The following responses describe the actions taken to address the comments offered by the US EPA in response to the DSO data assessment and review document submitted on December 19, 2008. The comments and their associated responses are listed in the order that they were presented. In every case, a good faith effort was made to correct or expand upon the information contained in the original report. This included a concerted effort aimed at obtaining the full reports needed to prepare many of the robust summaries requested by the Agency. Unfortunately, discussions with the sponsor failed to yield mutually acceptable terms for accessing and summarizing the DMDS test data. This necessitated the use of secondary information sources that often contained an incomplete description of the work performed. Although these studies were assigned a low reliability score (i.e.; 4, not assignable), the results were deemed to be adequate for the purposes of this evaluation.

Comment #1:
Some of the stated conclusions are not convincingly supported, or are somewhat contradicted, by the cited data or publications. For example, the test plan states on p. 20 that ecotoxicity data confirm that “DMDS is the most toxic member of the disulfide series in DSO.” However, the fish toxicity data cited do not show a clear trend vs. structure, and the values in Daphnia given for DMDS and the diethyl derivative cannot be considered different, especially given the differing test durations.

Response #1:
The conclusions have been modified to bring them more in line with the supplied test data. The cited statement in the ecotoxicity section has been modified to read, “Taken together, these data indicate that DMDS is a reliable surrogate for the remaining dialkyl disulfides and that the hazards associated with lower members of the series are less than or equal to the ecotoxicity of DMDS.”

Comment #2:
-------- the submitter’s assertion that secondary and tertiary alkyl groups will decrease the toxicity compared to DMDS and unbranched dialkyl disulfides is reasonable. The available evidence supports a more modest conclusion that, for both ecotoxicity and health effects, DMDS is likely to be at least as toxic as the other disulfides and is an acceptable source of toxicity data for the disulfide components of the sponsored mixture for screening purposes.

Response #2:
A comparison of the no-effect levels of DMDS with comparable information on several newly examined congeners suggests that the subchronic toxicity of the dialkyl disulfides and trisulfides in DSO is relatively similar and that differences between these various substances is associated with potency differences once the threshold is exceeded. Consequently, all statements suggesting that DMDS is the most toxic member of the mixture have been replaced with
sentences such as the following, “The test data for DMDS is therefore offered as a reliable and mechanistically supportable substitute for DSO, since the toxicity of the remaining substances are equal to or less than this chemical.”

Comment #3:
The test plan does not address potential trisulfide toxicity. Although trisulfides make up a small percentage of the mixture (four components totaling approximately 3% of DSO (data from Appendix 1 of the Test Plan)), available data show that trisulfides are more biologically potent than disulfides.

Response #3:
The health effect section has been extensively modified to incorporate additional information on the health effects of trisulfides. Repeated-dose testing with dipropyl trisulfide has been presented and analyzed relative to the available test data on DMDS and selected other disulfides in DSO. The information suggests that although the toxic potency of trisulfides is greater than corresponding disulfides, there is no substantial difference in the no-effect levels.

Comment #4:
These data suggest that the trisulfides are more potent hemolytic agents than the disulfides and could contribute to overall DSO toxicity even at low relative concentrations. The submitter needs to revise the test plan to adequately address this potential health effects concern.

Response #4:
The requested changes have been incorporated and an examination of new subchronic test data for dipropyl disulfide suggests that the toxic threshold for the trisulfides is not appreciably different than the corresponding disulfides.

Comment #5:
As one approach, EPA recommends that the submitter provide data from one or more in vitro studies as described in Munday et al. (2003) comparing the response of the DSO mixture to the responses of the individual sulfides examined in the Munday paper, to support the contention that the trisulfides do not contribute to overall toxicity.

Response #5:
No additional testing is deemed necessary since repeated-dose dose testing has been performed with dipropyl trisulfide, one of the key trisulfides in DSO. These data indicate that the toxic no-effect level for disulfides and trisulfides does not differ appreciably.

Comment #6:
EPA recommends that the submitter report the range of values for individual endpoints rather than (or in addition to) the individual values for representative chemicals. EPA considers this approach more reasonable for a complex mixture and has begun to apply it in evaluations of HPV data.
Response #6:
Table 3 had been added to the assessment document, which is patterned after the rosin and rosin salts example provided by the EPA in their comments. The new table shows the range in estimated and measured physical property values for DSO and its major constituents.

Comment #7:
Some data were reported for constituent disulfides in addition to DMDS. However, no robust summaries were provided for these substances. The submitter needs to provide the data for DSO and the various supporting chemicals discussed in the test plan in a DSO robust summary format for each endpoint.

Response #7:
Robust summaries have been prepared in IUCLID 5.2 format for all of the supplied test data on DSO, DMDS, and its related congeners. In some cases, the summaries were generated using secondary information sources, since a full report could not be acquired from the original sponsor.

