

June 4, 2001

Timothy B. Adams, Ph.D.
The Flavor and Fragrance HPV Consortia
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Washington D.C. 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Cinnamyl Derivatives, posted on the ChemRTK website on February 7, 2001. I commend the Aromatic Consortium of the FFHPVC for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

In general, the Consortium's category approach is reasonable. However, as detailed in the attached Comments, the Consortium needs to better support inclusion of *p-t*-butyl-*m*-methylhydrocinnamaldehyde in the category for health effects by clarifying existing metabolism data; supply clarification for certain physicochemical and fate endpoints; and revise the test plan to correct the placement of the developmental toxicity discussion and include an appropriate discussion of reproductive toxicity. The robust summary for the cinnamaldehyde algal toxicity study is inadequate as submitted because it lacks key study conditions.

In addition, the group needs to explain the selection of representative chemicals for aquatic toxicity testing. EPA recommends *m*-hexylcinnamaldehyde as one representative test substance on the basis of its predicted toxicity.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that the Consortium advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsc-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

EPA Comments on Chemical RTK HPV Challenge Submission: Cinnamyl Derivatives

Summary of EPA Comments

The sponsor, the Aromatic Consortium (one of the Flavor and Fragrance High Production Volume Consortia, or FFHPVC), submitted a Test Plan and Robust Summaries to EPA dated December 27, 2000, for the Cinnamyl Derivatives category. EPA posted the submission on the ChemRTK Web site on February 7, 2001. The proposed information-gathering plan is for four substances (see Category Definition, below) considered by the sponsor to constitute a category.

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

1. The submission comprised an acceptable category submission and test plan overall. The submission generally supports the proposed relationship among the four substances on the basis of chemical structure and existing data. However, more information is needed to establish p-*t*-butyl-" -methylhydrocinnamaldehyde as a category member for health endpoints.
2. Physicochemical and Environmental Fate Data. Most endpoints have been satisfied. However, clarification is needed for melting point and water solubility (see Test Plan comments), and EPA recommends including additional information for biodegradation (see Robust Summary comments). For the fugacity model, the sponsor needs to provide the assumptions and data input values to the model.
3. Health Endpoints. Most SIDS endpoints have been satisfied. However, the test plan needs to be revised to include an appropriate discussion of reproductive toxicity. In addition, data need to be provided to support the use of the existing developmental toxicity data for unsaturated cinnamyl derivatives as appropriate to represent the saturated derivative p-*t*-butyl-" -methylhydrocinnamaldehyde.
4. Ecotoxicity (a) The Sponsor needs to explain the selection of representative chemicals for aquatic testing. (b) EPA recommends " -hexylcinnamaldehyde as a representative test substance, since in this set it is predicted to have the highest toxicity towards aquatic organisms (see Test Plan comments). (c) The robust summary for the cinnamaldehyde algal toxicity study is inadequate because it lacks key study conditions (see Robust Summary comments).

EPA is requesting that the Sponsor advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Cinnamyl Derivatives

Category Definition

The definition of the category as four specific unsubstituted or alkyl-substituted cinnamaldehyde or 2,3-dihydrocinnamaldehyde derivatives is clear and unambiguous. The substances are cinnamaldehyde (3-phenyl-2-propenal, CAS No. 104-55-2), " -amylcinnamaldehyde (2-amyl-3-phenyl-2-propenal, CAS No. 122-40-7), " -hexylcinnamaldehyde (2-hexyl-3-phenyl-2-propenal, CAS No. 101-86-0) and p-*t*-butyl-" -methylhydrocinnamaldehyde (3-(p-*t*-butylphenyl)-2-methylpropanal, CAS No. 80-54-6).

Category Justification

The submission presents a case for considering the cinnamyl derivatives as a category. The sponsor provided information showing that in mammals cinnamaldehyde and its " -amyl and " -hexyl derivatives are all rapidly absorbed, metabolized, and excreted. The test plan states (p. 4, Section 2.5.1, first paragraph) that such data are available for the saturated analog p-*t*-butyl-" -methylhydrocinnamaldehyde, but provides no supporting reference. The position and size of substituents are said to not significantly affect the metabolic pathways, but the presence or absence of " , δ -unsaturation as a factor is not directly addressed. The saturated analog 3-(*p*-isopropylphenyl)propionaldehyde is cited as an example of *p*-substitution, but the (possibly cancelling) effect of side-chain saturation is ignored, and again the appropriate citation was lacking. Any available information on compounds differing only by the presence or absence of the double bond would be helpful. While reserving judgement on the inclusion of p-*t*-butyl-" -methylhydrocinnamaldehyde for health effects, EPA believes the presentation adequately supports treating this group of chemicals as a category for health effects, ecological effects, and chemical fate.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The sponsor's approach to boiling point, vapor pressure and partition coefficient is acceptable.

Melting Point

The Test Plan Table on page 26 designates the melting point endpoint as NA, "not applicable due to physical/chemical properties", for all four chemicals. However, in section 3.1 the submitter reports a melting point of -7.5 °C for cinnamaldehyde and 4.0 °C for " -hexylcinnamaldehyde. The submitter also provides calculated melting point data for all four chemicals in its Robust Summary but points out the poor agreement of calculated and measured values. No explanation is given as to why the properties of " -amylcinnamaldehyde and p-*t*-butyl-" -methylhydrocinnamaldehyde preclude determining their melting points experimentally. The submitter needs to reconcile the discrepancies.

Water Solubility

The submitter states that "because of the wide discrepancies between measured and calculated values for water solubility, it is recommended that water solubilities be measured using OECD guidelines for cinnamaldehyde and p-*t*-butyl-" -methylhydrocinnamaldehyde" (Test Plan, page 10).

