

201-14910

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR


**American
Chemistry
Council**
*Good Chemistry
Makes it Possible*

December 15, 2003

RECEIVED
OPPT 0810
03 DEC 17 PM 3:36

Via U.S. Mail and E-mail

Michael Leavitt, Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

Re: Hydroquinone Precursors and Derivatives Panel-Hydroquinone Monomethyl Ether (HQMME) Task Force Consortium No. Hydroquinone Monomethyl Ether Testing Rationale Response to EPA's Comments of May 13, 2003 on ACC Panel's Original Submission of December 20, 2002

Dear Administrator Leavitt:

The Hydroquinone Precursors and Derivatives Panel (HQPD) Hydroquinone Monomethyl Ether (HQMME) Task Force of the American Chemistry Council is pleased to submit the attached response to EPA's comments of May 13, 2003 on its initial test plan submission of December 20, 2003 for 4-hydroxyanisole (CAS No. 150-76-5). The attached response is provided on behalf of the following companies who are members of the HQMME Task Force: Rhodia, Inc., Eastman Chemical Company, Borregaard, and Specialtychem Products Corporation.

This submission includes the following documents:

- Item by Item Response to EPA's Comments of May 13, 2003 on ACC Panel's Original Submission of December 20, 2002;
- Revised Background Information;
- Revised Test Plan;
- Revised Robust Summaries (Appendix A);
- HQMME Production and Industrial Hygiene Overview (Appendix B).



Responsible Care®

Michael Leavitt
HQPD HQMME HPV Chemical Challenge Program
December 15, 2003
Page 2 of 2

This submission is also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov

Chem.rtk@epa.gov

If you require additional information, please contact F. J. "Sonny" Maher, HQPD Panel Manager at (703) 741-5605 or sonny_maher@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: HQMME Task Force

**AMERICAN CHEMISTRY COUNCIL
Hydroquinone Precursors and Derivatives Panel
Hydroquinone Monomethyl Ether Task Force
Consortium Number
December 15, 2003**

**Item by Item Response to EPA's Comments of May 13, 2003 on ACC Panel's Original Submission
of December 20, 2002**

SUMMARY OF EPA COMMENTS

The sponsor, the Hydroquinone Precursors and Derivatives Panel (HQPD) Hydroquinone Monomethyl Ether (HQMME) Task Force of the American Chemistry Council, submitted a test plan and robust summaries to EPA for 4-hydroxyanisole (CAS No. 150-76-5) dated December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 21, 2003.

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

1. Physicochemical Properties and Environmental Fate. Adequate data are available for all endpoints except for vapor pressure. The submitter needs to provide measured data for vapor pressure.
2. Health Effects. (a) Adequate data are available for the acute and repeated-dose toxicity endpoints. The submitter needs to address deficiencies in the acute toxicity study robust summary. (b) Data are inadequate for gene mutations. (c) EPA reserves judgment on the adequacy of data for the chromosomal aberrations and reproduction/developmental toxicity endpoints pending submission of information on bioavailability of this chemical, since available data are via the dermal route and oral/inhalation are the major routes of exposure for this chemical.
3. Ecological Effects. (a) Submitted data for fish acute toxicity are adequate; however, the submitter needs to provide missing study details in the robust summary. (b) EPA reserves judgment on the adequacy of data for invertebrate toxicity pending submission of additional information. (c) For algae, the submitter needs to conduct a test according to OECD TG 201.

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

**SPECIFIC EPA COMMENTS ON THE 4-HYDROXYANISOLE CHALLENGE SUBMISSION
AND HQMME TASK FORCE RESPONSES**

Test Plan

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

Available data for melting point, boiling point, water solubility, and partition coefficient endpoints are adequate for the purposes of the HPV Challenge Program.

Vapor Pressure. The submitter states that measurement of vapor pressure of 4-hydroxyanisole is not applicable since it is a solid. However, EPA believes that the submitter needs to provide the measured vapor pressure value because the EPIWIN estimated vapor pressure is 8.3×10^{-3} mm Hg at 25°C (1.103 Pa) and OECD TG 104 states that measured data are required for addressing this endpoint when the estimated vapor pressure is greater than the cutoff value of 7.5×10^{-8} mm Hg (1×10^{-5} Pa) at 25°C.

