October 16, 2002

Sonny Maher, Ph.D. MBA
Panel Manager
American Chemistry Council
Fatty Nitrogen Derivatives Panel Cationics Task Group
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. Maher:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for Fatty Nitrogen Derived Cationics Category posted on the ChemRTK HPV Challenge Program Web site on January 25, 2002. I commend The American Chemistry Council Fatty Nitrogen Derivatives Panel Cationics 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 American Chemistry Council Fatty Nitrogen Derivatives Panel Cationics Task Group advise the Agency, within 90 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

Enclosure

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

EPA Comments on Chemical RTK HPV Challenge Submission:
Fatty Nitrogen Derived Cationics Category

SUMMARY OF EPA COMMENTS

The sponsor, the American Chemistry Council's Fatty Nitrogen Derivatives Panel Cationics Task Group, submitted a test plan and robust summaries for the fatty nitrogen derived (FND) cationics category to EPA on December 20, 2001. EPA posted the submission on the Chemical RTK HPV Challenge Website on January 25, 2002. The category consists of 13 quaternary ammonium compounds. Supporting data on these structurally related compounds are also provided.

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

1. Category Justification. The submitter's approach for grouping the chemicals under this category is acceptable. In addition, the analog data are generally adequate to fill data gaps for this category. However, EPA does not agree with using data for the analog ADBAC (CAS No. 68424-85-1) to satisfy the human health toxicity endpoints due to significant differences in structure between this chemical and the category members.

2. Physicochemical Properties and Environmental Fate. Measured melting point and water solubility data need to be provided. The submitter needs to reassess its conclusions on biodegradation and provide biodegradation data for CAS No. 67784-77-4. The submitter also needs to specify the input data used in the fugacity models and present these data in a robust summary format.

3. Health Effects. EPA recommends conducting a reproduction/developmental screening test on CAS No. 68607-29-4 to address the reproductive and developmental endpoints for the mono-alkyl category members.

4. Ecological Effects. The submitter needs to provide additional green algal and 21-day chronic daphnid toxicity data to support a read-across approach for these endpoints among category members. EPA suggests conducting these studies on CAS No. 112-00-5. In addition, critical data elements are missing from several robust summaries. Therefore, EPA reserves judgement on the adequacy of these studies pending submission of the missing data.

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

EPA COMMENTS ON THE FATTY NITROGEN DERIVED CATIONICS CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposes a category of 13 quaternary ammonium chlorides or sulfates consisting of four monoalkyltrimethyl, seven dialkyldimethyl, one trialkylmethyl, and one dimeric monoalkylpentamethyl compound.

The names and CAS Nos. of these compounds are:

Name	CAS Number
(1) Dodecyltrimethylammonium chloride	112-00-5
(2) Hexadecyltrimethylammonium chloride	112-02-7
(3) Quaternary ammonium compounds, trimethyltallow alkyl, chlorides	8030-78-2
(4) Trimethyloctadecylammonium chloride	112-03-8
(5) Quaternary ammonium compounds, dicoco alkyldimethyl, chlorides	61789-77-3
(6) Quaternary ammonium compounds, di-C_{12-18}-alkyldimethyl, chlorides	68391-05-9
(7) Quaternary ammonium compounds, di-C_{14-18}-alkyldimethyl, chlorides	68002-59-5
(8) Quaternary ammonium compounds, dimethylditallow alkyl, chlorides	68783-78-8
(9) Quaternary ammonium compounds, di-C_{14-18}-alkyldimethyl, Me sulfates	68002-58-4
(10) Quaternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, chloride	61789-80-8
(11) Quaternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, Me sulfates	61789-81-9
(12) Quaternary ammonium compounds, bis(hydroxyethyl)methyltallow alkyl, chlorides	67784-77-4
(13) Quaternary ammonium compounds, pentamethyltallow alkyltrimethylenedi-, dichloride	68607-29-4

The submitter also provides supporting data on three structurally similar chemicals, tricetylmethyl ammonium chloride (TMAC, CAS No. 52467-63-7), didecyldimethylammonium chloride (DDAC, CAS No. 7173-51-5), and dimethylbenzylammonium chloride (ADBAC, CAS No. 68424-85-1).

Category Justification

The submitter bases the category on 1) structural and functional similarities of cationic surfactants; 2) similar physicochemical properties; 3) similar biodegradability; 4) similar aquatic toxicity; 5) low mammalian toxicity; and 6) similar uses and environmental disposition patterns. Furthermore, the submitter states that all compounds in the FND cationics category are structurally similar to Group I compounds in EPA's clustering scheme for toxicity testing in support of re-registering quaternary ammonium compounds under FIFRA (U.S. EPA, 1988). The test plan further states that the analog DDAC can be used to address data gaps because it was designated by EPA as a representative member of Group I. The submitter states that the toxicological profile of the proposed analog ADBAC is similar to that of DDAC and therefore, data for ADBAC can be used for the FND cationics category.

