i> -Cymene Cumene Cumene	96-hr LC50=48 mg/L, NOEC=10ppm 96-hr LC50=5.2 mg/L, NOEC=1.2ppm 96-hr LC50=18 mg/L	Heitmuller, 1980 Glickman, 1995 Yoshioka, 1993
<i>Aquatic Invertebrates</i>	<i>p</i> -Cymene	48-hr LC50=6.5 mg/L	LeBlanc,1980
<i>Aquatic Plant</i>	<i>p</i> -Cymene	72-hr EC50= 2.40 mg/L using the number of cells/mL. The 72-hr NOEC=1.40 mg/L	Ward, 2003,
<b>Human Health</b>			
<i>Repeat Dose</i> <sup>4</sup> (route)	Cumene	500 ppm (inhalation, 90d)	Cushman, 1995
<i>Reproduction (route)</i>	Cumene	1200 ppm (inhalation, 90d)	Cushman, 1995
<i>Developmental (route)</i>	Cumene	Maternal NOAEL=488 ppm (rat, inhalation, 21 days) Developmental NOAEL=1211 ppm (rat, inhalation, 21 days) Maternal NOAEL=1208 ppm (rabbit, inhalation, 21 days) Developmental NOAEL=1208 ppm (rabbit, inhalation, 21 days)	Darmer, 1977
<b>Genotoxicity<sup>5</sup></b>			
<i>In vitro</i>	Cumene	- AMS - CHO mutation - ABS	Lawlor, 1987; Yang, 1987 Putnam, 1987
<i>In vivo</i>	Cumene	- MN - MN	NTP, 1995 Khan, 1985

<sup>1</sup> Surrogate is a structurally related substance that may include a metabolic product or precursor of the named substance. Range of values may be reported for substance, surrogate or chemical category.

<sup>2</sup> Experimental value or values for a substance or group of substances in the chemical category

<sup>3</sup> not biodegradable, (-); readily biodegradable, (+); ready and ultimately biodegradable, (++)

<sup>4</sup> Value is the NOAEL or NOEL(route, duration)

<sup>5</sup> (-), no significant genotoxic potential; (=/-), equivocal evidence; (+), positive evidence of genotoxicity. AMS, Ames assay; MLA, Mouse Lymphoma assay; ABS, chromosomal aberration assay; UDS, Unscheduled DNA Synthesis; MN, Micronucleus test, SCE, Sister Chromatid Exchange assay, SLA, Sex-linked Lethal assay.



## 2 Category Analysis

### 2.1 Introduction

In October of 1999, members of the U.S. flavor and fragrance industries as well as other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia are committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The terpene consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for terpene substances under the Chemical Right-to-Know Program. Twenty-one (21) companies are current members of the Terpene Consortium. The Terpene Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and where needed, conducting additional testing. The test plan, testing, category analysis and robust summaries presented here represent the Consortium's continuing commitment to the Chemical Right-to-Know Program.

### 2.2 Background Information

This category analysis and test plan provides data for *p*-cymene and other structurally related aromatic terpene hydrocarbons. *p*-Cymene is currently permitted by the U.S. Food and Drug Administration (FDA) for direct addition to food for human consumption as a flavoring substance and is considered by the Flavor and Extract Manufacturers' Association (FEMA) Expert Panel to be "generally recognized as safe" (GRAS) for its intended use as a flavoring substance [Hall, 1960]. *p*-Cymene occurs naturally in more than 200 foods [CIVO-TNO, 2000]. Quantitative natural occurrence data indicate that oral intake of *p*-cymene occurs predominantly from consumption of foods such as butter, carrots, nutmeg, orange juice, oregano, raspberries, and lemon oil, and almost every spice [Stofberg and Grundschober, 1987]. It has been estimated that approximately, 30,000 kg of *p*-cymene is consumed annually as a natural component of butter, carrots, lemon oil,

orange juice, oregano, and raspberry [Stofberg and Grundschober, 1987]. Based on more recent and extensive natural occurrence data [CIVO-TNO, 2000] and annual volume of use data [Lucas *et al.*, 1999; Lawrence, 1985] intake of *p*-cymene from consumption of traditional food approaches 100,000 kg.

### 2.3 Structural Classification

This chemical category contains aromatic terpene hydrocarbons. *p*-Cymene is a C<sub>10</sub> terpene hydrocarbon that is recognized chemically as *p*-methylisopropylbenzene. As a terpene hydrocarbon, it is closely related in structure to another naturally occurring plant component, cumene or isopropylbenzene. Based upon the similarity in physical properties, chemical reactivity, and pharmacokinetic and metabolic data, *p*-cymene and cumene represents the chemical category designated aromatic monoterpene hydrocarbons.

### 2.4 Industrial and Biogenic Production

Crude sulfate turpentine (CST) is a complex mixture of C<sub>10</sub> monoterpene hydrocarbons composed mainly of *alpha*-pinene (60-65%), *beta*-pinene (25-35%) and other monocyclic terpenes such as limonene (2-4%) and *p*-cymene (0.2%). It has been estimated that the worldwide production of turpentine is approximately 330,000 metric tons of which almost 100,000 metric tons is gum turpentine and the bulk of the remainder is sulphate turpentine [National Resources Institute, 1995]. In 1977, the annual United States production of CST and wood turpentine was reported to be 92,750 and 9,150 tons, respectively [McKibben, 1979]. The annual amount of *p*-cymene present in CST used in the United States is approximately 20 metric tons (20,000 kg).

Level-three fugacity calculations indicate that the environmental distribution of turpentine and its components is essentially entirely into the air [Mackay, 1996a, 1996b]. If it were conservatively assumed that through the various industrial processes approximately 2% is lost, the total annual worldwide emission of *p*-cymene from turpentine would be 400 kg. This can be compared with the biogenic emissions into the air discussed below.

As an important plant terpene hydrocarbon, *p*-cymene is an important component of the earth's atmosphere [Guenther *et al.*, 2000]. *p*-Cymene is relatively volatile and widely distributed in plants, especially conifers [Helmig *et al.*, 1999a]. Measurements of emissions from sixty-three vegetation species in this study reported the occurrence of *p*-cymene so commonly as to lead to the conclusion that *p*-cymene is practically ubiquitous in plants. In determining the impact on the environment of the industrial production and use *p*-cymene, it is also important to examine the impact as a result of emissions from biogenic sources [Guenther *et al.*, 2000].

