

July 10, 2002

Mr. Richard Henrich
Manager, Regulatory Affairs
Great Lakes Chemical Corporation
Highway 52 N.W.
West Lafayette, IN 47996

Dear Mr. Henrich:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for phosphoric acid tris(methylphenyl) ester (tricresyl phosphate), posted on the ChemRTK HPV Challenge Program Web site on December 19, 2001. I commend Great Lakes Chemical Corporation 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 Great Lakes Chemical Corporation 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,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

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

**EPA Comments on Chemical RTK HPV Challenge Submission:
Tricresyl Phosphate**

The sponsor, Great Lakes Chemical Corporation, submitted a test plan and robust summaries to EPA for tricresyl phosphate (CAS number 1330-78-5) on November 29, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web Site on December 19, 2001.

SUMMARY OF EPA COMMENTS

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

1. General. The submitter needs to state the isomeric composition of the test substance in the robust summaries. The submitter should also discuss differences in the isomeric composition between the test substances used in all studies and the product as currently manufactured.
2. Physicochemical and Environmental Fate Data. The submitter needs to provide values for water solubility, photodegradation, stability in water, and transport and distribution and state why a value for melting point is not applicable. The biodegradation study provides results for primary biodegradation and not for ultimate biodegradation. The submitter needs to provide measured ready biodegradation data according to OECD Guideline 301.
3. Health Endpoints. The submitter noted that testing is needed for the developmental toxicity endpoint. Effects on male reproductive organs were consistently observed in the existing reproduction studies, suggesting a concern for potential developmental effects. Therefore, EPA recommends that the submitter conduct a developmental toxicity study according to OECD Guideline 414.
4. Ecotoxicity. Adequate acute invertebrate toxicity data are available. EPA reserves judgment on the adequacy of the fish toxicity data pending adequate explanation of the difference in acute LC₅₀ values presented in the two submitted summaries. EPA agrees with the submitter that an acute algal toxicity test is necessary. In addition, a chronic test in aquatic invertebrates needs to be conducted because the Log K_{ow} for this chemical is greater than 4.2 and thus EPA expects that this chemical has the potential to exhibit chronic toxicity.

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

EPA COMMENTS ON TRICRESYL PHOSPHATE CHALLENGE SUBMISSION

General

The submitter needs to state the isomeric composition of the test substance for all studies that have been submitted (where available) and for all robust summaries that will be submitted on completion of new testing. In addition, the submitter needs to specify the isomeric composition and range of the product as currently manufactured. Differences between the test substances and the manufactured product (if any) should be clarified. This clarification is important because of the variation in toxicity of the tricresyl phosphate isomers.

Test Plan

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

Boiling Point, Vapor Pressure, Partition Coefficient. Adequate data are available for boiling point, vapor pressure, and octanol/water partition coefficient for the purposes of the HPV Challenge Program. However, the submitter needs to identify the isomeric composition of the test substance.

Melting Point. The submitter needs to explain why testing is not applicable to this endpoint.

Water Solubility. The submitter plans to test for water solubility. EPA recommends that the submitter provide measured data according to OECD Guideline 105.

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

The submitter plans to measure or estimate photodegradation, stability in water, and fugacity. Specific EPA recommendations on several endpoints are discussed below.

Stability in Water. The submitter needs to measure water stability for this chemical rather than provide an estimated value. EPA prefers measured data in this case to assist in understanding the results of the submitted ecotoxicity tests as well as the needed chronic reproduction test in aquatic invertebrates. Also, the identity and percentages of the hydrolysis products for tricresyl phosphate (TCP) should be reported in the robust summary for this endpoint.

Biodegradation. The biodegradation data reported by the submitter are inadequate for the purposes of the HPV Challenge Program because the submitted data mainly reported primary biodegradation (loss of the parent compound) into its corresponding metabolites, and not ultimate biodegradation (complete degradation into carbon dioxide and water). The submitter needs to provide measured ready biodegradation data on this chemical based on OECD Guideline 301.

Transport and Distribution (Fugacity). The submitter needs to provide the assumptions and data inputs used in the fugacity model (see Draft Guidance on Developing Robust Summaries). 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 is available at: <http://www.trentu.ca/academic/aminss/envmodel/>.

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

Acute Toxicity, Repeated Dose Toxicity, Genetic Toxicity. Adequate data are available for acute toxicity, repeated-dose toxicity, and genetic toxicity endpoints. However, the submitter needs to describe the relevance of the isomeric composition of the test substances to the composition of currently-produced TCP. This information is particularly important to explain differences in results. For example, in the 28-day dietary study in rats, almost all animals died when given 1.0% TCP in the diet (roughly 500 mg/kg body weight/day) whereas a dose of 1000 mg/kg/day administered to rats by gavage for three months resulted in minimal toxicity.

Reproductive Toxicity. Four studies were submitted for this endpoint: one 1-generation reproduction toxicity study, two modified continuous-breeding protocol studies (98 and 135 days), and one *in vitro* Sertoli and Leydig cell toxicity study. Although NOAELs were not determined in any of the studies, all studies demonstrated significant effects on male reproductive parameters. From the collective data on reproductive toxicity in these studies, EPA considers that this endpoint has been addressed for the screening purposes of the HPV Challenge Program. However, the submitter needs to describe the relevance of the isomeric composition of the test substances to that of currently-produced TCP.

Developmental Toxicity. The submitter acknowledged a lack of developmental toxicity data and noted that testing is needed for this endpoint. EPA strongly recommends that the submitter conduct a developmental

toxicity study according to OECD Guideline 414 because adverse effects on testes were observed in the reproduction studies and there is a concern for potential effects on the developing fetus.

Ecotoxicity (fish, invertebrates, and algae)

EPA agrees with the submitter's plan to conduct an algal acute toxicity test. EPA also recommends conducting a 21-day reproduction study in aquatic invertebrates. Because this chemical may have low water solubility (as estimated using EPIWIN software), the submitter should consult the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (available at <http://www.oecd.org/ehs/test/monos.htm>) when conducting additional tests.

Fish. EPA reserves judgment on the adequacy of the fish toxicity data. Robust summaries submitted for the studies show a broad range of acute LC₅₀ values in fish, which may indicate problems with the way these studies were conducted or the reporting of results. The submitter needs to provide the isomeric composition of the test substances and explain the significant differences in results of the existing studies.

Invertebrates. The data from the single acute toxicity study in *Daphnia magna* were adequate. However, given a reported log K_{ow} of > 4.2 and the consequent potential to exhibit chronic toxicity, the submitter needs to conduct a 21-day reproduction test in aquatic invertebrates according to OECD Guideline 211 to fulfill the purposes of the HPV Challenge Program.

Algae. No robust summaries were submitted for this endpoint. EPA agrees with the submitter that algal testing is necessary.

Specific Comments on the Robust Summaries

All Applicable Robust Summaries

The robust summaries should characterize the test substance composition.

Health Effects

Genetic Toxicity. The robust summaries for *in vitro* genetic toxicity lack the following information: the use of positive and negative controls, cytotoxic concentrations, and statistical methods.

Ecotoxicity

Fish. Missing details include the type and concentration of solvent used, the percent purity of the test substance, and the isomeric composition of the test substance.

Invertebrates. Water chemistry parameters need to be provided.

Followup Activity

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