EPA concurs with the submitter's category justification and the use of TMAC and DDAC for supporting data. The submitter, however, needs to provide full robust summaries for DDAC. EPA believes that ADBAC should not be used as an analog for the human health endpoints because of structural differences from the category members. However, the use of ADBAC for ecological effects is acceptable and the submitter should provide the necessary robust summaries.

Test Plan

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

Melting Point. The submitter provided measured data for 1 of the 13 test substances and estimated values for 3 other substances. Generally, the models used are inappropriate for melting point estimation. In order to adequately assess the melting points for these chemicals, the submitter needs to provide measured data, according to OECD guidelines, for the following chemicals: CAS # 61789-77-3, CAS # 68002-59-5, CAS # 61789-80-8, and CAS # 61789-81-9.

Water Solubility. The submitter provided measured data for 1 test mixture and estimated values for the 3 discrete compounds in this category. It is not possible to extrapolate the water solubility for the chemicals in this category based solely on the information provided by the submitter. The submitter needs to provide measured data, according to OECD guidelines, for the following chemicals: CAS # 8030-78-2, CAS # 67784-77-4, and CAS # 68607-29-4.

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

Photodegradation and Stability in Water. EPA considers the data adequate for the purposes of the HPV Challenge Program.

Biodegradation. The submitter indicates in its test plan that "there are adequate measured data across the FND Cationics Category to allow the conclusion that these chemicals are biodegradable although tests are frequently confounded by adsorption phenomena." While there are adequate data for most of the chemicals in this category, EPA believes that the submitter's conclusion is misleading. The data provided by the submitter, in addition to data available from other sources, show that these chemicals have widely varying rates of biodegradation, indicating that some biodegrade rapidly and others don't. The submitter needs to revise its conclusions in order to reflect this more accurate description of the data. Furthermore, EPA believes that the structure of CAS No. 67784-77-4 is sufficiently different from other compounds in the category that the submitter needs to provide data for this chemical following OECD guidelines.

Transport and Distribution (fugacity). Results from a level III fugacity model are presented only in Table 3 of the test plan and details on the input parameters used to run the model are not provided. The submitter needs to provide these data in robust summary format and present the inputs used to run the model.

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

Acute, Repeated-Dose, and Genetic Toxicity. Despite deficiencies in some studies, data for these endpoints are adequate for the purposes of the HPV Challenge Program.

Reproductive Toxicity. No reproductive toxicity studies were submitted for any of the category members. This endpoint is addressed by adequate histopathology of the reproductive organs in subchronic studies conducted on two category members and data from two developmental toxicity studies conducted on DDAC. However, EPA recommends also conducting a reproduction/developmental screening test (OECD Guideline 421) on CAS No. 68607-29-4

because there is no reproductive/developmental toxicity information for the monoalkyl category members.

Developmental Toxicity. The data for the category members were not adequate to address this endpoint; however, two studies on DDAC appear to provide adequate data and provide data for two different species. As stated above, EPA recommends that the submitter conduct a test using OECD Guideline 421 on CAS No. 68607-29-4 to adequately cover this endpoint for the monoalkyl category members.

Ecological Effects (fish, invertebrates, and algae).

The submitter needs to provide additional algae toxicity data and a daphnid 21-day chronic toxicity study to complete a read-across approach for this category. EPA recommends providing these data for CAS No. 112-00-5 because this chemical has a short chain length (and is thus likely to be fairly water soluble). The chemical's water solubility plus the toxicity observed in 7-day fish and daphnid studies indicate that it is likely to be toxic in the recommended 21-day daphnid study (for the invertebrate chronic toxicity endpoint, EPA considers only the 21-day daphnia study (e.g., OECD guideline 202) acceptable for the purposes of the HPV Challenge Program).

In Table 3 of the test plan, the first entry of acute LC50 fish toxicity values for CAS No. 68783-78-8 should be "0.62 to 3.0 mg/L." The table states that the range is up to 24.0 mg/L; however, this upper limit involved a different aspect of the test in which suspended solids were added.

The submitter needs to correctly identify the chemical associated with CAS No. 112-02-7 (see robust summary comments for CAS No. 112-00-5).

Specific Comments on the Robust Summaries

Health Effects

For all endpoints, robust summaries should be prepared for the DDAC studies presented in Appendix B and assign reliability codes to these studies.

Acute Toxicity. The submitter needs to add the following information to summaries where the data are missing: age and weight of the test animals, length of the acclimation period, housing and feeding conditions, purity of the test compound, and/or analytical methods used.

Repeated-Dose Toxicity. Robust summaries were submitted for three dermal studies and three oral studies. Because the submitter did not identify key studies for this category, EPA identified (and evaluated) three oral studies as key studies (one for a category member, CAS No. 61789-81-9, and two for non-category members DDAC and TMAC. The robust summary for TMAC provided adequate data. However, the submitter needs to provide a robust summary for DDAC and the purity of the test substance for CAS No. 61789-81-9.

