March 5, 2009

J. Lawrence Robinson
President
Color Pigment Manufacturers Association, Inc.
300 North Washington Street
Suite 102
Alexandria, VA 22314

Dear Mr. Robinson:

The Office of Pollution Prevention and Toxics is transmitting EPA's preliminary comments on the robust summaries and test plan for 3,3'-Dichlorobenzidine Dihydrochloride, posted on the ChemRTK HPV Challenge Program Web site on August 25, 2006.

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.

This submission lacks important details in the robust summaries, which need to be thoroughly revised to be minimally acceptable for the HPV Challenge Program. EPA reserves judgment on the adequacy of the submission pending the receipt of the information discussed in EPA's comments.

EPA will post this letter and the enclosed preliminary comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Association advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. EPA has moved energetically from the HPV Challenge Program to the Chemical Assessment and Management Program, or ChAMP (www.epa.gov/champ), and is relying on Challenge chemical sponsors to provide, as expeditiously as possible, the data that are the key to this effort.

Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov. If you have any questions about this response, please contact me 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.

Thank you in advance for your revised submission, and I look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
3,3'-Dichlorobenzidine dihydrochloride

Summary of EPA Comments

The sponsor, the Color Pigment Manufacturer's Association, Inc., submitted a test plan and robust summaries to EPA for 3,3'-dichlorobenzidine dihydrochloride (CAS No. 612-83-9) on June 9, 2006. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 25, 2006.

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

The submission is lacking in important details for all HPV Challenge endpoints. Inadequacies in the robust summaries need to be addressed to be minimally acceptable for the HPV Challenge Program. EPA reserves judgment on the adequacy of the submission for the purposes of the HPV Challenge Program pending the receipt of the information detailed below.

EPA's preliminary comments appear below. EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the 3,3'-Dichlorobenzidine Dihydrohydrochloride Challenge Submission

The test plan states that the sponsored chemical is no longer manufactured in the U.S. However, as long as it is imported in HPV quantities, it still meets the HPV Program criteria.

Analog Justification

The submitter proposed on page 3 of the test plan to use data for two analogs, 3,3'-dichlorobenzidine (CAS No. 91-94-1) and 3,3'-dichlorobenzidine sulfate (CAS No. 74332-73-3), to satisfy the data requirements for the sponsored substance. However, no data were provided for the sulfate in the robust summaries and this substance should be deleted from the test plan.

The use of the proposed analog, 3,3'-dichlorobenzidine, is not supported for the physical property endpoints. The sponsored dihydrochloride will be less volatile and more soluble than the free amine. This analog is supported for the environmental fate, aquatic toxicity, and human health endpoints. The sponsored substance and proposed analog are expected to show comparable results for these endpoints.

Test Plan

The chemical structure in the test plan has one chlorine atom misplaced.

The submitter does not propose to perform any testing. EPA cannot determine whether testing is needed because the submitted robust summaries are inadequate for the purposes of the HPV Challenge Program and it is not possible to determine data adequacy except for some physical chemical and environmental fate endpoints. The submitter needs to revise the robust summaries to allow determinations of data adequacy.

On page 3 of the Test Plan, the submitter states that DCB is a closed system intermediate (CSI). If, as the submitter believes, all health effects data are adequate, then there is no CSI issue. However, if certain data prove inadequate, then EPA would require more specific information to determine if those toxicity tests may be waived (see guidance at http://www.epa.gov/chemrtk/pubs/general/closed9.htm).

Physical Chemical Properties (melting point, boiling point, vapor pressure, partition coefficient, water solubility)

Submitted data are adequate for the boiling point and partition coefficient endpoints for the purposes of the HPV Challenge Program.

Melting Point. The submitter reports measured data for 3,3'-dichlorobenzidine. The melting point of the free amine is not representative of the salt. The data are not adequate for this endpoint.

Boiling Point. The submitter gave a measured boiling point for the free amine analog of 402 °C. The boiling point of the free amine is higher than the HPV cut-off value of 300 ˚C, indicating that the dihydrochloride, expected to boil at a higher temperature than the free amine, will also boil at a temperature above the HPV cut-off. The data for this endpoint are adequate.

Vapor Pressure. The submitter reports an estimated vapor pressure for the free amine of ".45", with no units. In EPA's hands the cited program provided an estimated value for the free amine of 4.1×10^{-6} mm Hg. While the value is not below the HPV cut-off value, the salt is expected to have a much lower vapor pressure. The reviewer needs to revise the submission to reflect these comments.

Water Solubility. The submitter needs to provide measured data for the sponsored chemical.

<u>Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)</u>

Submitted data are adequate for photodegradation, biodegradation and fugacity for the purposes of the HPV Challenge Program.

