201-15775

NCIC OPPT/DC/USEPA/US
Sent by: JuanB Perez

01/13/2005 02:37 PM

To NCIC HPV@EPA
cc
bcc
Subject Re: Submission of Letter of Respnse to EPA Comments, Final Revised Test Plan, and Final Revised Robust Summaries

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01/13/2005 01:11 PM

To NCIC OPPT@EPA, Rtk Chem@EPA
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Subject Submission of Letter of Respnse to EPA Comments, Final Revised Test Plan, and Final Revised Robust Summaries

Dear Administrator: On behalf of the Flavor and Fragrance High production Volume Consortia, I wish to submit the following documents:
1) Submission of Letter of Respnse to EPA Comments
2) Final Revised Test Plan, and
3) Final Revised Robust Summaries

for the chemical substance. "Phenethyl Alcohol (Benzenemethanol)"(CAS No. 60-12-8). The FFHPVC Aromatic Consortia Registration Number is If there are any problems with the electronic transfer of these files, please contact me at 202-331-2325 or by email. Thank you for the opportunity to participate in the HPV "Right to Know" Program.

Respectfully,
Timothy B. Adams, Ph.D.
Technical Contact person for FFHPVC

Final Responses to EPA Comments on PEA.pdf Final Revised Test Plan Phenethyl alcohol.pdf

Final Revised Robust Summaries for Phenethyl alcohol-FINAL.pdf

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January 11, 2005

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 "Phenethyl alcohol" (benzene methanol). The Aromatic 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 Aromatic Consortium have supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing for "Phenethyl alcohol".

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the Aromatic Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to submit the following revised test plan and robust summaries for "Phenethyl alcohol". The revised test plan and robust summaries contain the results of additional ecotoxicity and animal toxicity studies and additional physical properties information that is related to the questions and comments made by the EPA in its letter dated 12/20/2002. 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 Aromatic Consortium concludes that the current test plan and robust summaries for this chemical 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 phenethyl alcohol. A summary of the key hazard data has been included in this letter and also in the revised test plan for phenethyl alcohol.

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 Aromatic Consortium felt responsible to report endpoint data for these substances. 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 phenethyl alcohol and structurally related phenethyl alcohol derivatives (*e.g.*, phenylacetic acid) 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 on ongoing program of review of the safety of food additives (WHO Technical Series Nos. 38, 40, 42, 44, 46, 48, 50). In 2003, phenethyl alcohol derivatives [WHO Food Additive Series: 50, 2003; see Revised Test Plan] were recognized as safe for use in food.

Phenethyl alcohol is also recognized as "Generally Recognized as Safe" (GRAS) for their 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 phenethyl alcohol in food are published in the Food Chemical Codex [FFC, 1996; see Revised Test Plan].

Based on the long history of phenethyl alcohol both as 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 Aromatic 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 Phenethyl Alcohol

ENDPOINT	SUBSTANCE/SURROGATE /CHEMICAL CATEGORY[1]	VALUE/RANGE[2]	REFERENCE
Physical Properties			
Vapor pressure	Phenethyl alcohol	0.097 mm Hg (25^{o}C)	Vuilleumier,1995
Partition Coefficient	Phenethyl alcohol	1.36	Sangster, 1989
Environmental Fate			
Biodegradation[3]	Phenethyl alcohol	+ (OECD 301B)	Quest, 1994
Ecotoxicity			
Fish	Phenethyl alcohol	96-hr LC50=215 mg/L	BASF, 1998c
Aquatic Invertebrates	Phenethyl alcohol	48-hr EC50=287 mg/L	BASF, 1998a
Aquatic Plant	Phenethyl alcohol	72-hr EC50=490 mg/L	BASF, 1998b
Human Health			
Repeat Dose[4] (route)	Phenethyl alcohol	500 mg/kg (dermal, 90d)	Owston, 1981
Reproduction (route)	Phenylacetic acid	300 mg/kg (gavage, 28d)	Vollmuth, 1995
Developmental (route)	Phenethyl alcohol	266 mg/kg (diet, 13 wks) 143 mg/kg (dermal, 13 wks)	Bottomley, 1987 Palmer, 1986
Genotoxicity[5]			
In vitro	Phenylacetic acid Phenethyl alcohol Phenethyl alcohol, 2-methyl	-	Heck, 1989; Norppa,1983 Wild, 1983
In vivo	Phenyacetaldehyde, 2-methyl Phenylacetic acid, isoeugenyl ester	-	Wild, 1983