HQMME Task Force Response: The US HPV program allows for the use of EPIWIN estimations for the completion of physical chemical properties. Accordingly, a robust summary containing the EPIWIN estimation has been added to the robust summaries.

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

Available data for these endpoints are adequate for the purposes of the HPV Challenge Program.

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

Adequate data are available for the acute and repeated-dose toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the acute toxicity study robust summary.

Acute Toxicity.

HQMME Task Force Response: See below under “Health Effects”.

Genetic Toxicity. Gene Mutations: The data for gene mutations were not adequate because one study was a spot test and provided only limited information and in the other study, only two strains were tested.

HQMME Task Force Response: The Task Force acknowledges the fact that the studies submitted for assessing HQMME’s potential to induce gene mutations were not as robust as a study following current OECD guidelines. However, the Task Force believes that no new studies need to be conducted under the program, as the primary objective of the two genotoxicity endpoints is to gain an understanding of the carcinogenicity risk of the compound. Thus, the Task Force believes the data from both these mutation assessment studies, in conjunction with the negative chromosomal aberration data, and the various negative carcinogenicity studies that have been summarized fulfill the intent of this endpoint.

This conclusion for a lack of mutagenicity potential for HQMME is further supported by the body of evidence that such an effect is not commonly induced by hydroquinone (HQ), a chemical that is very structurally similar to HQMME (DeCaprio, Crit. Rev. Toxicol. 29:3, 1999).

EPA notes that the micronucleus, cancer, two-generation reproductive, and developmental toxicity tests were performed in 1997 and submitted to the FDA as part of a New Drug Application (NDA). All these studies were conducted using the dermal route of exposure because the applicant was seeking approval for a minor use of 4-hydroxyanisole in a topical dermatological product (by prescription only) to lighten skin.

EPA questions whether this route of test substance administration was dermally bioavailable to produce any systemic toxicity and was appropriate for these endpoints for the purposes of the HPV Challenge Program. Most importantly, the submitter stated that the inhalation route is of most concern in the occupational environment. Therefore, EPA reserves judgment on the adequacy of these data and requests that the submitter either provide information on relative bioavailability of the oral/inhalation route versus the dermal route (for which they have the most data), provide adequate analog data, or conduct appropriate testing.

HQMME Task Force Response: The Task Force believes the studies submitted for the characterization of the potential for HQMME to induce genotoxicity (chromosomal aberrations), reproductive, and developmental toxicity endpoints conducted by the dermal route are sufficient to fulfill those endpoints. The rationale used for this conclusion is that dermal toxicokinetic experiments were conducted in both rats and humans to support the NDA approval for a topical solution used for skincare. Results from these studies demonstrated significant levels of HQMME in the blood following dermal exposure (http://www.fda.gov/cder/foi/nda/99/20-922_Solage_biopharmr.pdf and http://www.fda.gov/cder/foi/nda/99/20-922_Solage_prntlbl.pdf). Further evidence of significant dermal absorption is based on the presence of systemic toxicity (reduced weight gain) noted in animals that received the highest dose level in some of these studies. Efficacy of the drug product is also dependent upon dermal penetration into the lower dermal layers where blood capillaries and melanocytes (the site of action) are present. A reference to the FDA website has been added to the robust summaries studies utilizing the data submitted to support the NDA approval.

Developmental and reproductive toxicity are also not anticipated from exposure to HQMME based on the lack of such effects following oral exposures to hydroquinone (HQ). HQ is structurally similar to HQMME and showed no evidence of developmental or reproductive toxicity following oral studies utilizing OECD 414 and 416 protocols (OECD SIDS dossier).

