

201-15901A

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

FINAL SUBMISSION

For

HPV Group 1: ALKYL SULFIDES

**Prepared by
American Chemistry Council
Petroleum Additives Panel
Health, Environmental and Regulatory Task Group**

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**LIST OF MEMBER COMPANIES IN THE
HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP**

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

Afton Chemical Corporation (formerly Ethyl Corporation)

Chevron Oronite Company, LLC

Crompton Corporation

ExxonMobil Chemical Company

Ferro Corporation

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

SNPE

EXECUTIVE SUMMARY

The American Chemistry Council (ACC) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its member companies, submit for review and public comment their Final Submission for the “*alkyl sulfide*” category of chemicals under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. As discussed in the report that follows, these alkyl sulfides, which are used as petroleum lubricant additives, were collectively characterized by having structural similarity and limited reactivity, low biological activity, very low water solubility, and low vapor pressure.

Alkyl Sulfide Category. Relying on several factors specified in EPA’s guidance document on “Development of Chemical Categories in the HPV Challenge Program,” in which use of chemical categories was encouraged, the HERTG concluded that the following four closely related chemicals constituted a chemical category:

- 2-propanol, 1-(tert-dodecylthio) - (CAS # 67124-09-8, referred to in this report as propanol/dodecylthio derivative)
- 1-propene, 2-methyl-, sulfurized (CAS # 68511-50-2, referred to in this report as methyl propene derivative)
- Pentene, 2,4,4-trimethyl-, sulfurized (CAS # 68515-88-8, referred to in this report as trimethyl pentene derivative)
- Alkenes, C15-18 alpha-, sulfurized, (CAS # 67762-55-4, referred to in this report as C15-C18 alkene derivative).

Fate and Transport Characteristics. Based on their physicochemical properties and molecular structures, the HERTG concluded that these chemicals were most likely to adsorb strongly to soil and sediments. To verify this conclusion, the HERTG calculated fugacity data on a number of homologues of the alkyl sulfide category chemicals. Compounds in the group were highly hydrophobic such that hydrolysis testing was not technically feasible and the lack of hydrolyzable moieties made hydrolysis modeling unnecessary. Two of the four alkyl sulfides were subjected to biodegradability testing and found to be poorly biodegradable. Even though it was anticipated that alkyl sulfides would not absorb sufficient sunlight and photodegrade given their tendency to bond to soil, the HERTG developed computer modeled data that indicated the alkyl sulfides do not readily photodegrade.

Aquatic Toxicology. Data on acute fish toxicity, acute invertebrate toxicity, and alga toxicity were reviewed and some additional aquatic toxicity studies were completed. The findings of the completed tests and available studies indicated low acute toxicity to fish and aquatic invertebrates, and low alga toxicity when environmentally relevant test methods were used.

Mammalian Toxicology - Acute. Data on acute mammalian toxicity (oral, dermal, and inhalation) were reviewed. Oral LD₅₀ levels for three Group 1 substances were very high, indicating essentially no toxicity, even for the group member most likely to show the upper bounds of toxicity (CAS #67124-09-8). Similarly, acute dermal toxicity tests for three of the alkyl sulfide substances, including the compound most likely to show the upper bounds of

toxicity, showed essentially no toxicity. Inhalation toxicity test data for rats, mice, and guinea pigs again indicated low toxicity.

Mammalian Toxicology - Subchronic Toxicity. The HERTG reviewed six repeated-dose studies with rats and/or rabbits for three of the four substances, including the substance with the predicted upper bound potential for toxicity. No substance-specific toxicity was demonstrated. The changes that did occur in the laboratory animals were determined to be adaptive changes to liver or kidney effects that are not relevant to humans.

Mammalian Toxicology - Reproductive and Developmental Toxicity. The HERTG reviewed the reproductive and developmental toxicity testing for the propanol/dodecylthio derivative (CAS # 67124-09-8), the member of the group with the likely upper bound potential for toxicity. The test showed marginal effects on developmental toxicity (decreased birth weights of pups after administration of the mid and high doses, 167 and 500 mg/kg, respectively) and no reproductive toxicity.

Mammalian Toxicology - Mutagenicity. Bacterial reverse mutation assay test data were reviewed for all of the members of the alkyl sulfide category. In each case the results were negative, both with and without metabolic activation. One of the members of this category was tested in an *in vitro* chromosomal aberration assay. Again, the results were negative for clastogenicity, both with and without metabolic activation. *In vivo* chromosome aberration studies were reviewed for two of the alkyl sulfide substances, as well as a structurally similar analogue. All *in vivo* chromosome aberration data reviewed demonstrated that these alkyl sulfides are non-genotoxic, including the chemical in the group with the likely upper bound potential for genotoxicity.

Conclusion. Based on the physiochemical, environmental fate, aquatic toxicology and mammalian toxicology studies completed for this submission and the data reviewed in this report, the HERTG concluded that the alkyl sulfides do not readily pose a risk to the aquatic and mammalian environments and would likely partition into the soils. As this final submission was completed, careful consideration was given to the number of animals required for tests and conditions to which the animals would be exposed. In consideration of the concerns of some non-government organizations about animal welfare, the use of animals was minimized.

