SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL
Disulfides, Diethyl and Diphenyl, Naphtha Sweetening
CASRN 68955-96-4

SUPPORTING CHEMICALS

Dimethyl Disulfide	**CASRN 624-92-0**
Dipropyl Disulfide	**CASRN 629-19-6**
Diethyl Disulfide	**CASRN 110-81-6**
Diisopropyl Disulfide	**CASRN 4253-89-8**

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

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[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

OPPT may not develop HCs for those HPV chemicals which have recently been assessed and published internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments. HCs may be created if new data suggest a need to update the case work where the OECD document will be used as key support documentation.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**Sponsored Chemical** **68955-96-4** **Supporting Chemicals** **624-92-0** **629-19-6** **110-81-6** **4253-89-8**
Chemical Abstract Index Name	**Sponsored Chemical** **Disulfides, Diethyl and Diphenyl, Naphtha Sweetening** **Supporting Chemicals** **Disulfide, dimethyl** **Disulfide, dipropyl** **Diethyl disulfide** **Disulfide, diisopropyl**
Structural Formula	**Sponsored Chemical** **Complex Mixture** **Supporting Chemicals** **See Appendix**

Summary

Diethyl and diphenyl disulfides, naphtha sweetening (CASRN 68955-96-4, aka disulfide oil) is a complex mixture consisting primarily of 10 dialkyl disulfide components (Test Plan: "Despite the official nomenclature, [disulfide oil] does not contain appreciable amounts of diphenyl disulfides."). At ambient temperatures, disulfide oil and the supporting chemicals exist as liquids with moderate to high water solubility and moderate to high vapor pressure. Disulfide oil and the supporting chemicals are expected to have moderate to high mobility in soil. Volatilization from water is expected to be high based on the Henry's Law constants of the components of this mixture. The mixture components are not subject to hydrolysis because they lack water-sensitive functional groups. The rate of atmospheric photooxidation is considered rapid. Data from one component suggest the main components are not readily biodegradable. The overall weight of experimental evidence and data from structurally similar compounds suggest that the sponsored mixture and its supporting constituent chemicals will have moderate persistence (P2) and low (B1) bioaccumulation potential.

The acute oral toxicity of disulfide oil and supporting chemical dipropyl disulfide is low in rats. The acute oral toxicity of supporting chemical dimethyl disulfide is moderate in rats. The acute

dermal toxicity of disulfide oil and dimethyl disulfide is moderate and low, respectively, in rabbits. The acute inhalation toxicity of disulfide oil and supporting chemicals dimethyl disulfide and diethyl disulfide is moderate in rats. In a 90-day inhalation repeated-dose toxicity study in rats with dimethyl disulfide, microscopic changes in the nasal mucosa were observed at 0.039 mg/L/day; the NOAEC for systemic toxicity was not established. A 90-day inhalation repeated-dose toxicity study with dimethyl disulfide showed a decrease in mean body weight gain in females at 0.096 and in males at 0.048 mg/L/day; the NOAEC for systemic toxicity is 0.019 and 0.096 mg/L/day in female and male rats respectively. A 4-week dermal repeated-dose toxicity study in rabbits with dimethyl disulfide showed no treatment-related effects at 106.3 mg/kg/day (highest dose tested). Supporting chemical dipropyl disulfide showed no treatment-related effects in rats in a 90-day dietary repeated-dose toxicity study at 7.3 mg/kg-bw/day in males and 8.2 mg/kg-bw/day in females (highest doses tested). No specific reproductive toxicity data are available; however, in the 90-day inhalation repeated-dose toxicity study with dimethyl disulfide, no treatment-related effects were observed on reproductive organs. In an inhalation prenatal developmental toxicity study in rats with dimethyl disulfide a decrease in body weight gain was observed in dams at 0.058 mg/L/day; the NOAEC for maternal toxicity is 0.019 mg/L/day. In the same study, a decrease in litter size, fetal weights and increased retarded fetal ossification were observed at 0.19 mg/L/day; the NOAEC for developmental toxicity is 0.058 mg/L/day. Dimethyl disulfide is not mutagenic in bacteria and Chinese Hamster Ovary (CHO) cells *in vitro*. Dimethyl disulfide did not induce chromosomal aberrations in human lymphocytes *in vitro* and did not induce micronuclei in mice *in vivo* or induce unscheduled DNA synthesis in rat hepatocytes *in vitro* or *in vivo*. Disulfide oil is irritating to the rabbit eye and skin and is not a skin sensitizer in guinea pigs. Dimethyl disulfide is irritating to the rabbit eye and skin and is not a sensitizer to guinea pig skin. Diethyl disulfide is irritating to the rat eye.