Photodegradation. The submitter did not address indirect photolysis. Because the salt is not volatile, atmospheric oxidation is not likely to be an important fate process and the submitter's data are adequate despite the omission. The submitter did provide measured data for the direct photolysis for the free amine in water. Because this is a rapid and important fate process and bears on the interpretation of ecotoxicity data, the submitter needs to provide more details of the study in the robust summary.

Stability in Water. The submitter reports a half-life of 100 days for the free amine, 3,3'-dichlorobenzidine in water. EPA did not find a hydrolysis half-life in the cited source; this discrepancy needs to be resolved. The document states "there are no data to suggest that the hydrolysis of 3,3'-dichlorobenzidine is an environmentally significant process" (Callahan 1979). This is consistent with the observation that there are no hydrolysable functional groups. With the inclusion of EPA's comments, the data for this endpoint are adequate.

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

All the data submitted for health effects for 3,3'-dichlorobenzidine dihydrochloride are based on 3,3'-dichlorobenzidine studies. All of the study summaries lack very basic information and so EPA reserves judgment on the test plan for health effects pending receipt of adequate robust summaries.

<u>Ecological Effects (fish, invertebrates, and algae).</u>

As indicated earlier, the submitter's proposal to use data on 3,3'-dichlorobenzidine to evaluate ecological effects of the sponsored chemical dihydrochloride is reasonable.

Data were submitted only for acute toxicity to fish for the analog 3,3'-dichlorobenzidine. The information presented for this study lacks sufficient detail to determine study adequacy. In addition to all the summaries being inadequate, the submitter needs to address the possible role of photodegradation relative to aquatic toxicity (the fish study was apparently performed in the dark). EPA reserves judgment on the test plan for ecological effects pending receipt of adequate robust summaries and clarification of the environmental fate of the sponsored chemical in water beyond the statement that "(D)ue to characteristics in water and light, there are very few data on the toxicity of 3,3'-dichlorobenzidine to aquatic organisms."

For acute invertebrate and algae toxicity, modeled estimates were used to predict toxicity. The submitter needs to provide measured data for these endpoints.

Specific Comments on the Robust Summaries

The summaries did not provide enough detail. The submitter needs to consult EPA's guidance document for the preparation of robust summaries (http://www.epa.gov/chemrtk/pubs/general/robsumgd.htm) and upgrade the summaries to a useable level.

Environmental Fate

The stability in water summary mentions a study with a "similar substance" identified only as a “biazoaryl pigment.” Without sufficient information to clarify its relevance, this comment should be deleted.

Health Effects

Acute Toxicity. Information missing from the summary included test substance purity and composition, group size, sex and strain tested, doses tested, gross necropsy findings, signs of clinical toxicity, and whether or not the post-exposure observation period was 14 days. The LD_{50} value is ambiguously presented.

Repeated-Dose Toxicity. Given the description of doses and the NOAEL listed, it was unclear in the mouse study if the route of exposure was oral or inhalation. Information missing from the summary included test substance purity and composition, mouse strain, vehicle (if used), initial group size, mortality, food consumption and body weight data, statistical methods used, list of organs weighed and examined histologically, and whether or not hematology and clinical chemistry were studied. If the study was by the inhalation route, additional inhalation-specific information missing from the summary included description of test atmosphere generation/concentration control system, exposure type (whole-body or nose-only), airflow rate, temperature and humidity of air, nominal test concentrations, measured test concentrations in the breathing zone, and particle size characteristics if animals were exposed to an aerosol. From the title, this study (in Japanese) appears focused on hepatoma formation rather than the parameters normally studied to assess repeated-dose systemic toxicity.

Information missing from the summary of the oral study in dogs included test substance purity and composition, vehicle (if used), initial group size, doses tested, mortality, body weight and food consumption data, statistical methods used, list of organs weighed and examined histologically, and whether or not hematology and clinical chemistry were studied. From the title, this study may have been focused on tumor formation rather than the parameters normally studied to assess repeated-dose systemic toxicity.

Genetic Toxicity.

Gene Mutation. Information missing from the summary of a study in *Salmonella typhimurium* included test substance purity and composition, test substance concentrations, number of replicates per concentration, solvent/vehicle used, number and identity of tested bacterial strains, whether testing was done in the absence as well as the presence of metabolic activation, results expressed separately for testing in the presence and absence of metabolic activation, use and response of positive controls, criteria for a positive response, and statistical methods used.

Chromosomal Aberrations. Details missing from the summary of a bone marrow and fetal micronucleus study in mice included study protocol(s) used (particularly for examination of fetal liver), test substance purity and composition, mouse strain and group size, doses tested and response by dose, statistical methods used, route of administration (listed as gavage in the title of the cited reference), exposure period, and signs of systemic toxicity.

Ecological Effects

Fish. Information missing from the summary included test substance purity and composition, fish characteristics at study initiation (age, mean weight), number of fish per concentration, temperature, water quality parameters (dissolved oxygen, pH, hardness), and 96-h LC50 value. It is unclear why this study is titled “EPA Bioconcentration Study”.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.