TABLE OF CONTENTS

LIST OF MEMBER COMPANIES IN THE HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP..... 2

EXECUTIVE SUMMARY 3

1.0 INTRODUCTION 7

2.0 GENERAL SUBSTANCE INFORMATION..... 8

3.0 EXPOSURE INFORMATION..... 8

4.0 PHYSIOCHEMICAL PROPERTIES 9

5.0 ENVIRONMENTAL FATE DATA..... 10

5.1 FUGACITY MODELING 10

5.2 HYDROLYSIS 10

5.3 BIODEGRADABILITY 11

5.4 PHOTODEGRADATION..... 11

6.0 ECOTOXICOLOGY DATA..... 13

6.1 FISH ACUTE TOXICITY 13

6.2 INVERTEBRATE ACUTE TOXICITY 13

6.3 ALGA TOXICITY..... 13

7.0 MAMMALIAN TOXICOLOGY DATA 15

7.1 ACUTE MAMMALIAN TOXICITY 15

 7.1.1 Acute Oral Toxicity..... 15

 7.1.2 Acute Dermal Toxicity..... 15

 7.1.3 Acute Inhalation Toxicity..... 15

7.2 REPEATED DOSE TOXICITY OF THE ALKYL SULFIDE CATEGORY..... 16

7.3 REPRODUCTIVE/DEVELOPMENTAL TOXICITY 17

7.4 MUTAGENICITY 22

 7.4.1 Bacterial Gene Mutation Assay..... 22

 7.4.2 In vitro Chromosomal Aberration Assay 22

 7.4.3 In vivo Chromosomal Aberration Assays 22

FIGURE 1. CHEMICAL STRUCTURES..... 7

TABLE 1. PHYSIOCHEMICAL PROPERTIES OF ALKYL SULFIDES 9

TABLE 2. FUNCTIONAL GROUP, CHEMICAL CLASSES, AND HYDROLYTIC POTENTIAL OF ALKYL SULFIDE CATEGORY COMPOUNDS..... 10

TABLE 3. EVALUATION OF ENVIRONMENTAL FATE INFORMATION 12

TABLE 4. EVALUATION OF ECOTOXICOLOGY INFORMATION..... 14

TABLE 5. EVALUATION OF ACUTE TOXICITY INFORMATION.....16
TABLE 6. EVALUATION OF REPEATED DOSE TOXICITY INFORMATION..... 18
TABLE 7. EVALUATION OF MUTAGENICITY INFORMATION 23
TABLE 8. SUMMARY OF DATA FOR ALKYL SULFIDE CATEGORY MEMBERS...24

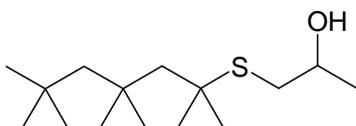
1.0 INTRODUCTION

In March 1999, the American Chemistry Council (ACC) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address data needs for certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program). This Final Submission follows up on that commitment. Specifically, this Final Submission illustrates how the HERTG addressed testing requirements for the four substances listed in Table 1 and identified structurally in Figure 1. These four substances, shown below in Figure 1, are:

- 2-propanol, 1-(tert-dodecylthio) - (CAS # 67124-09-8, referred to in this report as propanol/dodecylthio derivative)
- 1-propene, 2-methyl-, sulfurized (CAS # 68511-50-2, referred to in this report as methyl propene derivative)
- Pentene, 2,4,4-trimethyl-, sulfurized (CAS # 68515-88-8, referred to in this report as trimethyl pentene derivative)
- Alkenes, C15-18 alpha-, sulfurized, (CAS # 67762-55-4, referred to in this report as C15-C18 alkene derivative).

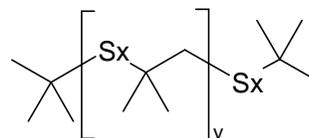
FIGURE 1. CHEMICAL STRUCTURES

**1. Propanol/dodecylthio derivative
CAS # 67124-09-8**



MW = 260 g

**2. Methyl propene derivative
CAS # 68511-50-2**



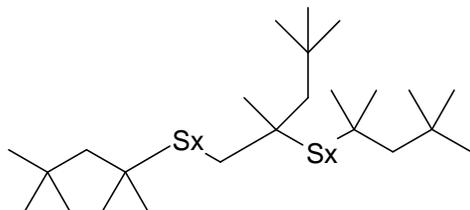
x = 1 - 5

y = 1 - 20

MW = 160 - 1600 g

Mean = 480 g

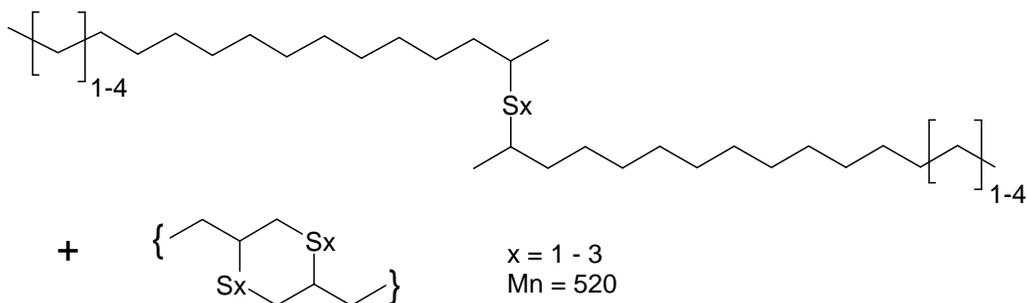
**3. Trimethyl pentane derivative
CAS # 68515-88-8**



x = 4 - 5

MW = 594 - 658 g

**4. C15-C18 Alkene derivative
CAS # 67762-55-4**



MW = Molecular weight; Mn = Mean molecular weight

In preparing this Final Submission, the following steps were undertaken:

Step 1: A review of the literature and confidential company data was conducted on the physiochemical properties, mammalian toxicity endpoints, and environmental fate and effects for the four alkyl sulfide derivatives shown in Table 1 and Figure 1. Searches included the following sources: MEDLINE, BIOSIS, CANCERLIT, CAPLUS, CHEMLIST, EMBASE, HSDB, RTECS, EMIC, and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index, and other references) for physiochemical properties.

Step 2: The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation. Where additional data was needed, testing was completed to meet the Screening Information Data Sets (SIDS) requirements.

2.0 GENERAL SUBSTANCE INFORMATION

The substances that are the subject of this final submission are currently used to formulate lubricating oils. This group of substances is named alkyl sulfides. The chemical names, CAS numbers, and structures for the four closely related members of the alkyl sulfide category are presented in Table 1 and Figure 1.

Studies conducted previously and to fulfill the SIDS requirements for this final submission were conducted primarily using the two members of Group 1 believed to be the most biologically reactive, the Propanol/dodecylthio derivative (CAS #67124-09-8) and the trimethyl propene derivative (CAS# 68511-50-2).

3.0 EXPOSURE INFORMATION

Manufacture

Alkyl sulfides are manufactured as described below:

All four substances are derived from similar starting materials (i.e., alkenes and sulfur), and all contain similar chain length olefinic hydrocarbons linked by sulfur to form linear, branched, or cyclic structures. Commercial alkyl sulfides are manufactured by reacting olefins (linear or branched) with sulfur in a controlled exothermic reaction and then sparged with nitrogen to remove hydrogen sulfide. The 1-propene, 2-methyl- and Pentene, 2,4,4-trimethyl derivatives require a pre-step where an adduct of the olefin and sulfur is first produced and then further reacted with additional sulfur to create the final product. Three substances include saturated long-chain hydrocarbons. Two of the substances contain mixtures of linear and cyclic alkyl sulfides. These substances can also contain cyclic structures made up of sulfur and carbon, and the alkyl groups can be linear or branched.

Use

Alkyl sulfides are used to formulate engine oils, industrial and metal working lubricating oils and greases. The typical concentration of alkyl sulfides in a finished oil or grease ranges from 0.1 to 2%. Alkyl sulfides are generally sold to finished oil blenders contained in additive packages, where the alkyl sulfide concentrations will be higher at 1 to 15%. These additive packages are then blended into finished oils. Alkyl sulfides are used as high temperature and anti-wear inhibitors to reduce deposits on pistons and in the engine crankcase, to control oxidation of the lubricant from high temperatures and reduce wear on moving parts. Additionally, members of the alkyl sulfide category are designed to be hydrophobic surface-active agents, and as a result, must have low solubility in water. Alkyl sulfides are but one of the additive components used to formulate additive packages and finished lubricants.

4.0 PHYSICOCHEMICAL PROPERTIES

The structural similarities of the four members of Group 1 help explain the similarities in physicochemical properties (shown below in Table 1). Although propanol/dodecylthio derivative (CAS # 67124-09-8) contains a hydroxyl moiety, it is still a long-chain saturated hydrocarbon (a hexane and propyl chain) bridged by a sulfide with side chains consisting of six methyl groups.

TABLE 1. PHYSICOCHEMICAL PROPERTIES OF ALKYL SULFIDES

CASRN	Mol. Wt. (g/mole)	MP	BP	Water Sol mg/L	Density g/ml	Vapor Pressure (Pa)	Log Kow
67124-09-8	260	Viscous liquid	Decomp. >200°C	4.84 ^a		<1X10 ⁻³	>6.0
68511-50-2	160-1600 Mean = 480	Viscous liquid	Decomp >200°C	1.29 ^b	1.135	<1X10 ⁻³	>6.0
68515-88-8	594-658	Viscous liquid	Decomp >200°C	2.35e ^{-6 c}		<1X10 ⁻³	>6.0
67762-55-4	520	Viscous liquid	Decomp. >200°C	1.59e ^{-10 c}		<1X10 ⁻³	>6.0

^a Measured value; using OECD 105 Shake Flask method, as part of Challenge Program testing

^b Conservative modeled value based on smallest of the three most common oligomers of CAS # 68511-50-2 (234, 406, and 498 g/mole) having only one sulfur between isobutylene moieties.

^c Modeled water solubility data.