Landscape flux potentials of *p*-cymene have been measured in three quite varied sites (an urban forest, a mixed deciduous and coniferous forest, and a mixed shrub oak forest) in the U.S. from each of 63 species of trees [Helmig *et al.*, 1999a, 1999b]. *p*-Cymene was detected in a substantial proportion of the species measured with fluxes ranging from 0.1 to 7  $\mu\text{gChr}^{-1}\text{gdw}^{-1}$  ( $\mu\text{g}$  carbon per hour per gram dry weight) [Helmig *et al.*, 1999a]. These fluxes have been used to calculate average hourly fluxes for each substance at each site [Helmig *et al.*, 1999b]. For *p*-cymene these were 88, 54 and 8  $\mu\text{gCm}^{-2}\text{hr}^{-1}$  ( $\mu\text{g}$  carbon per  $\text{m}^2$  per hour). These emissions of *p*-cymene amounted to 4.4, 1.2 and less than 0.2% of the total volatile organic compounds (VOC) emissions for each of the three sites, respectively. These figures can be used to estimate the total global emissions of these materials (see below).

In a recent review of natural emissions of volatile compounds [Guenther *et al.*, 2000] it was estimated that in North America the total annual emission of for *p*-cymene was 1.1 million metric tons. The total global emissions of *p*-cymene can be estimated in two ways. The total annual global emission of VOCs has been estimated as 1150 million metric tons [Guenther *et al.*, 1995]. If the same percentage of total emissions of VOCs as has been measured over 3 different forest types, 4.4, 1.2 and less than 0.2% (average = 1.9%) are used, it can be estimated that the total annual global emissions for *p*-cymene would be approximately 22 million metric tons. On the other hand, if the average rates of emission of *p*-cymene ( $50 \mu\text{gCm}^{-2}\text{hr}^{-1}$ ) (average of 88, 54 and  $8 \mu\text{gCm}^{-2}\text{hr}^{-1}$ ), *beta*-pinene ( $22 \mu\text{gCm}^{-2}\text{hr}^{-1}$ ) and camphene ( $58 \mu\text{gCm}^{-2}\text{hr}^{-1}$ ) are applied to the latest global forest coverage estimates of 3.9 billion hectares [Food and Agriculture Organization, 2000],

then annual global biogenic emissions of *p*-cymene is approximately 17.2 million metric tons can be calculated.

Based on the above estimates, it can be concluded that total annual atmospheric emission of *p*-cymene is predominantly from biogenic sources (17,200,000 kg/yr of biogenic emissions *versus* 400 kg/yr of anthropogenic emissions). The relative contribution from biogenic and industrial sources can be represented by a global emission ratio (GER = biogenic emission/industrial emission). In the case of *p*-cymene, the GER would exceed 1,000, suggesting that biogenic emissions far exceed man-made emissions. As a result, humans are unavoidably exposed to the naturally occurring aromatic terpene hydrocarbon *p*-cymene.

## 2.5 Metabolism of *p*-Cymene and Cumene

The metabolism of *p*-cymene has been studied *in vivo* using rats, rabbits, guinea pigs, brushtail possums, greater gliders (*Petauroides volans*), and ringtail possums [Boyle *et al.*, 1999; Matsumoto *et al.*, 1992; Walde *et al.*, 1983; Bakke and Scheline, 1970]. The pharmacokinetics, metabolism and distribution of cumene has been studied in rabbits and rats [Research Triangle Institute, 1989; Robinson *et al.*, 1954; van Doorn *et al.*, 1981]. In general, the studies indicate that *p*-cymene (*p*-methylisopropylbenzene) or cumene (isopropylbenzene) is rapidly absorbed by oral or inhalation routes. They undergo oxidation (hydroxylation) of the side chain isopropyl substituent and, in the case of *p*-cymene, the methyl substituent to yield polar oxygenated metabolites. These metabolites are either excreted unchanged in the urine or undergo Phase II conjugation with glucuronic acid and/or glycine followed by excretion in the urine. Unchanged *p*-cymene or cumene were not detected in the urine or feces.

A dose level of 33 mg/kg bw of [<sup>14</sup>C]-cumene given to male and female Fischer F/344 rats by either a single intravenous injection, a single oral gavage, or repeated oral gavage for 8 days is rapidly absorbed from the stomach. Rats exposed to atmospheres containing 100, 500 or 1500 ppm for 6 hours show detectable levels of [<sup>14</sup>C]-cumene within 5 minutes [Research Triangle Institute, 1989]. Tissue distribution data (tissue to blood

ratios) indicate that the lipophilic substance is distributed mainly to adipose tissue and those organs responsible for the metabolism (liver) and excretion (kidneys) of [<sup>14</sup>C]-cumene. Based on a two compartment open pharmacokinetic model, the distribution half-life of [<sup>14</sup>C]-cumene is 0.21 and 0.27 hours for male and female rats, respectively, given an intravenous dose of 33 mg/kg bw. The elimination half-life was calculated to be 8.6 and 7.3 hours for males and females, respectively [Research Triangle Institute, 1989].

Regardless of the route of administration, [<sup>14</sup>C]-cumene is eliminated predominantly in the urine. At lower oral dose levels or lower levels of inhalation exposure, a minimum of 70% is excreted in the urine. Relatively little radioactivity is present in expired air or in the feces at low dose levels. Overall dose levels and routes of administration (oral gavage or inhalation) greater than 50% of the urinary metabolites is accounted for by free or conjugated (glucuronide or sulfate) 2-phenyl-2-propanol, the product of benzylic hydroxylation. Smaller amounts of free or conjugated 2-phenyl-1,2-propanediol and 2-phenylpropionic acid are also present in the urine.

Rabbits given a 1720 mg dose of cumene excrete mainly 2-phenyl-2-propanol (40%) and lesser amounts of 2-phenyl-1-propanol (25%) and 2-phenylpropionic acid (25%) in the urine [Robinson *et al.*, 1954]. 2-Phenyl-2-propanol, 2-phenyl-1-propanol and 2-phenylpropionic acid were detected when 200 mg/L cumene was incubated with freshly prepared rabbit liver soluble enzyme preparation [Chakraborty and Smith, 1967].

