

September 23, 2004

Sarah Loftus McLallen
Manager, CHEMSTAR
The American Chemistry Council
Petroleum Additives Health, Environmental
and Regulatory Task Group
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. McLallen:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for C15-C18 Alpha Alkenes, Reaction Products w/Sulfurized Dodecyl Phenol, Calcium Salt, Sulfurized, posted on the ChemRTK HPV Challenge Program Web site on February 4, 2004. I commend The American Chemistry Council Petroleum Additives Health, Environmental and Regulatory 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 60 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 Dr. Ralph Northrop, of the HPV Chemicals Branch, at 202-564-7666. 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,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:
C15-C18 alpha Alkenes, reaction products with Sulfurized Dodecyl Phenol,
Calcium Salt, Sulfurized**

SUMMARY OF EPA COMMENTS

The sponsor, the American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), submitted a test plan and robust summaries to EPA for C15-C18 alpha alkenes, reaction products with sulfurized dodecylphenol, calcium salt, sulfurized (CAS No. 72275-86-6) dated December 18, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 4, 2004.

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

1. Physicochemical Properties. The submitter needs to clarify its proposal to provide data for boiling point and vapor pressure, and to incorporate in the robust summary the melting point, partition coefficient, and water solubility information for two analogs.
2. Environmental Fate. EPA agrees with the proposal to provide data for photodegradation and fugacity. The biodegradation data provided for CAS No. 122384-85-4 are adequate to satisfy that endpoint for the purposes of the HPV Challenge Program. The submitter needs to incorporate the hydrolysis technical discussion into a robust summary.
3. Health Effects. EPA reserves judgement on the acute toxicity, repeated-dose toxicity, and the genetic toxicity endpoint pending additional information on the tested substances and/or justification for the supporting chemicals used. The data are inadequate for the reproductive and developmental toxicity endpoints because CAS No. 67124-09-8 is not an adequate supporting chemical for the dialkyl sulfide component of the sponsored substance. Therefore, EPA recommends conducting a repeated-dose and reproductive/ developmental toxicity screening study using CAS No. 72275-86-6.
4. Ecological Effects. EPA agrees that adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

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

EPA COMMENTS ON THE C15-C18 ALPHA ALKENES, REACTION PRODUCTS WITH SULFURIZED DODECYLPHENOL CALCIUM SALT, SULFURIZED, CHALLENGE SUBMISSION

Substance Identity

The sponsored substance is C15-C18 alpha alkenes, reaction products with sulfurized *dodecyl* phenol, calcium salt, sulfurized (CAS No. 72275-86-6). The sponsor provided summaries for toxicity studies of a substance identified as C15-C18 alpha alkenes, reaction products with sulfurized *tetrapropenyl* phenol, calcium salt, sulfurized (CAS No. 72275-86-6); the latter chemical name implies the highly branched structure depicted in the Test Plan, while the former is ambiguous as to alkyl substituent structure. The robust summaries for the analog with CAS No. 122384-85-4 identify it as dodecyl. This inconsistency raises questions as to whether the health effects studies, for example, were all performed on a highly-branched tetrapropenyl derivative. The submitter needs to clarify whether the tetrapropenyl structure in the test plan always represents the sponsored chemical and all dodecylphenyl test substances; use consistent terms or explain deviations; and discuss any remaining ambiguities in test substance characterization and their significance for data interpretation.

Adding to the potential confusion is the fact that, while most of the robust summaries for “dodecylphenyl” test substances state that the percentage of lubricant base oil is typically 40% in the commercial form, the test plan states that the typical percentage for the title substance is only 19%. The submitter needs to address this difference in the test plan.

Test Plan

The following substances in the submission are referenced in these comments:

CAS No. 72275-86-6	The sponsored substance: C15-18 alpha alkenes, reaction products with sulfurized dodecylphenol, calcium salt, sulfurized
CAS No. 67124-09-8	1-(tert-Dodecylthio)-2-propanol
CAS No. 67762-55-4	C15-18 alpha-Alkenes, sulfurized, proposed analogs of the alkyl sulfide component of the sponsored substance
CAS No. 68511-50-2	2-Methyl-1-propene, sulfurized
CAS No. 91770-97-4	Alkyl C12-16 sulfide
CAS No. 122384-85-4	Sulfurized dodecylphenol, calcium salts, the alkylphenate sulfide component of the sponsored substance

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

The submitter proposes, without explaining further, to provide data for boiling point and vapor pressure. Because one component is a (presumably non-volatile) calcium salt, the sponsored substance occurs in an oil base, and both sulfide components are mixtures, the submitter needs to indicate how meaningful results

are to be obtained. The submitter needs to incorporate in the robust summary the melting point, partition coefficient, and water solubility information for chemical analogs having CAS Nos. 67762-55-4 and 122384-85-4. EPA agrees that, for these endpoints, the two latter substances are reasonable analogs for the sponsored chemical.

