

August 19, 2005

Robert J. Fensterheim
Executive Director
Quat HPV Challenge Task Group
1250 Connecticut Avenue, N.W.
Suite 700
Washington, DC 20036

Dear Mr. Fensterheim:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Quat Category posted on the ChemRTK HPV Challenge Program Web site on May 13, 2004. I commend Quat HPV Challenge Task Group 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 the Task Group advise the Agency, within 90 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 and 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 tsc-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: M. E. Weber
N. Patel
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:
Quats (Quaternary Ammonium Salts) Category**

Summary of EPA Comments

The sponsor, the Quat HPV Challenge Task Group, submitted a test plan and robust summaries to EPA for the Quats (quaternary ammonium salts) category dated April 27, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on May 13, 2004. The category consists of four sponsored substances: dimethylaminoethyl acrylate methyl chloride (ADAMMC), CAS No. 44992-01-0; dimethylaminoethyl acrylate dimethyl sulfate (ADAMDMS), CAS No. 13106-44-0; dimethylaminoethyl methacrylate methyl chloride (MADAMMC), CAS No. 5039-78-1; and dimethylaminoethyl methacrylate dimethyl sulfate (MADAMDMS), CAS No. 6891-44-7. Two substances: dimethylaminoethyl acrylate (ADAM, CAS No. 2439-35-2) and dimethylaminoethyl methacrylate (MADAM, CAS No. 2867-47-2), were proposed as analogs for the category members (EPA has posted final OECD SIDS assessments for these analogs on the Challenge Web site).

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

1. Category Definition. The category definition is clear.
2. Category Justification. Similarities in chemical structure and data for ecological and some mammalian toxicity endpoints support the category justification. However, the submitter needs to provide a clear test plan that shows the available data and how data gaps will be filled.
3. Analog Justification. Although similarities among the category members and analogs generally support the use of the analogs, the test plan is inadequate in justifying the analogs and showing how the analog data will be used to satisfy the endpoint data gaps. Mammalian toxicity data for ADAM should be used only for ADAMMC and ADAMDMS, and mammalian toxicity data for MADAM only for MADAMMC and MADAMDMS.
4. Physicochemical Properties. For three chemicals, the submitted data for boiling point and Log K_{ow} are adequate for the purposes of the HPV Challenge Program; these data are also needed for MADAMDMS. The submitter needs to provide measured melting point, vapor pressure, and water solubility values for all category members.
5. Environmental Fate. Some submitted data are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured stability in water data for the chlorides or the methylsulfates and measured ready biodegradation data for ADAMMC, and photodegradation and fugacity data for MADAMDMS. All fugacity data need to be calculated from measured inputs as appropriate.
6. Health Effects. EPA reserves judgement on the adequacy of data submitted for the genetic toxicity endpoint pending receipt of critical robust summary data. Although the submitter needs to better justify the analogs, the analog data referenced in the test plan are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the test plan and robust summaries and correct the description of ADAM's developmental toxicity.
7. Ecological Effects. EPA reserves judgement on the data provided for the category members pending submission of additional details in the robust summaries.

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

EPA Comments on the Quats Category Challenge Submission

General

The submitter needs to provide a test plan that clearly shows the available data and how data gaps will be filled. The "Test Data" table on p. 5 is misleading, as it implies incorrectly that all endpoints have been satisfied with measured data on each chemical. Mammalian toxicity data available for MADAM were not discussed in the test plan nor compared with the ADAM data. The submitter needs to address all these deficiencies.

Category Definition

The category definition is very clearly stated, although the nomenclature is misleading throughout because of improper spacing: for example, ADAMMC is correctly dimethylaminoethyl acrylate methyl chloride, not dimethylaminoethylacrylate methyl chloride.

Category Justification

The submitter bases the category on the structural similarity of the compounds and expected resulting similarities in their physicochemical and toxicological properties, as well as on limited toxicological data.

The acute oral toxicities (an LD50 of 1600 mg/kg for ADAMMC and an LD50 of 1300 mg/kg for MADAMMC) are similar. Genetic toxicity data provided for three of the four sponsored compounds may support the category with negative responses, although the validity of the negative findings for ADAMMC and MADAMMC can only be verified after the submitter provides additional information on the use of positive controls.

The measured ecotoxicity data provided, if confirmed by adequate revised robust summaries, support the submitter's conclusion that the sponsored substances have similar acute fish and invertebrate toxicities. LC₅₀ and EC₅₀ values are >100 mg/L for these two endpoints for all four sponsored substances. The data provided for the algae toxicity endpoint show a pattern of toxicities in which ADAM-based compounds have lower EC₅₀ values than MADAM-based compounds (the submitter's explanation that this difference is associated with the toxicities of the hydrolysis products, acrylic acid and methacrylic acid, is not consistent with the estimated hydrolysis half-lives).

Overall, the similar structures and measured data support the grouping of the category members.

Analog Justification

ADAM and MADAM, the non-quaternized parent chemicals of the sponsored substances, are proposed as data sources for the category members. However, no direct discussion that supports using these analogs was provided in the test plan; moreover, the submitter failed to use the abundant mammalian toxicity data on ADAM and MADAM to compare the two structure types. These deficiencies need to be addressed. Other information to help evaluate their suitability (e.g., pK_a values) also could have been provided.