The stereochemical metabolism of cumene has been studied in rabbits. Each of six rabbits were administered a daily 2000 mg dose suspended in 20 ml of water and Tween 80 by stomach tube. The dosing was repeated for two additional days. Total dose for six rabbits were 30 grams. Cumene urinary metabolites included 2-phenyl-1-propanol (90.3% in the R-(+) form), and 2-phenylpropanoic acid (99 % in the (S)-(+ form) formed by the successive oxidation of the methyl group of the isopropyl constituent. Additional oxidation of the benzylic position of cumene yielded 2-hydroxy-2-phenylpropanoic acid, 81% was present in the R-(-) form (Ishida and Matsumoto, 1992).

Humans exhibit normal background levels of cumene in exhaled air. Levels of 0.35 ng/L of cumene have been measured in the expired air of normal healthy urban men and women [Conkle *et al.*, 1975; Krotoszynski *et al.*, 1977]. Mean environmental levels of 6 ng/L of cumene resulted in mean alveolar, blood, and urine levels of 3, 199, and 202 ng/L in the 49 volunteers [Parbellini *et al.*, 1988]. A comparison of alveolar and blood cumene levels in hospital (58) and chemical workers (28) exposed to environmental concentrations of 6.4 and 10.7 ng/L showed no significant difference in alveolar cumene concentrations. Alveolar cumene retention ranged from 70% in hospital workers to 78% in chemical workers. Lower blood cumene levels in hospital workers were correlated with lower environmental concentrations [Brugnone *et al.*, 1989].

Humans (5 males and 5 females/group) exposed to an atmosphere containing 49, 98, or 147 ppm cumene for 7 hours showed 64% absorption at 0.5 hours and 45% at 7 hours. Maximum excretion is observed at 6 to 8 hours and is essentially complete at 48 hours. Approximately 35% of the dose inhaled was excreted as 2-phenyl-2-propanol [Senczuk and Litewka, 1976].

In conclusion, cumene is rapidly absorbed by oral administration or inhalation exposure. Following absorption, the ring substituent is oxidized to yield aromatic alcohol and carboxylic acid metabolites that are excreted free or conjugated in the urine. There is no evidence that cumene accumulates in the body even following high dose or repeat dose exposure.

Like cumene, *p*-cymene participates in the same metabolic pathways in a variety of species (rat, brushtail possum, greater glider and ringtail possum) [Boyle *et al.*, 1999]. In the rat, the two principle urinary metabolites are formed by benzylic oxidation. Forty-eight (48) hours after an oral dose, 2-*p*-tolylpropan-2-ol (34-39% of recovered dose) and 2-*p*-carboxyphenylpropan-2-ol (19-23% of recovered dose) are present in the urine. The former metabolite is the product of benzylic hydroxylation of the isopropyl substituent while the latter metabolite is the product of benzylic hydroxylation of the isopropyl substituent and the methyl substituent. 2-*p*-Carboxyphenylpropan-2-ol is the principle urinary metabolite in the ringtail possum (36% of recovered dose) and 2-*p*-

carboxyphenylpropan-1-ol is the principal urinary metabolite in the brushtail possum and greater glider (56-59% and 42% of recovered dose for brushtail possum and greater glider, respectively). The ringtail possum and greater glider also excrete 2-*p*-carboxyphenylpropionic acid as another principal urinary metabolite (41 and 46% of recovered dose, respectively). The authors noted that rats and brushtail possums excreted metabolites containing 2, 3, 4 oxygen atoms added through oxidation of *p*-cymene; whereas, greater gliders and ringtail possums, which are mammals accustomed to consuming a diet naturally high in terpenes, excreted metabolites containing 3 or 4 oxygen atoms, suggesting a more efficient oxidation system in the latter species.

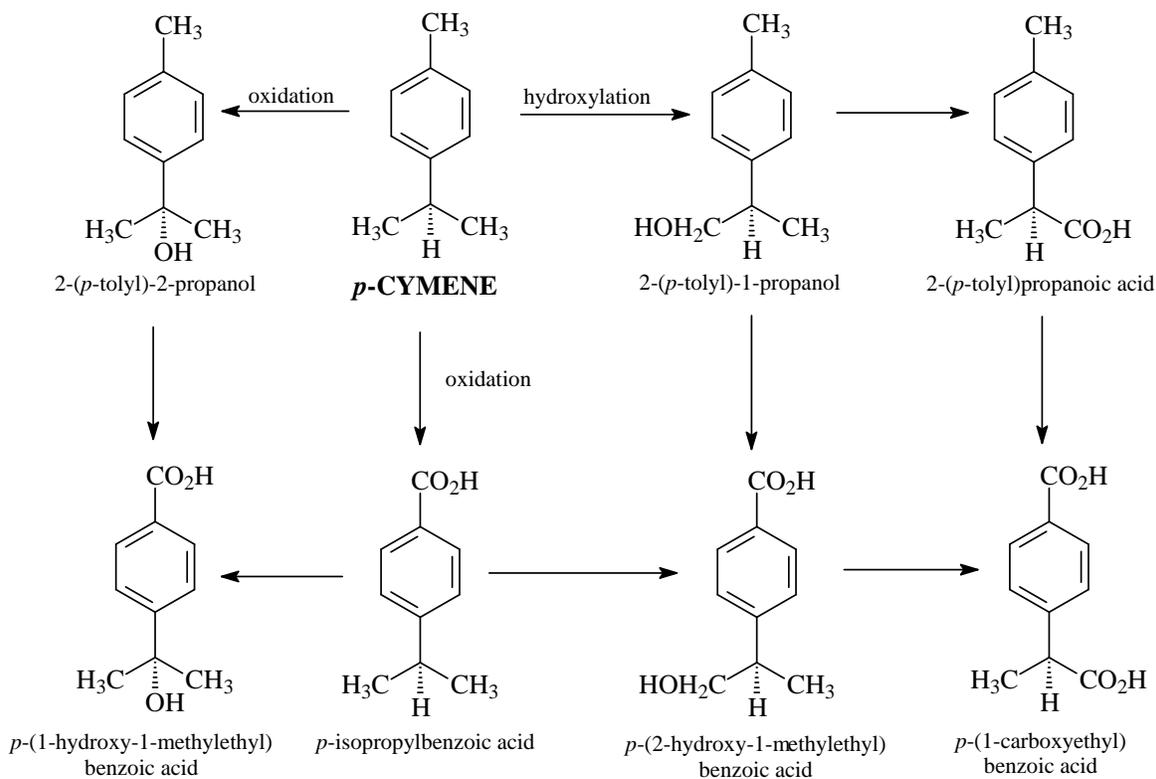
Both the greater glider and ringtail possum do not excrete detectable amounts of conjugated metabolites. In the rat, a larger percentage of metabolites were conjugated (34.2% free *versus* 65.8% conjugated) when *p*-cymene was orally administered at 0.37 mmol/kg bw (50 mg/kg bw) [Boyle *et al.*, 1999]. However, the percent conjugated was significantly reduced (81.9% free *versus* 18.1% conjugated) when a higher dose of *p*-cymene was administered (1.49 mmol/kg bw [200 mg/kg bw]). In the brushtail possum, percent conjugation was comparable between doses (0.37 mmol/kg bw: 59.9% free *versus* 40.1% conjugated; 1.49 mmol/kg bw: 44.3% free *versus* 55.7% conjugated).