Genetic Toxicity - Gene Mutations. Data from an Ames test using CAS No. 112-03-8 were judged to be inadequate because only two *S. typhimurium* strains were used and the

concentrations tested were not specified. Data from two Ames tests with CAS No. 112-02-7 were judged inadequate because only two strains were tested and in one of the two tests, concentrations were not provided. The results of all tests were negative with one exception. Positive results were seen in an Ames test using CAS No. 8030-78-2 in one of five *S. typhimurium* strains (TA1538) with and without metabolic activation.

Genetic Toxicity - Chromosomal Aberrations. Data from an *in vivo* rat bone marrow chromosomal aberration test with TMAC were judged inadequate because the cells were harvested too soon after treatment (8 and 12 hours).

Reproductive Toxicity. In addition to providing robust summaries for appropriate studies for DDAC from Appendix B and assigning a reliability rating to this study, EPA also recommends that the submitter include robust summaries that report results of the reproductive organ evaluation from the available repeated-dose studies.

Ecological Effects

The robust summaries need to be expanded to include additional information. Where appropriate, the submitter needs to provide information on the amount of suspended solids used in the test system because the addition of suspended solids can substantially change the toxicity of the FNDs. Also, the summaries need to discuss whether the purity of the chemicals was taken into consideration when determining the LC50s. In some cases, the purity of the test chemical was as low as 35 percent. Finally, in several cases, the submitter needs to add methodological details (e.g., DO, pH, water hardness) if available. Selected chemical-specific comments are discussed below.

CAS No.112-00-5

Fish. The second robust summary in Section 4.1 reports the chemical as docecyltrimethylammonium chloride but the CAS No. as 112-02-7 (which is the number for hexadecyltrimethylammonium chloride). In addition, the size and length of the fish at test initiation are identical in the first and second summaries. The submitter should clarify these issues. If the results are for the same chemical from the same test, the submitter should consider possible reasons that the 24-hr LC50 value is lower than the 96-hr value. Missing data elements include pH, water temperature, water hardness, total organic carbon (TOC), dissolved oxygen (DO) content, and whether results are corrected for test substance purity.

Invertebrates. Missing information includes water temperature, TOC, and percent active ingredient used to determine the results.

CAS No. 112-02-7

Fish. Data are invalid because only a 24-hour test was submitted rather than the accepted 96-hour test.

CAS No. 8030-78-2

Invertebrates (acute). All three tests should have separate robust summaries containing the following missing data: pH, DO, water temperature, TOC, and result values corrected for 100 percent active ingredient.

Invertebrate reproduction (21-day daphnid). Missing data elements include: DO, TOC, pH, water temperature for both river and well water experiments, LOEC value, and results corrected for 100 percent active ingredient.

CAS No. 112-03-8

Fish. Missing data elements are pH, water temperature, alkalinity, DO, TOC, number of fish per number of replicates, water hardness, and test value corrected for 100 percent active ingredient.

CAS No. 68783-78-8

Fish. For both tests using *Lepomis machrochirus*, missing data include TOC, DO, and the 95% confidence limit. The third test using *Cyprinidon variagatus* is missing water hardness, pH at the time of test, TOC, and DO. Also, the 96-hr LC50 is listed as 24.0 mg/L; however, the 95% confidence interval is stated as "9.5 – *6.3* mg/l." The submitter should correct this apparent error.

Invertebrates. For the daphnia study, missing critical missing data elements are water temperature, DO, TOC, and test results corrected for 100 percent active ingredient For *Mysidopsis bahia*, missing data elements are pH, water temperature, DO, TOC, water hardness, and test results corrected for 100 percent active ingredient.

Algae. Missing data elements from robust summaries include pH, water temperature, DO, TOC, and water hardness. Also, for studies that had lower algal toxicity values, the submitter only provided limited information in a table in Appendix A. These data should be presented in a full robust summary format.

CAS No. 61789-80-8

Fish. Several fish robust summaries were missing the following critical data elements: DO, water hardness, TOC, and test results corrected for 100 percent active ingredient.

Invertebrates. Key robust summaries need to be provided because only limited information was provided in a table format in Appendix A.

CAS No. 52467-63-7

Fish. Missing data elements are TOC and DO.

Invertebrates. The missing data element is TOC.

Algae. Missing data elements are water hardness, DO, TOC, and test results corrected for 100 percent active ingredient.

CAS Nos. 68424-85-1 and 7173-51-5

The submitter should provide all applicable robust summaries for these analogs.

Followup Activity

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

Reference

U.S. Environmental Protection Agency. 1988. Notice to Producers, Formulators, Distributors and Registrants: Clustering of Quaternary Ammonium Compounds. PR Notice 88-2.