While it is noted that exposure to HQMME in the workplace may occur via inhalation, total exposure is anticipated to be minimal via this route. This is because the primary expected window of opportunity for this to occur is limited to the period in which the material is solidified for packaging and vapor exposures are controlled through air control technologies, and good industrial hygiene practices by workers (See Appendix B). While this route of exposure was noted to be the most likely route, it is not the only route of potential exposure as dermal exposure to solidified material after flaking and packaging also represents a potential route of exposure.

The robust study for chromosomal aberrations has also been modified by the addition of the dose levels utilized in that study which were not originally noted in the robust summary.

Ecological Effects (fish, invertebrates, and algae).

Fish. The data are adequate for the purposes of the HPV Challenge Program; however, the submitter needs to provide missing study details in the robust summary.

HQMME Task Force Response: See discussion below.

Invertebrates. EPA reserves judgment on the adequacy of the data for this endpoint until missing study details are provided.

HQMME Task Force Response: See discussion below.

Algae. EPA believes that this endpoint has not been adequately addressed because the submitted study on *Microcystis aeruginosa* (cyanobacteria) is not the appropriate species for algal toxicity testing and the exposure period is too short (24-hours). The study on *Scenedemus quadricauda* (algae) is inadequate because the required study details are not available, the exposure period (10-days) is too long, and the data are insufficient for derivation of an EC₅₀ value. Therefore, EPA recommends that the submitter conduct an algal test according to OECD TG 201.

HQMME Task Force Response: The Task Force disagrees that these studies are not adequate to fulfill the endpoint for algae toxicity. While the first study did not use an appropriate species and the second study utilized an excessive exposure period, results from both studies indicate that the material is toxic to aquatic plants. Results from studies conducted on hydroquinone, a structurally similar antioxidant compound, showed algal growth to be completely inhibited at a concentration of 4.0 mg/L following study durations of 24, 48, and 72 hours. The EC₅₀ in that study was reported to be 1- 4 mg/L. Thus, the Task Force does not believe new testing is warranted, as it is anticipated to show similar results, i.e., the material is toxic to plants.

Specific Comments on the Robust Summaries

Environmental Fate

Photodegradation. The submitter needs to clarify whether the summarized test (Ref. 5) is for “INDIRECT PHOTOLYSIS” as stated in the robust summary. The summary methodology suggests that the study was for “DIRECT PHOTOLYSIS.”

HQMME Task Force Response: The robust summary has been modified to reflect that the data are for “DIRECT PHOTOLYSIS”.

Fugacity. The submitter needs to provide input parameters in the level III modeling summary.

HQMME Task Force Response: The fugacity distribution results were based on default values and no specific input parameters were utilized. A new robust summary has been generated utilizing input values from key studies. The input values have been added.

Health Effects.

Acute Toxicity. Omissions include: the gavage vehicle, length of the observation period, the strain and sex of rat, the exact doses administered on a mg/kg basis, information on target organs, and the method for estimating the LD₅₀.

HQMME Task Force Response: The acute toxicity study was conducted in 1949 and the requested data are not available in the published manuscript in which the study was identified.

Ecological Effects

Fish. Information missing includes GLP compliance, the number of fish tested, concentrations tested, mortality/effects seen at each concentration, water quality characteristics, and statistical methods used.

HQMME Task Force Response: Results from four different studies have been summarized. The first three studies contain essentially all the specific information requested above and have been assigned the highest reliability scores. The third study, with a reliability score of 2, is noted to lack study details. The fourth study was added for completeness and was assigned a score of 4, as the original report was not available for addition of requested details.

Invertebrates. Information missing includes GLP compliance, test methods/guidelines used, the number of daphnids tested, test substance purity, concentrations tested, mortality/effects seen at each concentration, water quality characteristics, statistical methods used, and whether the reported 48-hour EC₅₀ value was based upon measured or nominal concentrations.

HQMME Task Force Response: Results from three different studies have been summarized to their fullest extent and were assigned reliability scores of 2 due to a lack of study details. Much of the missing detail is the data being requested. However, results from all three studies indicate that the material is toxic to aquatic invertebrates. Accordingly, it is believed that these data in total are reliable for the assessment of this endpoint.

Followup Activity

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