Based on the lower molecular weight and anticipated higher solubility in water seen in Table 1, the environmental fate, aquatic toxicity, and mammalian toxicity data of the methyl propene derivative (CAS #68511-50-2) will be bridged to the trimethyl pentene derivative (CAS # 68515-88-8) and the C15-C18 alkene derivative (CAS # 67762-55-4).

5.0 ENVIRONMENTAL FATE DATA

5.1 FUGACITY MODELING

EQC (Equilibrium Criterion Model, Environmental Modeling Centre as developed by D. Mackay) modeling at Level I for the alkyl sulfides was conducted as part of the HPV test plan. Based on physical properties, it is expected that these chemicals are most likely to adsorb strongly to soil and sediments.

5.2 HYDROLYSIS

The four compounds in the alkyl sulfide category contain neither a functional group that could undergo hydrolytic reactions nor chemical components with a potential for hydrolysis (Table 2). Additionally, as shown in Table 1, the solubilities of the alkyl sulfide members in water are low. As a result, the small amount of the chemicals partitioning into water is expected to be stable. Therefore, no testing was conducted.

TABLE 2. FUNCTIONAL GROUP, CHEMICAL CLASSES, AND HYDROLYTIC POTENTIAL OF ALKYL SULFIDE CATEGORY COMPOUNDS

Members of the Alkyl Sulfide Category	Functional Group and Chemical Class	Potential for Hydrolysis
2-propanol, 1-(tert-dodecylthio)-	Alcohol	Low
	Alkane	Low
	Sulfide	Low
1-propene, 2-methyl-, sulfurized	Alkene	Low
	Alkane	Low
	Sulfide	Low
	Polysulfide	Low
Pentene, 2,4,4-trimethyl-sulfurized	Alkene	Low
	Alkane	Low
	Sulfide	Low
	Polysulfide	Low
Alkenes, C15-18, alpha, sulfurized	Alkene	Low
	Alkane	Low
	Sulfide	Low
	Polysulfide	Low

5.3 BIODEGRADABILITY

As depicted in Table 3, two of the members and one analogue of the alkyl sulfide category have been subject to biodegradability testing. Propanol/dodecylthio derivative (CAS # 67124-09-8), the most water-soluble member of the category (4.84 mg/L), exhibited a very slow rate of biodegradability (5.9% degradation, by OECD 301F, manometric test). Methyl propene derivative (CAS # 68511-50-2), potentially the second most soluble member (Table 1), showed a very slow rate of biodegradability (0.3% degradation by OECD guideline 301B, Modified Sturm Test). Therefore, the results indicated the alkyl sulfides do not readily biodegrade.

5.4 PHOTODEGRADATION

The tendency of these alkyl sulfides to photodegrade was evaluated by using the modeling program AOPWIN. This computer simulation of photo-oxidation was recommended in the Agency's recently released structure activity review (SAR) guidance for HPV chemicals. As shown in Table 3, the estimated photodegradation OH^\cdot rate constants and half-lives of the alkyl sulfides indicate the members of the group do not readily photodegrade.

TABLE 3. EVALUATION OF ENVIRONMENTAL FATE INFORMATION

CHEMICAL	BIODEGRADABILITY	HYDROLYSIS	PHOTODEGRADATION
propanol/dodecylthio derivative (CAS # 67124-09-8)	5.9% biodegraded after 28 days	No testing needed technical limitations ¹	AOPWIN Model Estimation: OH ⁻ Rate Constant (cm ³ /molec-sec) = 23.3 Half-life (hrs) = 5.5
methyl propene derivative (CAS # 68511-50-2)	0.3% biodegraded after 28 days	No testing needed technical limitations ¹	AOPWIN Model Estimation: OH ⁻ Rate Constant (cm ³ /molec-sec) = 35.7-90.7 Half-life (hrs) = 1.4-3.6
trimethyl pentene derivative (CAS # 68515-88-8)	No testing needed Bridging	No testing needed technical limitations ¹	AOPWIN Model Estimation: OH ⁻ Rate Constant (cm ³ /molec-sec) = 18.9-46.7 Half-life (hrs) = 2.8-6.8
C15-C18 alkene derivative (CAS # 67762-55-4)	No testing needed Bridging	No testing needed technical Limitations ¹	AOPWIN Model Estimation: OH ⁻ Rate Constant (cm ³ /molec-sec) = 77.2-300.5 Half-life (hrs) = 1.7-22.6

¹See technical discussion included in hydrolysis section.

6.0 ECOTOXICOLOGY DATA

6.1 FISH ACUTE TOXICITY

Methyl propene derivative (CAS # 68511-50-2) was tested using water accommodated fraction (WAF) and water soluble fraction (WSF) methodology. The results showed this product did not cause acute toxicity to fish at loading rates of 1,000 mg/L and 10,000 mg/L, as demonstrated using WAF and WSF methodology, respectively. An acute fish toxicity test with rainbow trout was conducted with the propanol/dodecylthio derivative (CAS # 67124-09-8) using OECD Guideline 203 Fish, Acute Toxicity Test. WAF methodology was used. The 96-hour LL50 was determined to be 0.42 mg/l.

