

October 8, 2002

Nigel J. Sarginson
Product Stewardship and Regulatory Affairs Manager
ExxonMobil Chemical Company
13501 Katy Freeway
Houston, TX 77079

Dear Mr. Sarginson:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Neoacids C5-C28 Category posted on the ChemRTK HPV Challenge Program Web site on January 11, 2002. I commend ExxonMobil Chemical Company 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 ExxonMobil Chemical Company 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:
Neoacids C5-C28**

SUMMARY OF EPA COMMENTS

The sponsor, ExxonMobil Company, submitted a test plan and robust summaries to EPA for Neoacids C5-C28 dated November 15, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 11, 2002. The category consists of 2,2,2-trialkylacetic acids and 2,2-dimethylpropanoic acid, methyl ester.

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

1. Category Definition. The proposed definition is generally clear, but the submitter needs to provide the typical percent composition of C9-C13 and C9-C28 neoacids. The CAS number provided for 2,2-dimethyloctanoic acid (26896-20-8) is for neodecanoic acid. The submitter needs to provide the correct CAS number for 2,2-dimethyloctanoic acid, and indicate if the data provided are indeed for this chemical or for neodecanoic acid.
2. Category Justification. Generally, the data support the grouping for those category members that are acids. EPA disagrees with the inclusion of 2,2-dimethylpropanoic acid, methyl ester as part of the category for ecological effects based on its structure and physical/chemical properties. In addition, unless metabolism and toxicokinetics data are provided, its inclusion for purposes of health effects testing is also questionable.
3. Physicochemical Properties and Environmental Fate. EPA prefers measured physicochemical data for melting point, boiling point (decomposition points if appropriate), vapor pressure, and water solubility. Also, the submitter needs to clarify whether data for a number of endpoints are measured or calculated. For transport and distribution, the submitter needs to provide a level III fugacity model.
4. Health Effects. (a) Except for some deficiencies in robust summaries, adequate data are available for acute toxicity for the purposes of the HPV Challenge Program. (b) EPA considers the data for repeated-dose toxicity inadequate. (c) For genetic toxicity testing, the submitter needs to clarify which substances will be tested to address these endpoints. (d) EPA considers the reproductive toxicity data inadequate. (e) Developmental toxicity data on C6-C8 neoacids do not represent the entire category. Therefore, EPA recommends that the submitter conduct a combined repeated-dose/reproductive/developmental toxicity study on the category members with the shortest and longest chain lengths.
5. Ecological Effects. EPA agrees with the submitter's proposed additional testing. The submitter also needs to conduct a chronic invertebrate test on the upper carbon range of neoacids because of the estimated log Kow values of ≥ 4.2 and their expected toxicity to aquatic organisms. Some data elements missing from the robust summaries need to be supplied.

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

EPA COMMENTS ON THE NEOACIDS C5-C28 CATEGORY CHALLENGE SUBMISSION

Category Definition

The sponsor proposed a category covering a group of 2,2,2-trialkylacetic acids, known as neoacids, with carbon numbers C₅ and C₉-C₂₈. The submitter also included the methyl ester of 2,2-dimethylpropanoic acid in this group. The specific compounds and substances to be sponsored are shown below.

<u>CAS Number</u>	<u>Chemical Name</u>
75-98-9	2,2-Dimethylpropanoic acid,
598-98-1	2,2-Dimethylpropanoic acid, methyl ester
29662-90-6	2,2-Dimethyloctanoic acid
26896-20-8	2,2,3,5-Tetramethylhexanoic acid
68938-07-8	Fatty acids, C9-13 neo
72480-45-6	Fatty acids, C9-28 neo
95823-36-2	Carboxylic acid, C6-8 neo

The submitter needs to provide the percent composition of typical carbon chain lengths for the C9-13 and C9-28 neo acids. The submitter provided an incorrect CAS number, 26896-20-8, for 2,2-dimethyloctanoic acid. The correct CAS number is 29662-90-6. The CAS number 26896-20-8 is actually the CAS number for 2,2,3,5-tetramethylhexanoic acid (neodecanoic acid), which is not a specified member of the category. The submitter needs to clarify which compound is being sponsored. The submitter has also provided data for the nonsponsored substance, C₆-C₈ neo carboxylic acid (CAS No. 95823-36-2), to bridge the data provided for the C₅ and C₉-C₂₈ sponsored neoacids in the test plan.

