

April 16, 2002

Henry Trochimowicz, Sc.D, D.A.B.T
Industrial Health Foundation
34 Penn Circle West
Pittsburgh, PA 15206-3612

Dear Dr. Trochimowicz:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for cyclohexanol, posted on the ChemRTK HPV Challenge Program Web site on November 14, 2001. I commend the IHF Committee on HPV Challenge for Cyclohexanol 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 HPV 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 attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the IHF Committee on HPV Challenge for Cyclohexanol advise the Agency, within 60 days of this posting on the Web site, 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 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" 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 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

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK Challenge Submission:
Cyclohexanol

SUMMARY OF EPA COMMENTS

The sponsor, the IHF Committee on HPV Challenge for Cyclohexanol, submitted a test plan and robust summaries to EPA for cyclohexanol (CAS No. 108-93-0) dated September 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on November 14, 2001.

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

1. Physicochemical and Environmental Fate Data. The submitter will conduct a hydrolysis test. All other appropriate SIDS-level tests/estimations have been performed.
2. Health Endpoints. The submitter concluded that existing testing for cyclohexanol is adequate for acute toxicity (oral and dermal) and genetic toxicity, and that there is no testing or inadequate testing for repeated dose toxicity and reproductive/developmental toxicity. EPA agrees with this overall assessment of the submitted data. However, EPA does not agree with the submitter's proposal to conduct a 90-day repeated-dose inhalation toxicity study, with the results from a histopathological examination of the gonads determining the direction of further testing; if positive, a reproductive inhalation toxicity test, and if negative, a developmental inhalation test. To address the repeated-dose toxicity and reproductive/developmental toxicity endpoints, the submitter should conduct OECD TG 422, the combined protocol for these endpoints.
3. Ecotoxicity. Adequate data exist for acute fish and algal toxicity testing. Since a definitive EC_{50} value was not determined in the acute daphnid toxicity test, the submitter should conduct further testing in invertebrates.

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

EPA COMMENTS ON THE CYCLOHEXANOL CHALLENGE SUBMISSION

Test Plan

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

The submitter's approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

Fate (photodegradation, stability in water, biodegradation, transport/distribution)

The submitter's approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

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

EPA agrees that adequate data are available for acute toxicity and genetic toxicity, and has the following comments on the submitted data and proposed testing.

Acute toxicity. Acute toxicity studies were conducted prior to the establishment of GLP or OECD guidelines.

EPA agrees that the acute oral toxicity study in rats was adequate even though group sizes were small (2-3/sex). Since three out of six dose levels were at dose levels ≥ 2000 mg/kg, a sufficient number of animals fulfilled the requirements for a limit test.

EPA does not agree that the submitted acute inhalation toxicity study is adequate, since the particle size distribution of the aerosol was unknown, raising uncertainty about the reason for the absence of toxic effects. Furthermore, the study used a single concentration that is lower than that recommended for a limit test under OECD guideline 403 (acute inhalation toxicity). However, no further acute inhalation toxicity studies are recommended, because of the availability of adequate acute oral and dermal toxicity data.

EPA agrees that the submitted acute dermal toxicity study in rabbits is adequate. With respect to methodology, the study appeared to be largely consistent with OECD guideline 402 (acute dermal toxicity). Although the group sizes were small (one male or female per dose), this may be justified for larger animals and is not inconsistent with the use of single rodents in the up-and-down protocol for acute oral toxicity described in OECD guideline 425.

Genetic toxicity. Two adequate studies fulfill SIDS-level testing needs for genetic toxicity. A bacterial reverse mutation assay in *Salmonella typhimurium* was conducted prior to the establishment of GLP or OECD guidelines, but was largely consistent with OECD guideline 471. An *in vivo* micronucleus assay in mice was conducted under GLP and used a method that was the basis for OECD guideline 474.

Repeated dose/Reproductive/Developmental toxicity. The submitter found only inadequate data for repeated dose and reproductive toxicity, and no data for developmental toxicity. The submitter proposed a repeated dose inhalation toxicity study (following OECD test guideline 413), with results from a histopathological examination of the gonads determining the direction of further testing; if positive, a reproductive inhalation toxicity test (using OECD guideline 415), and if negative, a developmental inhalation test (using OECD guideline 414).

EPA agrees that the data for these endpoints are inadequate, but the submitter should conduct a single test using OECD guideline 422 (combined repeated dose toxicity with the reproductive/developmental toxicity screening) to satisfy testing needs for all three endpoints under the HPV Challenge Program (see 65 FR 81695).

Environmental Effects

The submitter is proposing no additional environmental effects testing. Although the data are adequate for the fish and algae studies, the study on invertebrate toxicity was considered inadequate.

Invertebrates. One study in *Daphnia magna* was presented in the test plan. The study followed an EEC guideline and was assigned a reliability code of 2, but a definitive EC_{50} value was not determined. The highest concentration tested (assumed to be 500 mg/L) is lower than the preferred limit concentration of 1000 mg/L stated in the OECD guideline for this endpoint. Therefore, further testing is recommended.

Specific Comments on the Robust Summaries

The majority of the robust summaries gave incomplete reference citations for the evaluated studies. The submitter needs to provide full titles for all studies and any identifying information (e.g., report number, full date of report) for the unpublished industrial studies.

Health Effects

In general, the robust summaries included most of the information necessary to understand the study design and results, but none were complete. None of the summaries reported the date that the study was conducted or the methods of statistical analysis that were used.

Acute toxicity.

Acute oral toxicity. For the adequate key study, the submitter needs to add the incidences of mortality, clinical signs, and effects observed at necropsy for each sex at each dose level.

Acute dermal toxicity. The submitter needs to add details of both the methods (all dose levels by sex, the site and area of skin that was treated, the method of application, the frequency of data collection for clinical signs and body weight) and the results (incidence of mortality and other toxic effects by dose and sex).

Genetic toxicity.

Mutation in bacteria. For the key study, the submitter needs to state the full names of the control chemicals and describe the method used to apply the test material. For the supporting study by Haworth (1983), the results need to be stated clearly (as stated in the test plan, page 13).

Chromosomal aberration in vitro. The submitter needs to identify which of the two cited references is the key study and explain the assignment of reliability code "4" (not assignable), rather than "3" (invalid).

In vivo studies. The submitter needs to state the incidence and nature of toxic effects observed in the mouse micronucleus assay. In addition, the submitter needs to define the acronym "SLRL" mentioned in the *Drosophila* gene mutation assay.

Followup Activity

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