6.2 INVERTEBRATE ACUTE TOXICITY

Existing data for methyl propene derivative (CAS # 68511-50-2) showed this material did not demonstrate acute toxicity to *Daphnia magna* at a loading rate of 1,000 mg/L using the WAF methodology. An acute invertebrate toxicity test with *Daphnia magna* was conducted with the propanol/dodecylthio derivative (CAS # 67124-09-8) using OECD Guideline 202 *Daphnia* sp., Acute Immobilization Test. WAF methodology was used. The 48-hour EL50 was determined to be 1.3 mg/l.

6.3 ALGA TOXICITY

Existing data for methyl propene derivative (CAS # 68511-50-2) showed this chemical demonstrated toxicity to alga at loading rates greater than 100 mg/L using WAF methodology. An acute algal toxicity test with *Scenedesmus subspicatus* was conducted with the propanol/dodecylthio derivative (CAS # 67124-09-8) using OECD Guideline 201 Alga, Growth Inhibition Test. WAF methodology was used. The 96-hour EL50 was determined to be greater than 100 mg/l. The remaining members of this category are expected to demonstrate toxicity equivalent to methyl propene derivative (CAS # 68511-50-2) because of their similar higher molecular weights and correspondingly low water solubility.

TABLE 4. EVALUATION OF ECOTOXICOLOGY INFORMATION

CHEMICAL	ACUTE TOXICITY TO FISH 96-HOUR LC50¹ (mg/L)	ACUTE TOXICITY TO INVERTEBRATES 48-HOUR EC50¹ (mg/L)	TOXICITY TO ALGAE 96-HOUR EC50¹ (mg/L)
Propanol/dodecylthio derivative (CAS # 67124-09-8)	0.42 (WAF ² , T)	1.3 (WAF ³ , D)	R > 100 (WAF ³ , Sc) B > 100 (WAF ³ , Sc)
Methyl propene derivative (CAS # 6811-50-2)	> 1,000 (WAF ² , F) > 10,000 (WSF ⁴ , S)	> 1,000 (WAF ³ , D)	R > 100 (WAF ³ , P) B = 34 (WAF ³ , P)
Trimethyl pentene derivative (CAS # 68515-88-8)	No testing Bridging	No testing Bridging	No testing Bridging
C15-C18 alkene derivative (CAS # 67762-55-4)	No testing Bridging	No testing Bridging	No testing Bridging

¹Toxicity endpoints for the chemicals are expressed as median lethal concentration (LC₅₀) for fish and median effective concentration (EC₅₀) for *Daphnia* and algae. The EC/LC₅₀ is defined as the concentration that adversely effects 50% of the test organisms exposed to the chemical during a specific time. The greater the EC/LC₅₀ the lower the toxicity. See report text for information regarding differences between reported LC₅₀ and EC₅₀ values and lethal loading rate (LL₀) and effective loading (EC₀) values.

²WAF = Water accommodated fraction static renewal test.

³WAF = Water soluble fraction static non-renewal test.

⁴WSF = Water soluble fraction static renewal test.

F = fathead minnow, *Pimephales promelas*.

T = rainbow trout, *Oncorhynchus mykiss*.

D = freshwater cladoceran, *Daphnia magna*.

P = freshwater algae, *Pseudokirchneriella subcapitata* formerly called *Selenastrum capricornutum*.

Sc = freshwater algae, *Scenedesmus subspicatus*.

S = sheepshead minnow, *Cyprinodon variegatus*.

R = growth rate

B = biomass

7.0 MAMMALIAN TOXICOLOGY DATA

7.1 ACUTE MAMMALIAN TOXICITY

7.1.1 Acute Oral Toxicity

Acute oral toxicity studies (OECD 401) in rats were conducted for three of the four chemicals in the alkyl sulfide category: propanol/dodecylthio derivative (CAS # 67124-09-8), methyl propene derivative (CAS # 68511-50-2), and trimethyl pentene derivative (CAS # 68515-88-8). The oral LD₅₀ for all three substances was greater than the 5,000 mg/kg limit dose indicating that these substances have relatively low toxicity.

7.1.2 Acute Dermal Toxicity

Three of the substances in the alkyl sulfide category were adequately tested for acute dermal toxicity (OECD Guideline 402) in rabbits: propanol/dodecylthio derivative (CAS # 67124-09-8), trimethyl pentene derivative (CAS # 68515-88-8), and C15-C18 alkene derivative (CAS # 67762-55-4). No mortality or treatment-related clinical signs of toxicity or gross lesions were observed for any substance when tested at the limit dose of 2000 mg/kg. Thus, the dermal LD₅₀ was greater than 2000 mg/kg for all three substances, including the Group 1 member with the highest expected toxicity, the propanol/dodecylthio derivative (CAS # 67124-09-8).