The metabolism of *p*-cymene has been studied in rats and guinea pigs. From 60 to 80 % of an oral or inhaled dose of 100 mg/kg bw of *p*-cymene is excreted in the urine within 48 hours [Walde *et al.*, 1983]. As in other studies with cumene and *p*-cymene, the principal metabolites involve oxidation of the side chain substituents. Following oral administration, the principle urinary metabolites were *p*-isopropylbenzoic acid (19%) and 2-*p*-carboxyphenylpropionic acid (16%). Following inhalation exposure, the primary urinary metabolite was 2-*p*-carboxyphenylpropionic acid (15%); *p*-isopropylbenzoic acid was a minor metabolite (9%). Other urinary metabolites in the rat included 2-*p*-tolylpropan-1-ol (oral: 8%; inhalation: 6%), 2-*p*-carboxyphenylpropan-2-ol (oral and inhalation: 9%), 2-*p*-(hydroxymethyl)phenylpropionic acid (oral: 4%; inhalation: 7%), 2-*p*-carboxyphenylpropan-1-ol (oral: 11%; inhalation: 9%), and *p*-isopropylbenzoylglycine (oral: 2%; inhalation: 3%).

In guinea pigs, similar urinary metabolites were identified. The primary urinary metabolite from both oral and inhalation exposure was *p*-isopropylbenzoylglycine (31%) indicating that conjugation with glycine was more prevalent in guinea pigs than in rats. In addition, where no ring hydroxylation of *p*-cymene was reported in rats [Bakke and Scheline, 1970; Walde *et al.*, 1983], trace amounts of carvacrol and hydroxycarvacrol were detected in guinea pigs following oral and inhalation exposure [Walde *et al.*, 1983].

The metabolism of *p*-cymene also was studied in rabbits following oral administration of approximately 1000 mg/kg of *p*-cymene to four (2M/2F) white rabbits [Matsumoto *et al.*, 1992]. Seven (7) metabolites were isolated from urine collected for 3 days after dosing. The oxidation of *p*-cymene occurs stereoselectively. Oxidation of the methyl group of the isopropyl substituent yields 2-(*p*-tolyl)-1-propanol in an R/S ratio of 65:35. The (R)-alcohol is then further oxidized to (R)-2-(*p*-tolyl)propanoic acid which undergoes complete stereochemical inversion to (S)-2-(*p*-tolyl)propanoic acid. Subsequently, the alcohol or acid metabolite may undergo oxidation of the tolyl methyl group to yield the corresponding hydroxy acid and diacid, respectively. If the tolyl methyl is oxidized before the isopropyl group, no stereochemical inversion is observed when the propanol is converted to the propanoic acid derivative. Based on the observed stereochemical changes, it is evident that *omega*-hydroxylation of *p*-cymene or *p*-isopropylbenzoic acid metabolite occurs preferentially at the *pro-S*-methyl group of the isopropyl substituent. The metabolic pathways of *p*-cymene in rabbits are shown in Figure 1.

**Figure 1 - Proposed Metabolic Pathways of *p*-cymene in Rabbits**



## 2.6 Summary for Category Analysis

*p*-Cymene, a natural component of the diet, and the structurally related homologue cumene are readily absorbed, metabolized and rapidly excreted *via* the urine as free and conjugated polar metabolites. The physiochemical properties and low toxic potential of *p*-cymene and cumene are consistent with their known reactivity and metabolic fate.

## 3 Test Plan

### 3.1 Chemical and Physical Properties

#### Melting Point

The melting point of *p*-cymene has been reported to be  $-67.94\text{ }^{\circ}\text{C}$  [Merck, 1996; CRC, 1986] and  $-68\text{ }^{\circ}\text{C}$  [International Programme on Chemical Safety & The Commission of the European Communities, 1993]. Based on these reported values the melting point of *p*-cymene is  $-68\text{ }^{\circ}\text{C}$ .

#### Boiling Point

The measured boiling point of *p*-cymene has been reported to be  $177\text{ }^{\circ}\text{C}$  [Furnas and Hine, 1958] and between  $176$  and  $177.1\text{ }^{\circ}\text{C}$  in several standard references [International Programme on Chemical Safety & The Commission of the European Communities, 1993; FMA; CRC, 1986; Merck, 1996]. Based on the consistency of these values, the boiling point of *p*-cymene is  $176\text{-}177\text{ }^{\circ}\text{C}$ .

#### Vapor Pressure

The vapor pressure of *p*-cymene has been reported to be  $1.50\text{ mm Hg}$  ( $200\text{ Pa}$ ) at  $20\text{ }^{\circ}\text{C}$  [International Programme on Chemical Safety & The Commission of the European Communities, 1993] and  $1.46\text{ mm Hg}$  ( $194\text{ Pa}$ ) at  $25\text{ }^{\circ}\text{C}$  [Mackay *et al.*, 1982]. The calculated vapor pressure for *p*-cymene according to the MPBPWIN program was  $1.11\text{ mm Hg}$  ( $148\text{ Pa}$ ) at  $25^{\circ}\text{C}$  [MPBPVP EPI Suite, 2000]. Based on these data the vapor pressure is approximately  $1.50\text{ mm Hg}$  ( $200\text{ Pa}$ ) at  $20\text{ }^{\circ}\text{C}$ .

#### Octanol/Water Partition Coefficients

The octanol/water partition coefficient for *p*-cymene was measured using GC analysis. The log KOW was reported to be  $4.1$  at  $23\pm 1.5\text{ }^{\circ}\text{C}$  [Banerjee *et al.*, 1980]. Log KOW was also calculated resulting in values of  $4.0$  [KOWWIN EPI Suite, 2000] and  $4.19$

[Interactive Analysis LogP and LogW Predictor]. The close agreement between measured and calculated values indicated that the log KOW for *p*-cymene is 4.1.