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

Photodegradation. EPA agrees with the submitter's proposal to provide data for photodegradation.

Stability in water. While EPA agrees that this chemical is not susceptible to hydrolysis, the submitter needs to explain this with a technical statement in robust summary format.

Biodegradation. The biodegradation data provided by the submitter for CAS No. 122384-85-4 are adequate to represent the sponsored substance for the purposes of the HPV Challenge Program. The biodegradation data for CAS No. 68511-50-2 were not reviewed because this highly branched chemical is not an adequate analog of CAS No. 67762-55-4.

Fugacity. EPA agrees with the submitter's proposal to provide data for fugacity. The submitter needs to provide Level III fugacity model data for this endpoint. When developing the fugacity model, the submitter needs to incorporate the data inputs to the model in the robust summary.

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

The sponsor used five supporting chemicals (CAS Nos. 67124-09-8; 67762-55-4; 68511-50-2; 91770-97-4; and 122384-85-4) to address the HPV health endpoints for the sponsored chemical in this submission (CAS No. 72275-86-6). CAS No. 122384-85-4 is the alkyl phenate sulfide portion of the sponsored mixture, whereas the four other supporting chemicals are alkyl sulfides that all vary to some extent in chemical structure from the alkyl sulfide component of the sponsored substance.

EPA reserves judgement on the acute toxicity, repeated-dose toxicity, and the genetic toxicity endpoint pending additional information on the tested substance and/or justification for the supporting chemical used. The data are inadequate for the reproductive and developmental toxicity endpoints because the dialkyl sulfide component of the sponsored substance is not addressed by data on CAS No. 122384-85-4, and the hydroxypropyl derivative, CAS No. 67124-09-8, is not an adequate supporting chemical for the sponsored substance. Therefore, EPA recommends conducting a repeated-dose and reproductive/developmental toxicity screening study according to OECD TG 421 or 422 using CAS No. 72275-86-6. Additional comments on the adequacy of the supporting chemicals and individual endpoint data are discussed below.

Chemical-Specific Comments. One of the supporting chemicals (CAS number 122384-85-4) is a component of the sponsored substance. Although the use of this chemical is reasonable, EPA reserves judgement on the submitted data. The sponsor needs to address the testing implications of the large percentage of lubricant base oil in CAS No. 122384-85-4 (40%) compared with the lower percentage in the commercial form of the sponsored mixture (19% as stated in the test plan). The sponsor also needs to discuss whether the test substance oil chemical composition is consistent across test substances.

EPA also has reservations about the use of data on three additional supporting chemicals (CAS Nos. 67762-55-4, 68511-50-2, and 91770-97-4). Although CAS No. 67762-55-4 is fairly close in structure to one component of the sponsored mixture, the test substance purity was not provided for the studies using this chemical. Given large differences in test substance identity, it is important to know whether this substance also has a similar concentration to that of the sponsored chemical mixture; therefore, the sponsor needs to adequately characterize this substance. In addition, the sponsor did not provide

adequate justification (e.g., similarities in chemical structure, physicochemical properties, or toxicity) for using CAS No. 68511-50-2 as a supporting chemical for CAS No. 67762-55-4. Further, the supporting chemical with CAS number 91770-97-4 was not listed in ChemID Plus (<http://chem.sis.nlm.nih.gov/chemidplus/>) or (contrary to the submitter's assertion) structurally identified in the earlier Alkyl Sulfides test plan, and thus cannot be evaluated.

CAS No. 67124-09-8 is not an adequate supporting chemical because of clear differences in structure that may result in important differences in metabolism (CAS No. 67124-09-8 has an OH group and is a smaller, highly branched molecule compared with the linear-alkyl sulfide component of the sponsored test substance).

Three of the supporting chemicals (CAS Nos. 67124-09-8, 67762-55-4, and 68511-50-2) were previously submitted in the Alkyl Sulfide Category HPV Submission (posted on June 13, 2000). In its comments (posted on October 6, 2000) EPA noted that the chemicals in that submission do not clearly constitute a category for human health endpoints given differences in toxicity, as well as the lack of support to show that the chemicals share similar structures, limited reactivity, and low biological activity.

Acute Toxicity. EPA reserves judgement on both the acute oral study in rats and a dermal study in rabbits, both putatively of CAS No. 72275-86-6, pending additional information on: (a) characterization of the tested substance; (b) the substance identity issues noted earlier.