7.1.3 Acute Inhalation Toxicity

Two of the substances in the alkyl sulfide category have been adequately tested for acute inhalation toxicity (OECD Guideline 403): methyl propene derivative (CAS # 68511-50-2) and trimethyl pentene derivative (CAS # 68515-88-8). The methyl propene derivative (CAS # 68511-50-2) was tested in rats, while the trimethyl pentene derivative (CAS # 68515-88-8) was tested in rats, mice, and guinea pigs. In a study conducted with the methyl propene derivative (CAS # 68511-50-2), the highest dose tested was 0.39 mg/L (with a whole-body exposure for 4 hours), resulted in no mortality and all animals fully recovered following depuration. No significant clinical, macroscopic, or microscopic signs were noted after the initial post-exposure observations at any dose level. The LC₅₀ for the methyl propene derivative (CAS # 68511-50-2) was greater than 0.39 mg/L (highest dose tested). Acute inhalation toxicity testing of the trimethyl pentene derivative (CAS # 68515-88-8), involved exposure to an aerosol of the test material. In one study, the LC₅₀ was >5.6 mg/L for male rats and equal to 2.17 mg/L for female rats. No treatment-related gross lesions were noted in surviving rats. Two other acute inhalation studies with aerosolized trimethyl pentene derivative (CAS # 68515-88-8) were conducted in rats, mice, and guinea pigs (rats, mice, and guinea pigs in one study and guinea pigs and mice in the second study). One study noted mortality in 3 out of 10 rats, 1 out of 10 mice, and 1 out of 10 guinea pigs at the maximum attainable concentration of 4.3 mg/L. No treatment-related clinical signs were noted for mice and guinea pigs. In another study in which mice and guinea pigs were also tested at the maximum attainable concentration of 4.3 mg/L, no mortality and no treatment-related clinical signs or gross

lesions were noted. For mice and guinea pigs, the LC₅₀ was considered to be >4.3 mg/L (maximum attainable concentration). The LC₅₀ for male rats in this study was considered to be >4.3 mg/L, and the LC₅₀ for females was <4.3 mg/L.

TABLE 5. EVALUATION OF ACUTE TOXICITY INFORMATION

CHEMICAL	ACUTE TOXICITY
propanol/dodecylthio derivative (CAS # 67124-09-8)	<ul style="list-style-type: none"> • Oral – LD50 > 5000 mg/kg (rat) • Dermal – LD50 > 2000 mg/kg (rabbit)
methyl propene derivative (CAS # 68511-50-2)	<ul style="list-style-type: none"> • Oral – LD50 > 5000 mg/kg (rat) • Oral – LD50 = 5.7 ml/kg (rat) • Inhalation – LC50 > 0.39 mg/L (rat) (highest dose tested)
trimethyl pentene derivative (CAS # 68515-88-8)	<ul style="list-style-type: none"> • Oral – LD50 > 5000 mg/kg (rat) • Dermal – LD50 > 2000 mg/kg (rabbit) • Inhalation – LC50 > 5.6 mg/L (male rat); 2.17 mg/L (female rat) • Inhalation – LC50 > 4.3 mg/L (male rat, mouse, guinea pig); > 4.3 mg/L (female rat) (maximum attainable concentration) • Inhalation – LC50 > 4.3 mg/L (mouse, guinea pig)
C15-C18 alkene derivative (CAS # 67762-55-4)	<ul style="list-style-type: none"> • Dermal – LD50 > 2000 mg/kg (rabbit)

7.2 REPEATED DOSE TOXICITY

As noted above and in Table 6, four subchronic dermal toxicity studies (in rats or rabbits) have been conducted with either the methyl propene derivative (CAS # 68511-50-2) or trimethyl pentene derivative (CAS # 68515-88-8). The predominant effect noted was dermal irritation at the site of test material administration with the highest dose (1000 mg/kg). Among the four subchronic dermal toxicity studies conducted for this category, the lowest reported NOEL was 50 mg/kg/day for a 13-week rat dermal study with methyl propene derivative (CAS # 68511-50-2).

A 28-day oral toxicity study in rats has been conducted with the propanol/dodecylthio derivative (CAS # 67124-09-8) and a 28-day inhalation study in rats has been conducted with the trimethyl pentene derivative (CAS # 68515-88-8). In both studies, gross and microscopic observations at study termination showed alterations in kidneys and liver which were similar in nature for both test materials. Gross observations included increased kidney and liver weights in both studies. Microscopic alterations in the kidneys

were seen primarily in male rats and consisted of increased incidences of globular casts and the presence of hyaline droplets in the proximal tubule cells. Although the globular casts were also seen after the recovery period, no hyaline droplets were seen in the recovery animals, indicating that this change was reversible after cessation of test substance administration. This effect was considered to be an organ-, gender- and species-specific (i.e., kidney, male, rat) response that was commonly observed following repeated administration of long-chain aliphatic hydrocarbon-based materials.^{1,2} The male rat was considered uniquely sensitive to such effects, however, these effects are considered irrelevant to humans.³ Microscopic examination of the liver showed hypertrophy of hepatocytes in all animals at termination of the dosing period and in the high-dose animals at the end of the recovery period. These alterations represented a compensatory increase in the activity of hepatic metabolic processes in response to a xenobiotic challenge, and normally are not considered to be pathological.