The calculated log KOW of cumene that is expected to be more water soluble than *p*-cymene is 3.63 [Mackay *et al.*, 1980].

### **Water Solubility**

The water solubility of *p*-cymene was measured using GC analysis and reported to be 23.35 mg/L at 25°C in distilled water [Banerjee *et al.*, 1980] and 20 mg/L at 25 °C [International Programme on Chemical Safety & The Commission of the European Communities, 1993]. Water solubility was also calculated resulting in a value of 11.675 mg/L [Interactive Analysis LogP and LogW Predictor]. Water solubility of cumene in synthetic seawater (500 mg/L at 25°C) is expected given the log KOW of this more polar substance (log KOW=3.63) [Price *et al.*, 1974].

#### **3.1.6 New Testing Required**

None.

### **3.2 Environmental Fate and Pathways**

#### **Photodegradation**

The calculated half-life value for *p*-cymene has been reported to be 15.03 hours [AOPWIN EPI Suite, 2000]. The fact that *p*-cymene contains a reactive benzylic hydrogen capable of reaction with hydroxyl and peroxy radicals supports the calculated short half-life.

#### **Stability In Water**

No hydrolysis is possible for this substance. Terpene hydrocarbons, lacking any functional group capable of hydrolysis are expected to be very stable in aqueous solution.

## Biodegradation

The biodegradation potential of substituted aromatic hydrocarbons was performed using a MITI protocol (Klopman and u, 1997). Biodegradation of the homologous series of *p*-cymene, ethylbenzene, and methylbenzene in the MITI test was 88, 39, and 100%, respectively, after 28 days. The result for *p*-cymene is similar to that for the structurally related substance cumene. Cumene, was tested for biodegradation in freshwater and synthetic seawater using a standard biochemical oxygen demand (BOD) procedure. Percent bio-oxidation was the difference between the cumulative oxygen uptake for oxidation of the carbonaceous material in the test sample bottle and the cumulative oxygen uptake in a blank. In freshwater, cumene was considered by the authors to be inherently biodegradable showing 70% bio-oxidation within 20 days. Conversely, in synthetic seawater, cumene was considered not biodegradable showing virtually no bio-oxidation (2%) after 20 days [Price *et al.*, 1974].

## Fugacity

Transport and distribution in the environment were modeled using Level III Fugacity-based Environmental Equilibrium Partitioning Model [Mackay, 1991a, 1996b] through the EPA EPI suite 2000 program. The input parameters used were molecular weight, measured melting point (-67.94 °C), vapor pressure (1.46mm Hg), water solubility (23.4 mg/L), and log KOW (4.10).

The model predicts that *p*-cymene is distributed mainly to the soil (65.3%), but also is distributed to water (27.7%) and, to some extent, air (4.73%) and sediment (2.22%).

The significance of these calculations must be evaluated in the context that *p*-cymene is a product of plant and animal biosynthesis and is, therefore, ubiquitous in the environment. The model does not account for the influence of biogenic production on partitioning in the environment nor does it take into account any biodegradation.

## New Testing Required

- No additional studies are recommended.

### 3.3 Ecotoxicity

#### Acute Toxicity to Fish

Suitable measured and calculated fish LC50s are available for *p*-cymene and its structural relative, cumene. Sheepshead minnows were used to determine LC50 of *p*-cymene at time intervals up to 96 hours in a static test [Heitmuller *et al.*, 1981]. At 24, 48, 72, and 96 hours, the LC50s were 56, 50, 48, and 48 ppm, respectively, with a no-observed-effect concentration (NOEC) of 10 ppm. The calculated 96-hour LC50 was reported to be 1.056 mg/L (neutral organics) and 0.668 mg/L (SW) and 14-day LC50 was reported to be 2.671 mg/L [ECOSAR EPI Suite, 2000].

Sheepshead minnows were used to calculate LC50 of cumene at time intervals up to 96 hours in a flow-through system [Glickman *et al.*, 1995]. At 24, 48, 72, and 96 hours, the LC50s were 8.1, 5.7, 4.8, and 4.7 mg/L, respectively, with a NOEC of less than 2.9 mg/L. Similarly, LC50s were calculated using rainbow trout. At 24, 48, 72, and 96 hours, the LC50s were 6.4, 5.8, 5.2, and 4.8 mg/L, respectively, with a NOEC of 1.9 mg/L. The authors concluded that cumene is moderately toxic to fish but cumene's high volatility would limit its toxicological impact to an aquatic environment. The 96-hour LC50 of cumene in red killifish was determined to be 18 mg/L following OECD Guideline 203 [Yoshioka and Ose, 1993].

Given the current database of information, it will not be necessary to perform additional acute fish toxicity tests for this endpoint.

#### Acute Toxicity to Aquatic Invertebrates

Measured and calculated aquatic invertebrate LC50s are available for *p*-cymene and its structural relative, cumene. In *Daphnia magna*, the LC50 of *p*-cymene was determined to be 9.4 and 6.5 mg/L at 24 and 48 hours, respectively, with a NOEC of less than 4.6 mg/L in a static test [LeBlanc, 1980]. In addition, calculated values were reported for 48-hour LC50 of 1.309 mg/L and a 16-day EC50 of 0.168 mg/L [ECOSAR EPI Suite, 2000]. A calculated 96-hour LC50 of 0.068 mg/L was reported for mysid shrimp [ECOSAR EPI Suite, 2000].

Mysid shrimp were used to determine LC50 of cumene at time intervals up to 96 hours in a flow-through system [Glickman *et al.*, 1995]. At 24, 48, 72, and 96 hours, the LC50 were greater than 2.0, 1.6, 1.4, and 1.3 mg/L, respectively, with a NOEC of 0.68 mg/L. Similarly, LC50 were calculated using *Daphnia magna*. At 24 and 48 hours, the LC50 were 4.8 and 4.0 mg/L, respectively, with a NOEC of 1.5 mg/L. The authors concluded that cumene is moderately toxic to invertebrates but cumene's high volatility would limit its toxicological impact to an aquatic environment. The median tolerance limit of cumene was determined to be 110 mg/L in a static test using brine shrimp (*Artemia salina*) over a period of 24 hours [Price *et al.*, 1974].