However, it is unclear why the submitter did not recommend testing the substances that are expected, on the basis of their calculated values, to be least water-soluble, i.e., " -hexylcinnamaldehyde (2.8 mg/L) and " -amylcinnamaldehyde (8.5 mg/L). EPA's preferred approach is to develop measured water solubility values for at least three of the four chemicals, or for the " -hexyl and " -amyl compounds if more confidence in the existing parent compound value can be established.

Fate (photodegradation, aqueous stability, biodegradation, and transport/distribution)

EPA believes that the sponsor's approach to these endpoints is acceptable provided that the sponsor addresses the discrepancy among different biodegradation studies on p-*t*-butyl-" -methylhydrocinnamaldehyde (see "Specific Comments on Robust Summaries").

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

Apparently-available metabolism data for p-*t*-butyl-''-methylhydrocinnamaldehyde (see Category Justification section above) need to be provided for the following reasons:

(1) This chemical has a saturated 3-phenylpropanal backbone versus the unsaturated 3-phenyl-2-propenal backbone of the other category members, and may undergo different metabolic reactions or rates.

(2) The submission includes repeat dose toxicity data on all four category members. The data (as presented in the robust summaries) indicate some concordance for target organ effects (liver and kidney effects from cinnamaldehyde and its ''-amyl and ''-hexyl derivatives; stomach/gastrointestinal tract effects from cinnamaldehyde and the ''-hexyl derivative; and effects on the reproductive organs from cinnamaldehyde and p-*t*-butyl-''-methylhydrocinnamaldehyde). The additional metabolism data might explain the differences in target organ effects.

(3) The repeat dose studies with p-*t*-butyl-''-methylhydrocinnamaldehyde appear to have focused on testicular effects without attempting to assess any other systemic effects. In addition, the effects observed were at much lower doses than were observed following cinnamaldehyde exposure. The additional metabolism data might account for the potency difference.

(4) Without such information it is not clear that the existing developmental toxicity studies with cinnamaldehyde, cinnamyl alcohol, and cinnamic acid can be extrapolated to p-*t*-butyl-''-methylhydrocinnamaldehyde.

Available data on mammalian toxicity are adequate to assess the potential human health hazard of cinnamyl derivatives via various exposure routes. However, the test plan discussion of reproductive toxicity should include the testicular effects observed in the repeat dose studies. In addition, the discussion of developmental toxicity studies in the reproductive toxicity section should be moved to the developmental toxicity section. These same changes should be made in the robust summary document.

Ecological Effects

The sponsor's approach to these endpoints is on the whole acceptable. However, although ECOSAR-predicted values were provided for all members of the series, the sponsor gave no rationale for selecting cinnamaldehyde and p-*t*-butyl-''-methylhydrocinnamaldehyde as test substances over the other members. Absent such a rationale, EPA recommends ''-hexylcinnamaldehyde as a test substance in addition to cinnamaldehyde. On the basis of aquatic toxicity values predicted by ECOSAR, this substance is likely to exhibit higher ecotoxicity than the sponsor's choices.

Specific Comments on Robust Summaries

Fate

For the fugacity model, the sponsor needs to provide the assumptions and data input values to the model (see Guidance for Robust Summary Preparation).

EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University, which allows full control of data inputs. This model can be found at the following web address: <http://www.trentu.ca/academic/aminss/envmodel/>.

Biodegradation

The Biodegradability Robust Summaries are deemed adequate. However, data for p-*t*-butyl-''-methylhydrocinnamaldehyde in the MITI biodegradation database (OECD 301 C; see reference below),

not cited by the sponsor, show that this chemical did not biodegrade to any appreciable extent through a 4 week period (only 8 % biodegradation). As these data appear substantially different from the submitted data, it would be useful, and provide a more complete picture, for the submitter to include any MITI data on the category members in the Test Plan.

Reference: Biodegradation and Bioaccumulation data of existing chemicals based on the CSCL Japan, edited by Chemical Inspection and Testing Institute Japan (ISBN 4-89074-101-1).

Health Effects Studies

The following discrepancies were noted between the Test Plan and the Robust Summary documents: (1) page 18 of the Test Plan states that a mouse micronucleus test was performed with "-amylcinnamyl alcohol, while the corresponding robust summary refers to "-amylcinnamaldehyde (Wild et al., 1983); (2) the study described on page 19 of the Test Plan (NTP, 1995) does not appear in the Robust Summary document.

In addition, clarification on which effects were reversible following the 4-week post-exposure observation period in the Givaudan-Roure (1990d) study should be provided (90-day study with p-*t*-butyl- -methylhydrocinnamaldehyde in rats).

Ecotoxicity Studies

The comments below reflect the information presented in the robust summary.

Algae. The algal toxicity data presented for cinnamaldehyde are inadequate for the following reasons: (1) an EC50 value was not derived and neither nominal nor measured concentrations were provided. (2) The majority of the required robust summary data elements were not submitted for this study. Specific information missing includes: total hardness; pH; TOC; exposure vessel size and type; lighting; temperature; and dissolved oxygen.

In addition, the green alga tested, *Chlorella vulgaris*, is not very sensitive and is being phased out of the OECD SIDS program (Minutes from Expert Meeting on Revision of OECD TG 201 Alga Growth Inhibition Test, SFT, Oslo, 3-4 November 1998); any further algal testing on this chemical should employ a more appropriate species.

Followup Activity

EPA requests that the Sponsor advise the Agency within 60 days of any modifications to its submission.