

**The Flavor and Fragrance High Production Volume Consortia
(FFHPVC)**

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Dear Administrator:

On behalf of the Flavor and Fragrance High Production Volume Consortia, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on "Aromatic Terpene Hydrocarbons". The Terpene Consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for chemical substances under the Chemical Right-to-Know Program. Since 1999, the companies that are current members of the Terpene Consortium have supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing for "Aromatic Terpene Hydrocarbons".

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the Terpene Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to submit the following revised test plan and robust summaries for "Aromatic Terpene Hydrocarbons". The revised test plan and robust summaries contain additional data on existing studies and the results of additional ecotoxicity and environmental fate studies that is related to the questions and comments made by the EPA in its letter dated 23/1/2003. This letter contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on these additional data, the Terpene Consortium concludes that the current test plan and robust summaries for the chemical, *p*-cymene, in this category is now complete. The experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent and provide a comprehensive basis upon which to evaluate the hazard potential of *p*-cymene. A summary of the key hazard data has been included in this letter and also in the revised test plan for Aromatic Terpene Hydrocarbons, *p*-cymene.

In an EPA letter dated 19 October 2001 concerning HPV-sponsored chemicals that are recognized as GRAS by the Food and Drug Administration, it was pointed out that:

“ It may well be, on the basis of experience gained over years of use, that most of the substances have little compelling evidence suggesting that testing is needed in the context of the HPV Challenge Program. Nonetheless, while this line of reasoning could have been used to support the recommendation not to test the substances in this category, the information was only provided as background; few examples, and no actual data, were cited.”

Without prior guidance from EPA, the Terpene Consortium felt responsible to report endpoint data for this substance. Most of these data have already been provided to the US Food and Drug Administration and the World Health Organization during their evaluation of these substances as food additives. Human health hazard data on *p*-cymene and structurally related aromatic terpene hydrocarbons have been reviewed by the World Health Organization/Food and Agriculture Organization Joint Expert Committee for the Evaluation of Food Additives (WHO/FAO JECFA) for use as flavoring substances in food. As part of its responsibility, JECFA maintains an ongoing program of review of the safety of food additives (WHO Technical Series Nos. 38, 40, 42, 44, 46, 48, 50, 52). In 2004, *p*-cymene and other terpene hydrocarbons [WHO Food Additive Series: 52, 2004; see Revised Test Plan] were recognized as safe for use in food.

p-Cymene is also recognized as “Generally Recognized as Safe” (GRAS) for its intended use in food by the United States Food and Drug Administration under the Code of Federal Regulations (CFR 172.515). Under supervision of the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, specifications for the commercial use of *p*-cymene in food are published in the Food Chemical Codex [FFC, 1996; see Revised Test Plan].

Based on the long history of *p*-cymene both as a naturally occurring component of food and as a substance intentionally added to food, the hazard assessments performed by the US FDA and WHO/FAO JECFA, and the current regulatory status for the addition of this substance to the food supply, there is no compelling evidence that this substance should be further tested for physiochemical properties and human health endpoints in the EPA Chemical “Right to Know” Program. We do, however, maintain that data on the environmental fate and ecotoxicity are relevant to the HPV Challenge program. In this context, we have sponsored ecotoxicity studies to provide a robust database on ecotoxicity endpoints. We consider that the test plan and robust summaries for this category are final and have no plans to provide additional data. The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the Terpene Consortium and the Environmental Protection Agency in the Chemical “Right to Know” Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for FFHPVC

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

ENDPOINT	SUBSTANCE/SURROGATE /CHEMICAL CATEGORY ¹	VALUE/RANGE ²	REFERENCE
Vapor pressure	<i>p</i> -Cymene	1.46 mm Hg (25°C)	Mackay, 1992
Partition Coefficient	<i>p</i> -Cymene	4.1	Banerjee, 1980
Environmental Fate			
Biodegradation³	<i>p</i> -Cymene	+ (MITI)	Klopman, 1997
Ecotoxicity			
Fish	<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
Aquatic Invertebrates	<i>p</i> -Cymene	48-hr LC50=6.5 mg/L	LeBlanc, 1980
Aquatic Plant	<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,
Human Health			
Repeat Dose⁴ (route)	Cumene	500 ppm (inhalation, 90d)	Cushman, 1995
Reproduction (route)	Cumene	1200 ppm (inhalation, 90d)	Cushman, 1995
Developmental (route)	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
In vitro	Cumene	- AMS - CHO mutation - ABS	Lawlor, 1987; Yang, 1987 Putnam, 1987
In vivo	Cumene	- MN - MN	NTP, 1995 Khan, 1985

¹ 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.

² Experimental value or values for a substance or group of substances in the chemical category

³ not biodegradable, (-); readily biodegradable, (+); ready and ultimately biodegradable, (++)

⁴ Value is the NOAEL or NOEL(route, duration)

⁵ (-), 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.

Responses to EPA Comments on *p*-cymene

EPA Comments on Chemical RTK HPV Challenge Submission: Aromatic Terpene Hydrocarbons

SUMMARY OF EPA COMMENTS

The sponsor, the Terpene Consortium of the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries to EPA for Aromatic Terpene Hydrocarbons dated June 26, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 30, 2002. The submission is for one chemical, *p*-cymene (*p*-methylisopropylbenzene, CAS No. 99-87-6).

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. The physicochemical properties and environmental fate data provided by the submitter are adequate for the purposes of the HPV Challenge Program. However, there are some deficiencies in the robust summaries that the submitter needs to address. EPA agrees with the submitter that *p*-cymene be tested for biodegradability.