Given the current database of information, it will not be necessary to perform additional acute toxicity tests for this endpoint.

### **Acute Toxicity to Aquatic Plants**

A calculated 96-hour EC50 of 0.923 mg/L was reported for green algae [ECOSAR EPI Suite, 2000]. In an experimental algal study (Ward, 2003), the acute toxicity of *p*-cymene measured as a 50% decrease in growth and reproduction of freshwater algae, *Selenastrum capricornutum*, was estimated to be 72 hr EC50=4.03 mg/L based on average specific growth rate; 72-hr EC50=2.40 mg/L calculated using the number of cells/mL; and 72-hr EC50=2.01 mg/L using the area under the growth curve. The 72-hr NOEC=1.40 mg/L.

### **New Testing Required**

No additional tests are recommended for the three ecotoxicity endpoints

## **3.4 Human Health Toxicity**

### **Acute Toxicity**

As described below, mammalian LD50 for *p*-cymene have shown it to have low toxic potential. Similar studies with cumene have concurred with these results. Oral LD50s in rats of 2,990-4,750 mg/kg bw and a dermal LD50 in rabbits of greater than 5,000 mg/kg bw have been reported [MacDonald, 1961, 1962a; Jenner *et al.*, 1964; Moreno, 1973; Smyth *et al.*, 1951].

Inhaled *p*-cymene at an atmospheric concentration of 9.7 mg/L over a period of 5 hours was reported to be irritating to rats and guinea pigs [MacDonald, 1962b]. Within 15 (rats) and 90 (guinea pigs) minutes, transient clonic convulsions were reported. However, these effects were fully reversible by the following morning. In mice, this same exposure scenario resulted in similar effects; however, two mice died during exposure and the third mouse died during the night [MacDonald, 1962b]. Necropsies of the mice showed hyperemic lungs, mottled liver, and pale kidneys.

The oral LD50 of cumene in rats was reported to be 1,400-2,910 mg/kg bw and the dermal LD50 in rabbits was reported to be 10,545 mg/kg bw [Smyth *et al.*, 1951; Wolf *et al.*, 1956]. In an inhalation study, rats were exposed to an atmosphere containing liquid cumene suspended at a concentration of 8,000 mg/L for 4 hours. Animals were observed for 14 days. Four (4) of 6 rats died [Smyth *et al.*, 1951].

Single exposure to inhaled cumene at concentrations up to 1,200 ppm for 6 hours was reported to produce reversible alterations (within 24 hours post-exposure) in the functional observational battery one hour post-exposure [Cushman *et al.*, 1995].

Rats exposed to atmospheres containing 5,000 to 10,000 ppm cumene for four exposures of 30, 20, 45, and 50 minutes duration resulted in local irritation, depression, and quivering or twitching [Furnas and Hine, 1958]. At necropsy, no gross or microscopic effects were reported other than those associated with respiratory irritation.

Given the numerous studies available, additional acute toxicity tests in mammals are not recommended.

### ***In vitro* and *In vivo* Genotoxicity**

#### *3.4.1.1 In vitro*

*p*-Cymene produced no increase in the frequency of mutations when tested in Sd-4-73 *Escherichia coli* [Szybalski, 1958]. Concentrations up to 2,000 µg/plate of cumene did not increase the number of revertants in *Salmonella typhimurium* strains (TA97, TA98,

TA100, TA1535, and TA1537) in the Ames preincubation assay with or without metabolic activation [NTP unpublished results (e); Lawlor and Wagner, 1987].

In cultured mammalian cells, cumene showed no consistent evidence of mutagenicity or genotoxicity at non-cytotoxic concentrations. Cumene did not increase mutations in the CHO/HGPRT test with or without metabolic activation at concentrations of up to 175 µg cumene/plate [Papciak, 1985; Yang, 1987]. Cultured rat hepatocytes treated with cumene up to 5,000 µg/ml showed cytotoxicity at concentrations of 128 µg/ml and higher and unscheduled DNA synthesis was reported at 16 µg/ml; however, the results between triplicates were highly variable and inconsistent [Brecher, 1984a]. In another study, cultured mouse fibroblasts treated with up to 90 µg/ml of cumene showed cytotoxicity at concentrations of 60 µg/ml and higher [Brecher, 1984b]. At non-cytotoxic concentrations, no increase in cell transformations was reported. No evidence of an increase in the incidence of chromosomal aberration was reported when Chinese hamster ovary cells were incubated with concentrations of cumene up to and including 156 µg/ml with or without metabolic activation [Putnam, 1987].

#### 3.4.1.2 *In vivo*

In a study conducted by the National Toxicology Program, male F344 rats were intraperitoneally injected with cumene and bone marrow cells were sampled 24 hours following treatment [NTP, 1994]. The authors reported a positive polychromatic erythrocyte trend of  $P = 0.011$ ; however, minimal dose-response was observed and deaths occurred at the highest dose of 2500 mg/kg bw. Since weakly positive results were reported in this study, a follow-up study was conducted using similar doses [NTP, 1995]. A positive polychromatic erythrocyte trend of  $P = 0.085$  also was reported and the authors concluded that cumene weakly induced micronuclei in F344 rats. Again, a lack of dose-response was observed. Conversely, when cumene was administered to Swiss mice by gavage at doses of up to 1,000 mg/kg bw/day for 2 consecutive days, examination of bone marrow cells showed no induction of micronuclei in either males or females [Khan, 1985].

### 3.4.1.3 Conclusions

The genotoxicity database on *p*-cymene and cumene shows no mutagenic potential in the Ames assay. In cytogenetic assays, there is no evidence of a genotoxic potential *in vitro*. In whole animals, the genotoxicity results for cumene are mixed showing weakly positive results in micronuclei induction in rats, but no evidence of genotoxicity in mice. Based on these results no additional genotoxicity tests are recommended.

## Repeat Dose Toxicity

### 3.4.1.4 Subacute Studies

Groups of 7 to 12 male rats were exposed to 0, 50, or 250 ppm of *p*-cymene for 6 hours/day, 5 days/week for 4 weeks with an 8-week recovery period [Lam *et al.*, 1996]. This study was designed to specifically examine the neurotoxic potential of inhaled *p*-cymene. However, a variety of general toxicity parameters were monitored. After the 8-week recovery period, rats were decapitated and the cerebellum was removed, weighed, and homogenized. The remainder of the brain was also weighed and homogenized. Synaptosomes were prepared using gradient centrifugation. The 2 homogenates and the synaptosomes were processed for neurotransmitter analyses (i.e., determination of noradrenaline [NA], dopamine [DA], and 5-hydroxytryptamine [5-HT]), and aliquots were taken for determination of enzyme activities (lactate dehydrogenase [LDH], acetylcholinesterase [AChE], and butylcholinesterase [BuChE]) and protein analysis.