7.3 REPRODUCTIVE/DEVELOPMENTAL TOXICITY

A one-generation reproductive toxicity study in rats by oral gavage with the propanol/dodecylthio derivative (CAS # 67124-09-8) was conducted using OECD Guideline 415 One-Generation Reproductive Toxicity Study. In this study, the No-observed-adverse-effect level (NOAEL) for parental systemic toxicity was determined to be 50 mg/kg/day; this level was based on the observation of a dose-related increase in post-dose salivation in the 167 and 500 mg/kg/day dose groups. The NOAEL for parental reproductive effects was determined to be 500 mg/kg/day (the highest dose tested); no impaired fertility or other reproductive effects were observed in any of the dose groups. The NOAEL for developmental effects was determined to be 50 mg/kg/day; this level was based on decreased pup weights noted for the 167 and 500 mg/kg/day group pups during the latter half of lactation.

¹ Halder, C.A., et al., Renal Toxicity of Gasoline and Related Petroleum Napthas in Male Rats, *Renal Effects of Petroleum Hydrocarbons*, M.A. Mehlman, C.P. Hemstreet, J.J. Thorpe and N.K. Weaver, eds., Princeton Scientific Publishers, Inc., Princeton, N.J., pp 73-88, 1984.

² Goldsworthy, Thomas L., et al., Potential Role of α -2 I-Globulin, Protein Droplet Accumulation and Cell Replication in the Renal Carcinogenicity of Rats Exposed to Trichloroethylene, Perchloroethylene and Pentachloroethane, *Toxicology and Applied Pharmacology*, Volume 96, pp. 367-379, 1988.

³ U.S. EPA. (1991b) Alpha2u-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment Forum. EPA/625/3-91/019F.

TABLE 6. EVALUATION OF REPEATED DOSE TOXICITY INFORMATION

CHEMICAL	REPEATED DOSE TOXICITY	REPRODUCTIVE/DEVELOPMENTAL TOXICITY
propanol/dodecylthio derivative (CAS # 67124-09-8)	<ul style="list-style-type: none"> ● STUDY: 28-Day Oral (rat) ● Dose Levels: 100, 300, or 1000 mg/kg/day ● Effects: \geq 100 mg/kg/day: increased liver and kidney weights; globular casts; hyaline droplets in proximal tubules; hypertrophy of hepatocytes ● NOEL: < 100 mg/kg/day (not defined in the report) 	<ul style="list-style-type: none"> ● STUDY: One-Generation Reproduction (rat) ● Dose Levels: 50, 167, or 500 mg/kg/day ● Effects: Dose-related increase in post-dose salivation in the 167 and 500 mg/kg/day dose groups; No impaired fertility or other reproductive effects observed in any of the dose groups; Decreased pup weights noted for the 167 and 500 mg/kg/day group pups during the latter half of lactation ● NOAEL for Parental systemic toxicity = 50 mg/kg/day; NOAEL for Parental reproductive effects = 500 mg/kg/day; NOAEL for Developmental effects = 50 mg/kg/day

TABLE 6. EVALUATION OF REPEATED DOSE TOXICITY INFORMATION (CONTINUED)

CHEMICAL	REPEATED DOSE TOXICITY	REPRODUCTIVE/DEVELOPMENTAL TOXICITY
methyl propene derivative (CAS # 68511-50-2)	<ul style="list-style-type: none"> • STUDY ONE: 13-Week Dermal (rat) • Dose Levels: 10, 50, 100, 250, 500, or 2000 mg/kg/day • Effects: ≥ 250 mg/kg/day: decreased body weight gain (males); decrease in RBC; increase in neutrophils; increase in spleen size and pigments in spleen; ≥ 100 mg/kg/day: increased production of WBC in spleen and bone marrow; $\geq 10\%$ (100 mg/kg/day) concentration: dermal irritation • NOEL: 50 mg/kg/day (systemic)10% (dermal irritation) 	No testing needed Bridging
methyl propene derivative (CAS # 68511-50-2)	<ul style="list-style-type: none"> • STUDY TWO: 28-Day Dermal (rabbit) • Dose Levels: 200 or 2000 mg/kg/day (intact and abraded skin) • Effects: ≥ 200 mg/kg/day: severe skin irritation; 2000 mg/kg/day: decrease in body weight and food consumption (males) NOEL: < 200 mg/kg/day (not defined in the report) 	No testing needed Bridging

TABLE 6. EVALUATION OF REPEATED DOSE TOXICITY INFORMATION (CONTINUED)

CHEMICAL	REPEATED DOSE TOXICITY	REPRODUCTIVE/DEVELOPMENTAL TOXICITY
methyl propene derivative (CAS # 68511-50-2)	<ul style="list-style-type: none"> • STUDY THREE: 21-Day Dermal (rabbit) • Dose Levels: 140, 560, or 2240 mg/kg/day • Effects: \geq 140 mg/kg/day: severe erythema and slight to moderate edema. Epithelial hyperplasia of the skin in all treated animals. • NOEL: < 140 mg/kg/day (not defined in the report) 	No testing needed Bridging
trimethyl pentene derivative (CAS # 68515-88-8)	<ul style="list-style-type: none"> • STUDY ONE: 28-Day Inhalation (rat) • Dose Levels: 15, 50, or 150 mg/m³ • Effects: \geq 15 mg/ m³: Trend toward lower body weight gain (all males and two highest doses in females); increased kidney weights (all males only); globular casts in cortico-medullary junction; hyaline droplets in proximal tubules (all males and recovery high dose males); increased liver weight (high-dose males and females and mid-dose males); 150 mg/L: decrease in hemoglobin concentration • NOEL: < 15 mg/ m³ (not defined in the report) 	No testing needed Bridging