Comment #8:
The introduction to this section [Physical Chemical Properties] of the test plan asserts that “…approximately 64% of DSO is composed of five dialkyl disulfides with an alkyl carbon number of C4 or less. Consequently, the chemical and physical properties associated with these disulfides will exert a disproportionate impact on the properties of the substance.” However, in the section on vapor pressure the submitter points out the “relatively high volatility of the non-disulfide [emphasis added] chemicals in DSO and their disproportionate contribution to the overall volatility of the substance.” The conflicting sentences need to be modified to eliminate the inconsistency.

Response #8:
The inconsistency has been eliminated by altering the statement in vapor pressure section to read, “The difference between the two values is likely due to the relatively high volatility of the non-disulfide chemicals in DSO and their appreciable contribution to the overall volatility of the substance.”

Comment #9:
The submitter needs to provide a DSO robust summary for each [Environmental Fate] endpoint that discusses the test plan data for DSO and the various supporting chemicals.

Response #9:
Robust summaries have been prepared on all available test data for DSO and the various dialkyl disulfides examined. This includes summaries on those values estimated using the EPI Suite estimation programs.

Comment #10:
For the stability in water endpoint, the summary needs to describe the likelihood of hydrolysis in terms of whether water-sensitive functional groups are present.
Response #10:
The following sentence has been added to the Water Stability section: “Furthermore, dialkyl disulfides all lack water-sensitive functional groups such as ester or epoxide linkages; therefore aqueous hydrolysis is not expected to be an important environmental fate process.”

Comment #11:
The submitter needs to provide robust summary data for fish, unless such data are provided in accordance with the test plan for DMDS (the submitter’s statement that DMDS chronic fish toxicity testing will be performed in conjunction with the previously submitted test plan for DMDS is incorrect and should be corrected to reference acute toxicity).

Response #11:
The reference to chronic fish toxicity testing for DMDS has been corrected in the assessment report and a robust summary has been prepared describing the acute testing performed by the sponsor of the DMDS test plan. Since the full report could not be obtained from the sponsor, a robust summary was developed from incomplete information extracted from their MSDS.

Comment #12:
The submitter of the DMDS test plan has informed EPA that it has completed testing for ecological effects and will provide robust summaries by June 30, 2010. That submitter has also provided EPA with the endpoint values. EPA judges the fish and other new values provided as tentatively adequate pending receipt of adequate robust summaries, because they were performed according to standard OECD guidelines and the results are consistent with other reported values. In addition to the 96-hour rainbow trout LC50 value of 0.97 that already appears in Table 6, the DSO submitter needs to incorporate these values into the revised DSO test plan: Daphnid 48-hr LC50 = 1.82 and algal 72-hr EC50 = 14.3 (growth rate), 11 (biomass) (all values cited as Dr. U. NOACK Laboratorien, 2007).

Response #12:
Robust summaries have been prepared for the ecotoxicity data cited above for DMDS; however, the information was taken directly from the comments supplied by EPA since new robust summaries have not yet been posted for DMDS and an agreement could not be reached with the sponsor to share the test results.

Comment #13:
The Test Plan refers to robust summaries on several endpoints using DSO constituents. The majority of these are with DMDS and the summaries are presented in Appendices III and IV. However, the robust summaries for all other data are missing:
- Health: acute toxicity data with DSO (Furedi-Machacek, 1991a-c and Drummond, 1991) and DPDS (cited as an MSDS from Chevron Phillips Chemical Co., 2005)); irritation and sensitization data with DSO (Furedi-Machacek, 1991d-f); repeated-dose toxicity data with DPDS (Posternak et al, 1969); and genetic toxicity data (Ames test) with DPDS (Tsai et al., 1996). In addition, a robust summary for the 90-day inhalation study with DMDS reported by Kim et al. (2006) is not included in either Appendix.
Response #13:
Robust summaries have been prepared for each of the health effects studies described. The summaries will be made available as a companion report to the revised assessment document.

Comment #14:
Agency files also contain the following TSCA Section 8(e) studies that should be included in the dataset for DSO.

1. A Minimal Toxicological Study With Diethyl Disulfide in Rats (Fiche #: OTS0544426; Doc#: 88-920005643; Old#: 8EHQ-0792-6997)
2. Acute Inhalation Toxicity Study with Diethyl Disulfide in Rats (Fiche #: OTS0544443; Doc#: 88-920005660S; Old#: 8EHQ-0792-7014S)
3. A 10-Day Repeated Inhalation Toxicity Study with Diethyl Disulfide in Rats (Fiche #: OTS0540990; Doc#: 88-920005016S; Old#: 8EHQ-0892-6370S)

Response #14:
The cited studies on diethyl disulfide have all been procured, analyzed, and summarized in both the assessment document and the robust summaries.

Comment #15:
Finally, the submitter should be aware of the comments that the Agency posted to Arkema regarding some deficiencies in the robust summaries for DMDS. Reproductive/Developmental Toxicity. There needs to be a discussion in the robust summary section for reproductive toxicity about the evaluation of reproductive organs in the 90-day inhalation study with DMDS.

Response #15:
As noted above, contact with the sponsor of the DMDS test plan failed to produce an agreement for sharing the DMDS test data. Consequently, this final comment could not be adequately addressed since a full report describing the results from the reproductive/developmental study DMDS was not available for inspection and summarization.