The acute oral toxicity values of the category members and analogs are 455 mg/kg or higher. EPA believes that the use of the analogs, which represent both structural types in the category, is consistent with the close structural similarities and the available acute toxicity data. However, as data on the sponsored substances are not available on any repeated-dose mammalian toxicity endpoints to compare with analogs, and structural differences between acrylates and methacrylates may result in different biological reactivities, the mammalian toxicity data for ADAM should only be used to address ADAMMC and ADAMDMS; MADAM data need to be used only for MADAMMC and MADAMDMS.

Although genetic toxicity data provided for three of the four sponsored substances show negative responses, ADAM and MADAM show one or more positive responses in genetic toxicity assays. This suggests that the analogs may be somewhat more toxic than the sponsored chemicals for some health effects endpoints; this uncertainty is acceptable because it is in the more conservative direction.

Thus, despite the deficiencies noted, and given the caveats on the use of the data, EPA agrees that the use of these chemicals as analogs is reasonable if supported by an adequate discussion.

Test Plan

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

The estimated values provided are adequate for the boiling point and the octanol/water partition coefficient for the purposes of the HPV Challenge Program; these data are also needed for MADAMDMS. The estimated values for melting point, vapor pressure, and water solubility are inadequate. Estimated values are adequate only for melting points below 0 °C, vapor pressures below 10⁻⁵ Pa, and water solubilities below 1 µg/L. The submitter needs to provide measured data following OECD guidelines for these endpoints.

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

Photodegradation. The photodegradation data provided by the submitter for ADAMMC, ADAMDMS, and MADAMMC are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide photodegradation data for MADAMDMS.

Stability in water. The estimated data provided for ADAMMC, ADAMDMS, and MADAMMC are inadequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured hydrolysis data for the chlorides or the methylsulfates following OECD TG 111.

Biodegradation. The ready biodegradation data provided by the submitter for MADAMMC are adequate for the purposes of the HPV Challenge Program. The inherent biodegradation data provided by the submitter for ADAMMC are inadequate because inherent biodegradation tests allow for bacterial adaptation, which does not provide a conservative picture of the biodegradation of a chemical. The submitter needs to provide measured ready biodegradation data for ADAMMC following OECD TG 301.

Transport between environmental compartments (fugacity). The fugacity data provided by the submitter are not adequate for the purposes of the HPV Challenge Program because they are estimated from default values. The submitter needs to calculate the fugacity values for all category members using the appropriate measured physicochemical values as inputs into the model. The use of estimated values introduces uncertainties that then become magnified in modeling applications.

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

Adequate data are available for the acute, repeated-dose, reproductive, and developmental toxicity endpoints for the purposes of the HPV Challenge Program, provided the concerns expressed under Analog Justification are addressed.

Acute Toxicity. The test plan (pages 8 and 9) cited acute oral toxicity test data for MADAMMC. Robust summaries of these data need to be provided.

Genetic Toxicity. EPA reserves judgement on the adequacy of the data submitted for the gene mutation (OECD TG 471 and 476) and chromosomal aberration (OECD TG 473) toxicity endpoints on the two sponsored chemicals, ADAMMC and MADAMMC, pending the receipt of revised summaries that provide critical missing details. The test plan (page 9) also cited negative *in vitro* gene mutation test results for MADAMDMS, but summaries of these studies need to be provided. The additional details for the sponsored chemicals need to be provided even though adequate analog data are available (see below), because adequate data on the sponsored substances are preferred over analog data.

The test plan (page 9) reported that the analogs ADAM and MADAM were tested for genetic toxicity both *in vitro* and *in vivo*. Although both analogs were reportedly negative in the mouse micronucleus test *in vivo*, positive results were obtained for gene mutations in the Ames test (ADAM) and for chromosomal aberrations in cultured human lymphocytes (ADAM) and in Chinese hamster cells (MADAM). These data are adequate for the purposes of the HPV Challenge Program. If the additional details requested in the previous paragraph are not provided and these analog data are therefore needed to support this endpoint on the sponsored substances, a discussion of these test results and their comparison with the category members will need to be included in the test plan or final category analysis.

Repeated-Dose, Reproductive, and Developmental Toxicity. The cited OECD TG's 408, 414, and 422 data on ADAM and the OECD TG 422 data for MADAM satisfy these endpoints. Data from the OECD TG 422 study on ADAM showed effects on fetal development (including malformations and variations) and viability, which does not support the submitter's conclusion of no teratogenic effects of ADAM stated on page 4 of the test plan. The test plan discussion needs to accurately reflect the data for this chemical.

Ecological Effects (fish, invertebrates, and algae)

EPA reserves judgement on the adequacy of the data for these effects because the robust summaries lack critical data elements. This information is particularly important because the toxicity of these substances may vary according to the test method used.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. The summary of the acute oral toxicity test by Collier (1985a) did not specify whether the clinical signs observed were seen in males, females, or both.

Genetic Toxicity. Some of the study summaries were missing critical details (i.e., the number of revertants seen at each test concentration, evidence of use of and appropriate response to positive controls, and statistical methods used).

Ecological Effects

Summaries need to report critical data elements such as total organic carbon and pH. They also need to (1) clarify whether the substance was neutralized, (2) be corrected for 100% active ingredient, and (3) report the measured concentration of the test substance.

Followup Activity

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