Response: Revisions to robust summaries and additional data on ecotoxicity and biodegradation have been included in the revised test plan and revised robust summaries.

2. Health Effects. Adequate data are available for all health endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Response: Revisions to robust summaries have been made where data is available.

3. Ecological Effects. EPA agrees with the test plan for these endpoints.

Response: An algal toxicity study has been performed to complete ecotoxicity endpoints for *p*-cymene.

EPA COMMENTS ON THE AROMATIC TERPENE HYDROCARBONS CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. Even though it is indicated in the test plan (page 12) that this chemical does not hydrolyze in water, the submitter needs to provide this information in a robust summary, and explain why hydrolysis is not possible.

Response: A robust summary containing information on the hydrolytic potential of *p*-cymene has been added.

Biodegradation. EPA agrees with the submitter's proposal to test the biodegradability of *p*-cymene following OECD guidelines. To evaluate this endpoint, the submitter should follow OECD Guideline 301-Ready Biodegradability.

Response: Robust summaries for the biodegradation of *p*-cymene (experimental and calculated) been added.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

EPA agrees with the submitter's test plan to use cumene as an analog to *p*-cymene, based on toxicokinetic data for both compounds, to provide supporting data for health endpoints. An additional reference on cumene metabolites in rabbits (Ishida and Matusmoto, 1992) would tend to enhance the case for using cumene as an analog; this reference mentions the omega-hydroxylation of cumene that is equivalent to the process discussed for *p*-cymene on page 9 of the test plan.

Response: Additional data on cumene metabolism (Ishida and Matusmoto, 1992) has been added to the test plan.

Adequate data are available for the acute toxicity of *p*-cymene and cumene, and for the repeated-dose, genetic, reproductive and developmental toxicity of cumene for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates, and algae).

The available data are adequate for fish and aquatic invertebrates. EPA agrees with the submitter's plan to conduct an algal inhibition study with *p*-cymene.

Response: A study on algal toxicity has been performed with *p*-cymene. A robust summary has been prepared and the data is summarized in the test plan.

Specific Comments on the Robust Summaries

Environmental Fate.

Photodegradation. The submitter needs to provide information on the concentration of hydroxyl radicals used to determine the reported half-life.

Response: These data have been added to the robust summary for photodegradation.

Fugacity. In the robust summary and test plan the submitter erroneously cited the fugacity model used as the "EQC Level III" model. In fact the submitter used the Level III model found in EPIWIN. The submitter also states that the model does not take biodegradation into account. This is incorrect. As a default, the Level III model derives biodegradation half-lives for soil, water and sediment from the results of the BIOWIN biodegradation model. Furthermore, EPIWIN version 3.10 allows these default values to be changed by the user (the EQC Level III model can be found in the website of the Canadian Environmental Modeling Centre at Trent University at <http://www.trentu.ca/cemc/EQC.html>).

The submitter needs to incorporate in its robust summary the values of the input parameters.

Response: The fugacity model data has been recalculated using the EPIWIN 3.10 model and a new robust summary has been prepared. Input parameters have been included in the robust summary.

Health Effects.

Acute Toxicity. Information missing from the acute oral study in rats exposed to *p*-cymene (MacDonald, 1961) includes the purity of the test material, the vehicle (if used), mortality results by sex, body weight changes, and statistical analysis.

Response: Data has been included in the robust summary where available. No statistical analysis was performed. The LD50 value was determined directly from the experimental data (see results section of robust summary).

Repeated-Dose Toxicity. The same reference (Cushman, et al 1995) is cited for two robust summaries for 13-week inhalation studies in rats on cumene with different protocols, different dose levels, different numbers of test animals and one with a 4-week recovery period, but same NOAEL and LOAEL. The submitter needs to clarify the discrepancies and specify which study is used for the reproductive toxicity endpoint. The submitter also needs to provide evaluation of the reproductive organs in the summaries.

Response: The two 13-week studies, one with a 4 week recovery and the other without a 4-week recovery were two different repeat-dose studies performed at the same concentrations and were reported in the same article (Cushman *et al.*, 1995). An independent 1997 EPA evaluation of the data in both studies concluded that the NOAEL in both studies was 500 ppm per day.

Genetic Toxicity. The submitter needs to provide the purity of the test substance for both the *in vitro* Ames reverse mutation test (Lawlor and Wagner, 1987) and the *in vivo* micronucleus assay studies and the statistical analysis for the *in vitro* study.

Response: The purity of the test substance has been added to the Ames and micronucleus assays.

Reproductive Toxicity. No studies were submitted. This endpoint is addressed by documentation of the evaluation of reproductive organs of male rats in a 13-week inhalation study on cumene and the availability of an adequate developmental toxicity study, but no data were submitted for females. The submitter needs to revise the robust summary to include histopathology results for female reproductive organs in this study.

Developmental Toxicity. A robust summary for a developmental toxicity study in rats gestationally exposed by inhalation to cumene provided sufficient information to evaluate the study, but incorrectly identified the maternal LOAEL (stated to be lower than the NOAEL). The submitter needs to correct this error.

Response: Additional information has been added to the robust summaries and the NOAEL error has been corrected.

References

Ishida, T. and T. Matsumoto. 1992. Enantioselective metabolism of cumene. *Xenobiotica*. 22(11): 1291-1298. [cited in NTP Nomination History and Review for Cumene CAS No. 98-82-8. online at http://ntp-server.niehs.nih.gov/Chem_Background/ExecSumm/Cumene.html]