The authors reported that there was no overt toxicity in the treated rats and no effect on body weight or terminal weight of the brain, cerebellum or whole brain. There was also no effect on regional enzyme activities, regional protein synthesis or regional neurotransmitter concentrations. The relative yield and total amount of synaptosomal protein were significantly reduced at 50 and 250 ppm in a concentration-related manner. The relative activity of LDH, AChE, and BuChE were significantly increased at 50 and 250 ppm. Total activity of LDH, AChE and BuChE were unaffected. In relation to the cytoplasmic marker (LDH), the relative synaptosomal choline esterase activities (AChE and BuChE) and synaptosomal concentrations of NA, DA, and 5-HT were unaffected by

*p*-cymene exposure. Relative to synaptosomal protein, relative NA and DA concentrations were significantly increased at 50 and 250 ppm, whereas 5-HT was unaffected. Conversely, the total amount of NA and DA in the synaptosomal fraction was unaffected by treatment, whereas, the total amount of 5-HT was significantly decreased at 250 ppm. At up to 250 ppm, *p*-cymene exposure did not produce signs of overt toxicity in male rats exposed for 4 weeks with an 8-week recovery period. Although, changes were reported in the synaptosomal fraction of homogenized brain, no generally accepted test system has been established for predicting neurotoxicity based on these measured parameters. Therefore, the results of the above measurements are not indicative of toxicity.

Cumene has been tested by the National Toxicology Program (NTP) in both rats and mice. Animals were exposed to up to 4,000 ppm cumene by whole-body inhalation for 12-13 days over a period of 16-17 days [NTP unpublished results (c, d)]. In rats, all animals died at 4,000 ppm, and about half the animals died at the next exposure concentration (2,000 ppm). Varying degrees of ataxia were reported in surviving rats exposed to 500 to 2,000 ppm cumene. Increased relative liver and kidney weights were reported in rats exposed to cumene. In exposed male rats, hyaline droplets in the renal cortical tubules were reported. At 2,000 ppm, superlative inflammation of the lung was reported in 40% of the rats. In mice, all animals died at the 2 highest exposures (2,000 and 4,000 ppm). At 1,000 ppm, 80% of the female mice died and male mice showed varying degrees of ataxia. Increased relative liver and kidney weights were reported in mice exposed to cumene. Decreased thymus weight was reported in male mice exposed to 1,000 ppm of cumene. No histopathological findings accompanied the organ weight changes. A NOAEL of 1,000 ppm was determined for female rats and male mice and a NOAEL of 500 ppm was determined for female mice based on mortality and histopathological findings.

#### *3.4.1.5 Subchronic Studies*

In a continuation of the NTP studies, rats and mice were exposed to concentrations of up to 1,000 ppm cumene by whole-body inhalation 6 hours/day, 5 days/week for up to 13

weeks [NTP unpublished results (a, b)]. All animals survived to study termination with the exception that 80% of female mice exposed to 1,000 ppm of cumene died. In rats, reported effects included mild ataxia in high-exposure animals, increased relative liver and kidney weights, decreased alanine aminotransferase, and increased hyaline droplet formation and tubular regeneration in renal cortical tubules and granular casts in tubules in the corticomedullary junction area of male rat kidneys. The renal lesions reported in the male rats were considered by the conducting laboratory to be similar to those "resulting from exposure to chemicals that induce accumulation of *alpha*-2 $\mu$ -globulin in renal cortical tubular cytoplasm". Other terpene hydrocarbons including limonene and camphene have been reported to produce *alpha*-2 $\mu$ -globulin-induced nephrotoxicity in male Fisher 344 rats. This phenomenon is specific to Fisher 344 male rats and has not been observed in other sexes or strains of rats, other rodents, nor in humans [EPA, 1991a]. In mice, the reported effects included transient ataxia, decreased final body weight of male mice at the 2 highest exposures, increased relative liver weight, centrilobular hypertrophy of the liver in all high-dose males, and squamous hyperplasia and inflammation of the mucosa of the forestomach in females exposed to 500 and 1,000 ppm. A NOAEL of 125 and 250 ppm was determined for rats and mice, respectively, based on serum chemistry, organ weight changes, and histopathological findings.

Two inhalation studies were conducted on cumene using rats. In the first study, rats were exposed to 100 to 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days. The second study included a 4-week recovery period. No animals died during the 13-week study. Reported effects predominantly in the two highest exposure levels (500 and 1,000 ppm) included ataxia, hypoactivity, decreased total motor activity in males, increased water consumption, increased leukocytes and platelets, increased lymphocytes (males only), decreased blood glucose (females only), increased total protein, albumin, globulin, calcium and inorganic phosphorus, increased absolute and relative liver, kidney, and adrenal gland weights, increased tubular proteinosis, interstitial nephritis and tubular cell hyperplasia/hypertrophy in kidneys of males, and increased hyaline droplet formation within the proximal tubules of males. In a review of these data performed by the Environmental Protection Agency (EPA) in 1997, it was concluded that the kidney

effects were related to *alpha*-2 $\mu$ -globulin-induced nephrotoxicity. The changes in liver weight were considered by EPA not to be toxicologically significant because they were not accompanied by an evidence of histopathology. It was also concluded that the NOAEL in the study is 496 ppm and the LOAEL is 1,202 ppm. The blood effects reported were also considered irrelevant since they were within normal ranges [Cushman *et al.*, 1995].

Other inhalation studies on cumene in a variety of animal species: rats, guinea pigs, dogs and monkeys have been conducted [Jenkins *et al.*, 1970]. In these studies, cumene exposure lasted from 6 weeks (244 ppm cumene) to 90 days (up to 30 ppm cumene) and no statistical analysis was conducted. The only notable effect in the rat studies was an increase in the number of leukocytes, which is consistent with the results discussed above. In guinea pigs, only reduced body weight gain was reported. Increased leukocyte count, and increased hemoglobin and hematocrit were reported in dogs during the 6-week study; however, these effects were not repeated at the 30 ppm in the 90-day study. Monkeys treated for 6 weeks at 244 ppm of cumene showed no adverse effects but during the 90-day study, terminal body weights were lower in treated animals than in controls.