The members of this category are synthesized from branched olefins, carbon monoxide, and water. Since some of the starting olefins are complex mixtures with unspecified types and locations of branching, the resulting acid mixtures potentially will have branching at more locations than the position alpha to the carboxylic acid moiety.

Category Justification

The submitter supports the category based on a common structural feature (a quaternary carbon alpha to the carboxylic acid moiety), an increase in carbon number across the category, and an anticipated regular pattern in the physicochemical, environmental, and toxicological properties for these compounds and substances across the category. Where gaps exist in the data for one or more members of the category, the submitter's strategy is to interpolate from data that include values from substances representative of the low and high carbon number members of the category. Generally, the data support the grouping for those category members that are acids; there is little support for the single ester member.

EPA disagrees with the submitter's inclusion of 2,2-dimethylpropanoic acid, methyl ester in the category on the basis of the compound's presumed rapid hydrolysis to the parent neoacid. EPA believes that the rationale presented is inconsistent with model data and does not support the grouping of the ester with the other members of the category for ecological effects testing. In addition, unless the submitter provides

additional metabolism and toxicokinetics data on the methyl ester, justification of its inclusion in the category is questionable for purposes of health effects testing.

Test Plan

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

The submitter indicates in its test plan that “physicochemical data...will be calculated for selected chemical components of the neo acid products in this category... In addition, measured data...will also be provided...where readily available.” This suggests that the physicochemical data set provided in the test plan is not complete and that the submitter will be carrying out further searches and estimations. Some physicochemical data are provided in table 2 (page 6 of the test plan). While the submitter states that the data in this table (melting point, boiling point, and vapor pressure) are measured values selected from material safety data sheets, no citations are provided, and in fact, several of these values may have been estimated as they are the same as values calculated by the EPIWIN software. EPA finds the data submitted to be insufficient to evaluate these endpoints. The submitter needs to clarify which data are measured and which calculated. EPA prefers measured physicochemical data for melting point, boiling point (decomposition points if appropriate), vapor pressure, and water solubility. The submitter needs to provide a robust summary for each physicochemical endpoint for each chemical. Measured data may also be available from published sources. However, the submitter should provide the source of these measured data.

A range of values has been submitted for each of the mixtures, C9 - C13 fatty acids and C9 - C28 fatty acids (68938-07-8 and 72480-45-6). EPA recommends that measured values should be provided for a C9, C13 and C28 fatty acid or for the major components of these mixtures.

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

Photodegradation. The submitter’s approach to this endpoint is adequate for the purposes of the HPV Challenge Program. However, the submitter needs to provide robust summaries for photolysis for each chemical instead of a technical document as it indicates in its test plan (page 15). The submitter can combine the photolysis and atmospheric oxidation information in the same robust summary for each chemical.

Stability in water. The submitter’s approach to this endpoint is adequate for the purposes of the HPV Challenge Program.

Biodegradation. The data provided for this endpoint are adequate for the purposes of the HPV Challenge Program.

Transport and Distribution (Fugacity). The sponsor plans to use the level I steady state model to develop distribution data on individual mixture components. Although EPA had previously recommended the use of level I, this model is somewhat limited. EPA now recommends the use of level III, which provides a more rigorous level of analysis. When developing the fugacity model, the sponsor needs to provide the assumption and data inputs to the model (see Guidance for Robust Summary preparation). The data inputs

should be obtained from measured data as much as possible because 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).

Acute Toxicity. EPA agrees that adequate data are available for the purposes of the HPV Challenge Program and considers the proposed read-across approach appropriate.

Repeated-Dose Toxicity. The submitter proposed no additional testing. The submitted data on the dermal toxicity of the lower molecular weight compounds (C5 to C10) are inadequate for the HPV Challenge Program because for all submitted studies (1) the exposure duration was only 14 days rather than the recommended 28 days for this endpoint, and (2) the study used only males. EPA recommends that the submitter conduct a combined repeated-dose/reproductive/developmental toxicity study (OECD TG 422) on the category members with the shortest and longest chain lengths.