[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

Responses to the EPA comments on phenethyl alcohol

SUMMARY OF EPA COMMENTS

The sponsor, the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries to EPA on August 2, 2002, for phenethyl alcohol (CAS No. 60-12-8). EPA posted the submission on the ChemRTK HPV Challenge Web site on August 22, 2002.

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

1. **Physicochemical Properties and Environmental Fate**. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

2. **Health Effects**. The data for acute, repeated-dose, and developmental toxicity are adequate for the purposes of the HPV Challenge Program. The submitter needs to either expand the robust summaries of the genotoxicity studies or provide additional data for both endpoints (gene mutations and chromosomal aberrations). EPA reserves judgment on the reproductive toxicity endpoint pending either additional information on the metabolism of this compound or the results of the 90-day histopathological examination of reproductive organs.

Response: With regard to genotoxicity studies, additional requested data on gene mutation and clastogenic assays (Ames, chromosomal assays, and *in vivo* Drosophila and mouse micronucleus assays) have been added to the respective robust summaries. Justification for the use of data on metabolic precursors and metabolites of phenethyl alcohol has been included in the test plan. In addition, new data for Ames assays with phenylacetic acid (Heck *et al*., 1989) and phenethyl alcohol, 2-methyl (Wild *et al*., 1983) were added to the robust summaries as was a mouse lymphoma assay for phenylacetic acid (Heck *et al*., 1989).

With regard to the reproductive toxicity endpoint, extensive pharmacokinetic data and metabolic data (see pages 4-11 of revised test plan) have been included to demonstrate that a related phenylethyl ester and phenylacetate do hydrolyze prior to absorption and that phenylacetic acid is the predominant metabolite of phenethyl alcohol in animals including humans. Also, the reproductive endpoints in the 90-day repeat-dose dermal study (Owston E. et al., 1981) have been included in the reproductive toxicity section. Based on the results of this study and reproductive/developmental and developmental studies showing no changes in monitored reproduction parameters, it is concluded that phenethyl alcohol exhibits a low potential for reproductive toxicity.

3. **Ecological Effects**. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. However, the submitter needs to provide more detailed data elements for fish, aquatic invertebrates, and algae in robust summaries.

Response: Additional data requested on individual ecotoxicity studies have been added to the test plan and robust summaries where appropriate.

EPA COMMENTS ON THE PHENETHYL ALCOHOL CHALLENGE SUBMISSION

Test Plan

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

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Water Solubility. The calculated water solubility value needs to be corrected to read 32,720 mg/L.

Response: the decimal point error in the robust summary has been corrected.

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

Stability in water. The submitter needs to state clearly in the test plan as well as the robust summary the rationale for not testing the hydrolysis of phenethyl alcohol. Phenethyl alcohol does not have a functional group that is susceptible to hydrolysis and so hydrolysis is not expected to occur in the environment.

Response: The stability of phenethyl alcohol in water is discussed in both the revised test plan and revised robust summaries.

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

The data for acute, repeated-dose, and developmental toxicity are adequate for the purposes of the HPV Challenge Program. The submitted data for genotoxicity may be inadequate (questions are raised below for clarification). EPA reserves judgment on the reproductive toxicity endpoint pending receipt of additional information on the metabolism of this compound or the results of the 90-day histopathological examination of reproductive organs.

