

October 20, 2005

Timothy Adams, Ph.D.  
Technical Contact  
Ciba Specialty Chemicals HPV Committee  
1620 I Street, N.W.  
Suite 925  
Washington, DC 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for IRGANOX 1330/ETHANOX 330 posted on the ChemRTK HPV Challenge Program Web site on September 2, 2004. I commend Ciba Specialty Chemicals 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 Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Ciba advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: [oppt.ncic@epa.gov](mailto:oppt.ncic@epa.gov) and [chem.rtk@epa.gov](mailto:chem.rtk@epa.gov).

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsca-hotline@epa.gov](mailto:tsca-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

Enclosure

cc: N. Patel  
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:  
Irganox 1330/Ethanox<sup>®</sup> 330 (1,3,5-Trimethyl-2,4,6-tris(3,5-di-t-butyl-4-hydroxybenzyl)benzene)**

**Summary of EPA Comments**

The sponsor, Ciba Specialty Chemicals Corporation, submitted a test plan and robust summaries to EPA for Irganox 1330 or Ethanox<sup>®</sup> 330 (1,3,5-trimethyl-2,4,6-tris (3,5-di-t-butyl-4-hydroxybenzyl)benzene, CAS No. 1709-70-2) dated July 27, 2004. EPA posted the submission on the ChemRTK HPV Challenge Website on September 2, 2004.

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

1. Physicochemical Properties. If the submitted melting point value is calculated, it is not adequate for the purposes of the HPV Challenge Program and the submitter needs to provide a measured value.
2. Environmental Fate. The submitter needs to provide a technical discussion if the chemical does not have the potential to hydrolyze.
3. Health Effects. The submitted data are adequate for the acute, reproductive and developmental toxicity and gene mutation endpoints. EPA reserves judgement on the adequacy of data for the repeated-dose toxicity endpoint, pending submission of a robust summary for the 28-day repeated-dose toxicity study that is mentioned in the test plan and the 90-day study that was the reference for the acute toxicity endpoint. The submitter needs to provide *in vitro* chromosomal aberration data.
4. Ecological Effects. All tests for aquatic toxicity endpoints were conducted above the water solubility limit. However, EPA considers that further testing is not necessary because on the basis of its physicochemical properties this chemical will not exhibit acute or chronic aquatic effects.

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

**EPA Comments on the Irganox 1330/Ethanox<sup>®</sup> 330 Challenge Submission**

**Test Plan**

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

The submitted data for boiling point, vapor pressure, partition coefficient, and water solubility are adequate for the purposes of the HPV Challenge Program.

*Melting point.* If the submitted data are measured, the submitter needs to provide the original standard reference or literature citation. If the data are calculated, they are not adequate for the purposes of the HPV Challenge Program and the submitter needs to provide measured data according to OECD TG 102.

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

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

*Stability in water.* The statement that the HYDROWIN Program could not evaluate the chemical does not provide any indication of its stability in water. The submitter needs to provide measured data following OECD TG 111 or describe in the robust summary a lack of water-sensitive functional groups.

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

The submitted data for the acute, reproductive and developmental toxicity and the gene mutation endpoints are adequate for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of data for the repeated-dose endpoint pending the submission of data from a 28-day repeated-dose toxicity study mentioned in the test plan and a published 90-day study. The submitter needs to provide chromosomal aberration data.

*Repeated-Dose Toxicity.* Although the submitter provided several studies to address this endpoint, they used dose levels significantly lower than the present guideline-recommended limit dose of 1000 mg/kg/day. The test plan mentioned a 28-day repeated-dose toxicity study that was conducted at up to 1000 mg/kg/day. Moreover, information on a 1965 90-day study using high doses, described in the same reference used for the acute toxicity endpoint (Stevenson et al. 1965), was not included. As these studies employed doses at or above the current limit dose, EPA suggests including robust summaries for these studies to support the data generated at lower dose levels.

*Genetic Toxicity. Chromosomal Aberrations.* Data were not submitted for the chromosomal aberrations endpoint, and the submitter referred to the negative 2-year chronic toxicity and carcinogenicity studies as the reason for not testing this endpoint. EPA disagrees with this position because both genotoxicity endpoints need to be characterized apart from any relationship to carcinogenic potential. Therefore, the submitter needs to address the chromosomal aberrations endpoint with *in vitro* test data according to OECD TG 373.

#### Ecological Effects (fish, invertebrates, and algae)

The submitted data are adequate for the purposes of the HPV Challenge Program. Although all tests for these endpoints were conducted above the water solubility limit, physicochemical properties suggest that further testing is not necessary because this chemical will not exhibit acute or chronic aquatic effects.

### **Specific Comments on the Robust Summaries**

#### Physicochemical Properties

*Water solubility.* The submitter needs to add the estimated value of  $9.11 \times 10^{-14}$  mg/L to the results section of the robust summary, since the measured value is given only as “< 1 mg/liter.”

#### Health Effects

*Reproductive Toxicity.* Details missing from the summary of the 3-generation study include the sexes of the pups, weights of the pups at days 0 and 4, weights of reproductive organs, data on spermatogenesis, data on the teratogenic effects observed in the F3c generation, histopathological examination data, and statistical analyses.

### **Followup Activity**

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

## **References**

Stevenson D. E. et al. 1965. Food and Cosmetics Toxicology, Vol. 3, pp. 281-288.