Genetic Toxicity. No data were submitted for genetic toxicity. EPA agrees with the submitter's proposal to test for mutagenicity in bacteria (Ames test) and in the mouse micronucleus assay on two category members, one of which is 2,2-dimethylpropanoic acid. The test plan is not consistent as to the identity of the second compound. Page 8 and Table 3 of the test plan identify fatty acids, C9-C28 neo as the second chemical, which would be consistent with the proposed strategy of the sponsor of testing the two extremes of the category. However, the Test Plan Summary on page 17/21 lists 2,2-dimethyloctanoic acid as the second chemical. The submitter needs to clarify which substance will be tested and, if appropriate, provide a rationale for the selection of 2,2-dimethyloctanoic acid as the second compound.

Reproductive Toxicity. EPA considers the submitted data inadequate for the purposes of the HPV Challenge Program. The submitted data on 2,2-dimethyloctanoic acid are inadequate because the testing was not done at high enough doses, no parental or pup toxicity was seen, and the highest dose tested was the NOAEL. EPA considers the submitted studies for isooctanoic acid and isononanoic acid unacceptable for read-across purposes. Isooctanoic acid and isononanoic acid do not have similar structures as those of the category members and it is unclear whether or not there is any substitution at the " " -position. A key feature of the category is lack of an " " -hydrogen, which has a critical effect on potential metabolism pathways. In addition, it is likely that isooctanoic acid is a mixture. Thus, EPA believes that data for these chemicals are not applicable to the category members.

EPA recommends that the submitter conduct a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test (OECD TG 422) on the category members with the shortest and longest chain lengths.

Developmental Toxicity. The submitted data are adequate for C6-C8 neo carboxylic acid, but this information alone is insufficient to characterize the category. As described under Reproductive Toxicity, the data for isooctanoic acid and isononanoic acid cannot be used to characterize the category members, and the submitter needs to conduct the combined repeated-dose toxicity study with reproduction/developmental toxicity screening tests (OECD TG 422) on category members with the shortest and longest chain lengths.

Ecotoxicity (fish, invertebrates, and algae).

EPA agrees with the proposed acute testing for the purposes of the HPV Challenge Program. The Test Plan needs to state that for the fish, invertebrate, and algal studies, the data submitted for the C6-C8 neoacid are from a C7 branched and linear aliphatic acid.

The submitter needs to conduct a chronic invertebrate test on a member of the higher-carbon neo acids because of their log Kow of \$4.2 and their potential to exhibit chronic toxicity in aquatic organisms.

Specific Comments on the Robust Summaries

Health Effects

The commonly missing information from all studies was the purity of the test material, body weight data, 95% confidence interval for the LD50 values, and the results of particle size determinations (inhalation studies). In addition, in the case of studies with 2,2-dimethyloctanoic acid, CAS No. 26896-20-8 is incorrectly assigned to neodecanoic acid and CAS No.29662-90-6 is incorrectly assigned to 2,2-dimethyloctanoic acid; thus, the identity of the tested compound is uncertain.

Reproductive Toxicity. 2,2-dimethyloctanoic acid: The robust summary reported dietary concentrations, but not doses (listed on page 12/21 of the test plan). The summary and test plan (page 12/21) give different citations for this study. Since CAS No. 26896-20-8 is incorrectly assigned to neodecanoic acid and CAS No.29662-90-6 is incorrectly assigned to 2,2-dimethyloctanoic acid, the identity of the tested compound is uncertain.

Ecological Effects

2,2-Dimethylpropanoic acid:

Fish. Missing data elements from the robust summary include chemical purity, dissolved oxygen content, water hardness and analytical monitoring results.

Invertebrates. Missing data element from the robust summary is test chemical purity.

C6-8 Neo carboxylic acid:

Fish. Missing data elements from the robust summary include chemical purity and water hardness.

Algae. Missing data element from the robust summary is chemical purity.

2,2-Dimethyloctanoic acid:

Fish. Missing data elements from the robust summary include water hardness and chemical purity.

Followup Activity

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