Response: The reproductive endpoints in the 90-day repeat-dose dermal study (Owston E. et al., 1981) have been included in a separate robust summary in reproductive toxicity section. Based on the results of this study and the results of reproductive/developmental screening study for the predominant metabolite phenylacetic acid (Vollmuth T.A., 1995) **showing no changes in monitored reproduction parameters, it is concluded that phenethyl alcohol exhibits a low potential for reproductive toxicity.**

Genotoxicity (gene mutations). Four robust summaries were submitted, but none of those assays were considered adequate. These summaries were for a reverse mutation assay in bacteria (Ames test) using phenethyl alcohol, an unscheduled DNA synthesis assay using phenylacetic acid in primary rat hepatocytes, and two sex-linked recessive lethal mutation assays in Drosophila melanogaster (using phenyacetic acid ester, isoeugenol phenylacetate and 2-methyl phenacetaldehyde).

In the Ames test, the test concentration of 366 g/plate is only a small fraction of the 5000 g/plate specified in OECD Guideline 471 as the limit concentration in the absence of precipitate and cytotoxicity; the robust summary made no mention of a precipitate or cytotoxicity.

Response: With regard to Ames assay, the study was a screening assay and, being performed in 1980, did not meet current OECD Guideline 471 protocols. However, additional more recent comprehensive Ames assays for data on metabolic precursors and metabolites of phenethyl alcohol have been included. These data for Ames assays with

phenylacetic acid (Heck *et al*., 1989) and phenethyl alcohol, 2-methyl (Wild *et al*., 1983) and a mouse lymphoma assay for phenylacetic acid (Heck *et al*., 1989) show no mutagenicity at levels below measured cytotoxic concentrations. Given these additional data, it can be concluded that phenethyl alcohol has a very low potential for mutagenicity.

In the tests conducted in Drosophila, there was no evidence of cytotoxicity at the maximum concentrations used. Also, isoeugenol phenylacetate may not be an appropriate surrogate because the chemical structure is too different from the chemicals in the phenethyl alcohol metabolic series. In particular, isoeugenol phenylacetate may not hydrolyze rapidly and therefore, the toxicological properties of this chemical's metabolites may differ from the metabolites of phenethyl alcohol.

Additional information in the Ames test or the Drosophila test using 2-methyl phenacetaldehyde needs to be provided to indicate that the cytoxicity issue has been addressed. Although well-conducted mutation assays in Drosophila using appropriate chemicals are also acceptable to meet this endpoint, the bacterial reverse mutation test in Salmonella typhimurium is preferred.

Response: With regard to the hydrolysis of phenethyl and phenylacetate esters, extensive hydrolysis data (see pages 4 & 5 of test plan) demonstrate that related phenylethyl ester and phenylacetate do hydrolyze prior to absorption and that phenethyl alcohol is rapidly converted to phenylacetic acid in animals including humans. Additional data on use of negative controls, solvent control, and positive controls have been added to the appropriate robust summaries. Also, the relationship of test concentrations to cytoxicity levels has been included in robust summaries where appropriate. Additional test condition data have been included in the appropriate robust summaries for both substances.

Genotoxicity (chromosomal aberrations). Three robust summaries were submitted, but none of those assays were considered adequate. There was one in vitro sister chromatid exchange assay of phenethyl alcohol (in human lymphocytes) and there were two mouse micronucleus tests using metabolites or surrogate chemicals.

The in vitro study had the following flaws: (1) no information on whether sister chromatid exchanges (SCEs) were the only effects measured (and no other chromosomal aberration as per OECD guideline studies); and (2) no metabolic activation in the human cultures.

Response: When compared to current protocols, the SCE assay (Norppa H. and Vainio, H., 1983) is deficient. However, when the negative result in this screening study is evaluated in the light of a more recent negative UDS assay (Heck et al., 1989) and negative results in two in vivo micronucleus assays (Wild *et al*., 1983) (revised to include additional requested data), it is highly unlikely that phenethyl alcohol would exhibit any significant genotoxic potential.