TABLE 6. EVALUATION OF REPEATED DOSE TOXICITY INFORMATION (CONTINUED)

CHEMICAL	REPEATED DOSE TOXICITY	REPRODUCTIVE/DEVELOPMENTAL TOXICITY
trimethyl pentene derivative (CAS # 68515-88-8)	<ul style="list-style-type: none"> • STUDY TWO: 28-Day Dermal (rat) • Dose Levels: 1000 mg/kg/day • Effects: Irritating to rat skin at 1000 mg/kg/day; Dermal irritation included well-defined erythema, scabbed areas, and dry flaking skin. Minimal to mild multifocal eschar and mild multifocal hemorrhage in the underlying dermis. <p style="text-align: center;">NOEL: < 1000 mg/kg/day</p>	No testing needed Bridging
C15-C18 alkene derivative (CAS # 67762-55-4)	No testing needed Bridging	No testing needed Bridging

7.4 MUTAGENICITY

A summary of the mutagenicity information for the alkyl sulfides is presented in Table 7.

7.4.1 Bacterial Gene Mutation Assay

For two of the test substances, methyl propene derivative (CAS # 68511-50-2) and trimethyl pentene derivative (CAS # 68515-88-8), various strains of *S. typhimurium* and *E. coli* were tested with and without metabolic activation at doses that included and/or exceeded the limit dose of 5000 µg/plate. For the other two test substances, propanol/dodecylthio derivative (CAS # 67124-09-8) and the C15-C18 alkene derivative (CAS # 67762-55-4), the highest dose tested using various strains of *S. typhimurium* was 1 µl/plate (highest dose at which no precipitation was formed) with and without metabolic activation. All tested chemicals were negative for mutagenic activity, with and without metabolic activation.

7.4.2 In vitro Chromosomal Aberration Assay

An *in vitro* chromosomal aberration assay (using Chinese hamster ovary cells) was conducted for the propanol/dodecylthio derivative (CAS # 67124-09-8). This study was conducted in accordance with OECD Guideline 473. The results of this study, performed with and without metabolic activation of the test material, were negative for clastogenicity.

7.4.3 In vivo Chromosomal Aberration Assays

In vivo chromosomal aberration assays (using bone marrow cells from mice that were dosed by oral gavage or intraperitoneal injection) were conducted with methyl propene derivative (CAS # 68511-50-2), trimethyl pentene derivative (CAS # 68515-88-8), and an analog of the products in this class (CAS # 91770-97-4). The analog is a C12-C16 alkyl sulfide (CAS # 91770-97-4) bearing a methyl substituted side chain, with a structure very similar to the other alkyl sulfides in this group. These studies were conducted in accordance with OECD Guideline 474. All test substances were negative for clastogenicity. One of the test substances, the methyl propene derivative (CAS # 68511-50-2) was also tested in an *in vivo* micronucleus assay in rats via the dermal route of exposure. The results of the micronucleus assay were also negative.

TABLE 7. EVALUATION OF MUTAGENICITY INFORMATION

CHEMICAL	BACTERIAL GENE MUTATION ASSAY	<i>IN VITRO</i> CHROMOSOMAL ABERRATION ASSAY	<i>IN VIVO</i> CHROMOSOMAL ABERRATION ASSAY
propanol/dodecylthio derivative (CAS # 67124-09-8)	Negative +/- S9	Negative +/- S9	No testing needed Bridging
methyl propene derivative (CAS # 68511-50-2)	Negative +/- S9	No testing needed Bridging	Negative (mouse) Negative (rat)
trimethyl pentene derivative (CAS # 68515-88-8)	Negative +/- S9	No testing needed Bridging	Negative (mouse)
C15-C18 alkene derivative (CAS # 67762-55-4)	Negative +/- S9	No testing needed Bridging	No testing needed
analog for C15-C18 alkene derivative (CAS # 91770-97-4)			Negative (mouse)

TABLE 8. SUMMARY OF DATA FOR ALKYL SULFIDE CATEGORY MEMBERS

CAS Number	Environmental Fate					Ecotoxicity			Human Health Effects				
	Physical Chem	Photodeg	Hydrolysis	Fugacity	Biodeg	Acute Fish Toxicity	Acute Invert Toxicity	Algal Toxicity	Acute Toxicity	Point Mutations	Chrom Effects	Sub-chronic	Repro/Develop
67124-09-8	C	C	NA	C	A	A	A	A	A	A	A	A	A
68511-50-2	C	C	NA	C	A	A	A	A	A	A	A	A	B
68515-88-8	C	C	NA	C	B	B	B	B	A	A	A	A	B
67762-55-4	C	C	NA	C	B	B	B	B	A	A	B	B	B

- A Adequate data available
- B Bridging
- C Computer modeling completed
- D Technical discussion completed
- NA Not applicable based on physiochemical properties of the substances