In the only oral toxicity study on cumene, rats were gavaged with cumene up to 769 mg/kg bw/day, 5 days/week for a period of 6 months [Wolf *et al.*, 1956]. Following necropsy and hematological examination, the only effect reported was an increase in average kidney weight (not specified if absolute or relative weight) in the 2 highest dose groups (no statistical analysis). This finding was not accompanied by histopathological renal changes. In all probability the kidney weight changes may be early indications of species and sex specific *alpha*-2 $\mu$ -globulin-induced nephrotoxicity.

#### 3.4.1.6 Chronic Studies

The US Environmental Protection Agency [EPA, 1997] and the Spanish government [Ministerio de Sanidad Y Consumo, 1997] have conducted risk assessments on cumene. In the EPA assessment, it was noted that the longest study conducted on cumene was that of Wolf *et al.* (1956), which was about 7 months in duration, and that this length of study

was “insufficient in duration to reveal the fate of the observed alterations in organ weights.” However, the EPA did proceed to state that there is “some evidence that suggests this compound may not be likely to produce a carcinogenic response (*i.e.*, numerous genotoxic tests, including gene mutation, chromosomal aberration, and primary DNA damage tests, all but one of which were negative or not reproducible, were conducted).” In addition, EPA noted that cumene does not appear to metabolize to highly reactive chemical species and in terms of metabolism, cumene is analogous to methyl benzene for which a 2-year inhalation study was conducted by NTP [NTP, 1990] and no evidence of carcinogenic activity was reported in either rats or mice [EPA, 1997]. Overall, the EPA concluded “there is not much suspicion that cumene would pose a significant carcinogenic hazard.” The Spanish assessment [Ministerio de Sanidad Y Consumo, 1997] also noted the lack of long-term data for cumene, but concluded based on the available data, that there “is at present no need for further information and/or testing or for risk reduction measures beyond which are being applied already.”

Given that the only structural difference between *p*-cymene and cumene is the presence of a second alkyl substituent (isopropylbenzene *versus* *p*-methylisopropylbenzene), similar conclusions can be drawn for *p*-cymene, particularly since the pharmacokinetic, metabolic and toxicologic data that are available support this conclusion. Therefore, it is not necessary to conduct additional studies on *p*-cymene.

### **Reproductive Toxicity**

Measurement of reproductive potential of this chemical category was incorporated into a subchronic study in rats. In the subchronic rat study described above, male rats were exposed to atmospheres containing up to 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days [Cushman *et al.*, 1995]. The epididymides of some rats were removed to evaluate sperm count and sperm morphology. In addition, the right testis of each male was frozen and homogenized to count spermatid and evaluate the stages of spermatogenesis. Testicular sperm head and epididymal spermatozoa counts were similar for all groups. One high-dose rat was reported to have diffuse testicular atrophy. However, the total % of normal epididymal sperm across all treatment groups

was greater than 96%, indicating no treatment related effects on epididymal sperm morphology. The slight increase in total head abnormalities noted at 500 ppm were considered by the authors to be irrelevant since no dose-response was observed and when evaluated as percentage of sperm assessed, sperm head abnormalities were infrequent. Given these results and taking into consideration the rapid metabolism and excretion of cumene, the EPA [EPA, 1997] concluded, “cumene has low potential for reproductive toxicity.” For this reason plus the developmental data provided below, additional reproductive tests on *p*-cymene are not recommended.

### **Teratogenicity/Developmental Toxicity**

A recent well-conducted developmental toxicity study was conducted with cumene in rats and rabbits. Rats and rabbits were used to assess the potential developmental toxicity of cumene [Darmer *et al.*, 1997]. Pregnant rats were exposed to atmospheres containing up to 1,200 ppm of cumene inhalation, 6 hours/day during gestation days 6-15 and pregnant rabbits were exposed at up to 2,300 ppm of cumene 6 hours/day during gestation days 6-18. In rats, reported effects included reduced food consumption, reduced body weight gain, perioral wetness, encrustation, and increased relative maternal liver weight. No statistically significant effects were reported in the fetuses. In rabbits, the reported effects included, death of 2 does at the highest concentration, reduced body weight gain, reduced food consumption, increased incidence of perioral wetness, lung color changes in 33% of high-dose does, and increased relative maternal liver weight. No statistically significant effects were reported in the fetuses. There was a significant increase in the incidence of skeletal and visceral variations; however, they were not exposure related. In reviewing this study, EPA [EPA, 1997] set the maternal NOAEL at 488 ppm in rats based on the significant decrease in body weight gain during exposure and increased relative liver weight. Even at maternally toxic concentrations, exposure to cumene vapor did not produce developmental toxicity in rats. In further review of this study, EPA [EPA, 1991] determined that the changes in gestational parameters of the rabbits, though not significant, were consistent in indicating possible developmental effects and therefore set the NOAEL in rabbits for both developmental and maternal effects at 1,206 ppm and the LOAEL at 2,297 ppm, respectively (as reported in EPA,

1997). Since both cumene and *p*-cymene exhibit such similar pharmacokinetic and metabolic profiles, and show no evidence of toxicity at levels of exposure similar to those experienced by humans, further teratogenic or developmental testing is not recommended.

### **New Testing Required**

None.

### 3.5 Test Plan Table

Chemical	Physical-Chemical Properties					
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility	
CAS No. 99-87-6 <i>p</i> -Cymene	A	A	A	A	A	
Chemical	Environmental Fate and Pathways					
	Photodegradation	Stability in Water	Biodegradation	Fugacity		
CAS No. 99-87-6 <i>p</i> -Cymene	Calc	NA	A, R	Calc		
Chemical	Ecotoxicity					
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Acute Toxicity to Aquatic Plants			
CAS No. 99-87-6 <i>p</i> -Cymene	A	A	A			
Chemical	Human Health Data					
	Acute Toxicity	Genetic Toxicity <i>In Vitro</i>	Genetic Toxicity <i>In Vivo</i>	Repeat Dose Toxicity	Reproductive Toxicity	Developmental Toxicity
CAS No. 99-87-6 <i>p</i> -Cymene	A	A, R	R	A, R	R	R

Legend	
Symbol	Description
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

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