Summaries were provided for two acute oral gavage studies of CAS No. 68511-50-2, one acute oral gavage study and two acute dermal studies of CAS No. 122384-85-4, and one acute dermal study of CAS No. 67762-55-4. EPA reserves judgement on these studies for reasons discussed under the section titled *Chemical-Specific Comments*.

Repeated-Dose Toxicity. EPA reserves judgement on the 28-day repeated-dose dermal toxicity study of CAS No. 72275-86-6 in male and female rats pending additional information on: (a) characterization of the tested substance; and (b) the substance identity issues noted earlier.

Summaries were also provided for 28-day repeated-dose oral toxicity studies of CAS No. 67124-09-8 and CAS No. 122384-85-4 in rats. Data using CAS No. 67124-09-8 are inadequate and EPA reserves judgement on using data for CAS No. 122385-85-4 for reasons discussed under *Chemical-Specific Comments*.

Genetic Toxicity. EPA reserves judgement on the gene mutation and chromosomal aberrations endpoints.

(a) *Gene Mutation.* EPA reserves judgement on a negative bacterial gene mutation assay, putatively of CAS No. 72275-86-6, pending additional information on: (1) characterization of the test substance; (2) missing study details in the robust summary (see "Specific Comments on the Robust Summaries"); and (3) the substance identity issues noted earlier.

Summaries were also provided for negative bacterial gene mutation assays of CAS No. 67762-55-4, CAS No. 122384-85-4, and CAS No. 68511-50-2. EPA reserves judgement on these data for reasons discussed under *Chemical-Specific Comments*.

(b) *Chromosomal Aberrations.* No data were submitted for the sponsored substance. Summaries were provided for negative micronucleus assays, including those for a study of CAS No. 122384-85-4 in mice, two studies of CAS No. 68511-50-2 (one in mice and one in rats), and a study of CAS No. 91770-97-4 in mice. EPA reserves judgement on the data for the reasons discussed under *Chemical-Specific Comments*.

Reproductive Toxicity. The data are inadequate. No data were provided for the sponsored substance. Summaries were provided for studies in rats, including a one-generation oral gavage reproductive toxicity study of CAS No. 67124-09-8, and a one-generation oral gavage reproductive/developmental toxicity screening study of CAS No. 122384-85-4. These data do not satisfy the reproductive toxicity endpoint for the reasons discussed under *Chemical-Specific Comments* and because even if the sponsor provides additional information on the study using CAS No. 122384-85-4, the data would represent only one component of the sponsored substance.

Developmental Toxicity. The data are inadequate. No data were provided for the sponsored substance. Summaries were provided for studies in rats, including a one-generation oral gavage reproductive toxicity study of CAS No. 67124-09-8, and a one-generation oral gavage reproductive/developmental toxicity screening study of CAS No. 122384-85-4. These data do not satisfy the developmental toxicity endpoint for the reasons discussed under *Chemical-Specific Comments* and because even if the sponsor provides additional information on the study using CAS No. 122384-85-4, the data would represent only one component of the sponsored substance.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the use of analog data, with the exception of CAS No. 68511-50-2, to satisfy the ecological effects endpoints for the sponsored chemical. The analogs are adequate to cover the major characteristics of the sponsored chemical in that they are structurally similar and poorly water-soluble. One limitation of the test data is that all aquatic tests referenced were performed using water-accommodated fractions (WAF) without using analytical techniques to determine test concentrations. EPA prefers analytical measurements when using this method. However, in this case the data reasonably suggest that the challenge chemical is not likely to show acute or chronic effects in aquatic species.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. Missing study details included test substance characterization, statistical methods, and statistical significance.

Repeated-Dose Toxicity. Missing study details included test substance characterization, a full list of tissues that were examined histologically, a full list of hematological and clinical chemistry parameters evaluated, specific organs weighed, a tabulation of signs of toxicity by dose level, and statistical significance of the observed changes.

Genetic Toxicity: Gene Mutation. Missing study details included test substance characterization, number of replicates per concentration, criteria for a positive response, whether or not controls gave the appropriate response, statistical methods, mean number of revertant colonies per plate for treated and control cultures, whether or not cytotoxicity was observed, and study reference.

Chromosomal Aberrations. Missing study details included test substance characterization, number of cells with chromosomal aberrations and type of aberrations observed for both treated and control cultures, and number of cells scored per animal.

Reproductive and Developmental Toxicity. Missing study details included test substance characterization, parental hematological and clinical chemistry parameters evaluated, specific organs weighed, tabulation of signs of toxicity by dose level, and statistical significance of the observed changes.

Ecological Effects

Fish. Missing study details noted in one or more summaries included control response, total organic carbon (TOC), and water hardness.

Invertebrates. Missing study details noted in one or more summaries included test substance characterization, total organic carbon (TOC), and water hardness.

Followup Activity

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