Both micronucleus assays also had several shortcomings. The doses are too low to provide an adequate test of the potential to induce chromosomal aberrations. However, there was no discussion in the robust summary of whether doses were reduced because of cytoxicity. Furthermore, in the test on 2-methyl phenylacetaldehyde, samples of bone marrow were taken at only one time (instead of 3 different times) during the proper sampling interval. The other test was conducted using the phenylacetic acid ester isoeugenol phenylacetate, which is not an appropriate surrogate. The submitter needs to provide appropriate information from the micronucleus study using 2-methyl phenylacetaldehyde or supply data from another study to satisfy the chromosomal aberrations endpoint for the purposes of the HPV Challenge program.

Response: Additional requested data on cytotoxicity data is included in the revised robust summaries. In addition, the additional hydrolysis data supports the inclusion of the phenylacetic acid ester. Hydrolysis will produce phenylacetic acid the predominant

metabolite of phenethyl alcohol. Although additional data on each micronucleus test has been added, the 1983 study does not contain all the study parameters included in current OECD protocols. Nevertheless, the negative results obtained at dose levels orders of magnitude greater than expected human exposure provide basic hazard screening data. In the context of other in vitro and in vivo genotoxicity data and the know metabolism of phenethyl alcohol in humans, it may be concluded that exposure to phenethyl alcohol is associated with no significant potential for genotoxic effects.

Reproductive toxicity. A single study (a reproductive/developmental toxicity screening study in the rat) was submitted using the metabolite phenylacetic acid. EPA agrees with the submitter based on the data provided that phenethyl alcohol will be at least partly metabolized to phenylacetic acid. However, in the single metabolism study in humans, only 26 percent of a 4,000 mg oral dose of phenylethyl alcohol was excreted in the urine after 24 hours as the glutamine conjugate of phenylacetic acid. Although a higher percentage of the acid may have been excreted if a lower dose was used in this study, it is difficult to draw definitive conclusions about the metabolism of this chemical from the available data. Also, animal data indicate variable rates of acid excretion.

The submitter is encouraged to further address this endpoint by submitting additional metabolic information, as well as results of the histopathological examination of the reproductive organs from the 90-day study on phenethyl alcohol by Owston et al. (1981).

Response: **Extensive pharmacokinetic data and metabolic data (see pages 4-11 of revised test plan) have been included to demonstrate that phenylacetic acid is the predominant metabolite of phenethyl alcohol in animals including humans. The additional data on reproductive organs (organ weights, histopathology, *etc*.) have been included in a robust summary (Owston *et al.,* 1981) in the reproductive toxicity section. A NOAEL for reproductive toxicity has been defined (0.5 ml/kg). A similar NOAEL for maternal toxicity (250 mg/kg bw/day) of phenylacetic acid (Vollmuth et al., 1995) supports the conclusion that phenethyl alcohol exhibits a low potential for reproductive toxicity.**

Ecological Effects (*fish, invertebrate and algal toxicity*)

The endpoints for fish, aquatic invertebrates, and algae have been adequately addressed for the purposes of the HPV Challenge Program. The submitter needs to provide additional information in the robust summaries.

Response: Additional requested data has been added to the ecotoxicity robust summaries.

Specific Comments on the Robust Summaries

In general, the submitter should include test guideline information or methodology where possible.

Physicochemical Properties

Water Solubility. The calculated water solubility value needs to be corrected to read 32,720 mg/L.

Environmental Fate and Transport

The submitter needs to add the missing stability in water section to the robust summary.

Fugacity. The submitter needs to provide the values of the input parameters for the fugacity calculations.

Response: The appropriate corrections and additions have been made to the robust

summaries.

Health Effects

Acute toxicity. For the three key studies: 1) for the 1982 dermal study, the submitter needs to provide information on the sex of the test animals and additional details on the test conditions (e.g., rat strain) and results (number of deaths at each dose); 2) for the 1982 oral study, the submitter needs to provide information on the purity of the test material, the age of the animals if different from the guidelines, and necropsy results; and 3) for the 1983 dermal study, the submitter needs to provide information on test substance purity, animal age, and necropsy data.

Response: Requested data has been added to the following robust summaries;

1. International Flavors & Fragrances, Inc., 1982.
2. Moreno O. M., 1982.
3. International Flavors & Fragrances, Inc., 1983.

Repeated-dose toxicity. In the 90-day dermal study, the submitter needs to provide information on the number of animals per test group, the weight and age of the animals, analytical and statistical methods used, and more quantitative results if available.

Response: Additional requested data has been included in the robust summaries.

Genotoxicity (gene mutations). Details missing or inadequate in the robust summary for the Ames test included: (1) use of negative, solvent, or positive controls, (2) use of only one replicate instead of the recommended 3 replicates, and (3) only one concentration tested (which was too low). In the robust summaries for both sex-linked recessive lethal Drosophila melanogaster tests, there is no indication that the tests were conducted up to a cytotoxic concentration.

Genotoxicity (chromosomal aberrations). The robust summaries for both micronucleus studies were considered inadequate because there was no indication that the highest dose was limited by toxicity and it was lower than the limit dose of 5000 mg/kg. Other deficiencies noted in the study on 2-methyl phenacetaldehyde included: (1) samples were taken at only one time (instead of 3 times) between 12 and 72 hrs; (2) the numbers of males and females per group were not specified; (3) there is no indication that a positive control was used; and (4) no information was reported on the ratio of polychromatic cells to normochromatic cells.

Response: Additional requested data has been included in the robust summaries and additional robust summaries have been added to the genotoxicity section.

Reproductive toxicity. The submitter needs to provide a reproductive toxicity robust summary using data from the 90-day dermal study on phenethyl alcohol.

Response: Additional requested data has been included in the robust summaries.

For Vollmuth et al. (1995), the robust summary and test plan both indicate that the NOAEL is the lowest dose of 250 mg/kg. However, the test plan states that there was a decrease in the mating index at the mid-dose, whereas the robust summary states that the decrease only occurred at the highest dose. The submitter needs to resolve this discrepancy. In the robust summary under "Parental data...", the value of 50 should be changed to 500. The submitter should provide more quantitative data for all reproductive effects.

Response: The discrepancies for maternal toxicity and reproductive performance (see Vollmuth *et a*l., 1995) in the test plan and robust summary have been reconciled.

Developmental toxicity. The critical study (Palmer et al., 1986) was conducted under GLP according to a modified OECD TG 414. In the robust summary there is a heading "Actual doses received..." followed by a dose level of 430 mg/kg. This heading is used to describe all doses received by the test animals. The submitter should provide additional quantitative data for all developmental effects.

Response: Actual doses received field has been corrected to add all doses received.

An apparent error in the test plan regarding the Palmer et al. study should be corrected. Specifically, the last two sentences on p. 18 are conflicting. The first sentence states that 0.14 mL/kg was without effects (this matches the robust summary discussion) but the next sentence notes slight differences in effects between this dose and the controls. It appears that the second sentence actually refers to the 0.43 mL/kg dose level (which would agree with the previously stated results and the robust summary). If so, the value in the second sentence should be changed to 0.43 mL/kg.

Response: The test plan has been corrected to reflect the appropriate NOAEL and LOAEL in the study (Palmer *et al*., 1986).

In the description of the results for the Mankes et al. (1983) study, both the robust summary and the test plan state that birth weights were lower in all treated groups but that the weights were greater in the mid-dose group than the controls. The submitter needs to resolve this discrepancy. Also, the developmental LOAEL is incorrectly given as 4300 mg/kg; this should be 430 mg/kg.

Response: The inconsistent statements concerning changes in birth weights at different dose levels in the test plan and robust summary have been reconciled. The LOAEL has been corrected.

Ecological Effects (*fish, invertebrates, and algae*).

The submitter needs to provide the following information: pH, dissolved oxygen, and water temperature; age of the testing organisms at test initiation; statistical analyses used; 95% confidence intervals; control mortality; composition of the algal medium used for this test; purity of the test substance; light intensity and quality; initial cell concentration; and growth rate of the control culture.

Response: Additional requested data has been added to each of the robust summaries in the ecotoxicity section.