For disulfide oil, using data for dimethyl disulfide, diisopropyl disulfide and dipropyl disulfide, the 96-h LC_{50} for fish ranges from 0.97 to 8.3 mg/L. Using data for dimethyl disulfide, the 48-h EC_{50} for aquatic invertebrates is 1.82 mg/L, and the 96-h EC_{50} for aquatic plants is 14.3 mg/L for biomass and 25.6 mg/L for growth rate, respectively.

No data gaps are identified under the HPV Challenge Program.

The sponsor, API (on behalf of the Petroleum HPV Testing Group), submitted a Test Plan and Robust Summaries to EPA for diethyl and diphenyl disulfides, naphtha sweetening (CASRN 68955-96-4; 9th CI name: disulfides dialkyl and diphenyl, naphtha sweetening, or disulfide oil [DSO]) on January 8, 2009. EPA posted the submission on the ChemRTK HPV Challenge website on March 10, 2009 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/disuloil/c16767tc.htm). EPA comments on the original submission were posted to the website on April 8, 2010. Public comments were also received and posted to the website. The sponsor submitted a revised test plan and robust summaries on December 21, 2010, which were posted to the website on March 28, 2011.

Justification for Supporting Chemicals

The sponsored chemical, diethyl and diphenyl disulfides, naphtha sweetening, is a complex mixture composed of 44 individual constituents (see Appendix). Despite the official nomenclature, it does not contain appreciable amounts of diphenyl disulfides. Five of the constituents are short-chain (C1 to C3) dialkyl disulfides that comprise ~ 87% of the mixture. Four of the ten dialkyl disulfides are present at concentrations > 10% (methyl ethyl disulfide [18.2%]; methyl isopropyl disulfide [14.4%]; dimethyl disulfide [12%]; diethyl disulfide [11.2%]; and ethyl 1-methylethyl disulfide [11.6%]). The sponsored chemical also contains four alkyl trisulfides, totaling approximately 3% of the mixture. The sponsor proposed the use of data for dimethyl disulfide (CASRN 624-92-0) to characterize the SIDS endpoints for the sponsored chemical.

EPA agrees with the use of dimethyl disulfide as a supporting chemical to satisfy the aquatic toxicity endpoints. In addition, EPA believes that the data for dimethyl disulfide provide a reasonable representation of possible human health effects for the di- and trisulfide components of the sponsored chemical. Additional short-chain alkyl disulfides that have been used as supporting chemicals in the characterization of the mammalian toxicity of the sponsored chemical are dipropyl disulfide (CASRN 629-19-6) and diethyl disulfide (CASRN 110-81-6).

While EPA originally commented that trisulfide toxicity might not be adequately addressed by the disulfide data, the sponsor argues in its revised submission (December 21, 2010) that dimethyl disulfide, dipropyl disulfide and dipropyl trisulfide have similar toxic thresholds, as evidenced by similar NOAEL values. EPA has decided that the data, while less than complete, are sufficient on a weight-of-evidence basis in this case to support the sponsor's approach.

For the ecotoxicity endpoints, in addition to dimethyl disulfide, EPA used diisopropyl disulfide (CASRN 4253-89-8) and dipropyl disulfide, which are constituents of disulfide oil, as supporting chemicals.

1. Chemical Identity

1.1 Identification and Purity

Disulfide oil consists of substances extracted from light hydrocarbon streams during petroleum refining. Disulfide oil is a product of mercaptan removal from selected C4 to C5 light hydrocarbon streams by a process known as sweetening, since it removes the "sour-smelling" hydrosulfides present in crude petroleum. The mercaptans are extracted from this feedstock in an entirely closed system referred to as a Merox® unit, which can be designed to operate with any of a variety of petroleum streams. The Merox unit uses a basic solution of caustic soda as the extracting solvent, which is recycled and reused in a continuous loop following each use. Once removed, the mercaptans are oxidized to disulfides, which are separated from the caustic soda solution. The final disulfide oil is then either disposed of on site or processed as: i) an internal fuel, ii) a feedstock for sulfuric acid production, or iii) an agent for conditioning refinery catalysts. The disulfide content of disulfide oil is around 87% (w/w). Disulfide oil carries the signal word DANGER! It is a pale yellow extremely flammable liquid with a pungent and unpleasant odor. Disulfide oil is a complex mixture of as many as 44 individual constituents (see Appendix for a sample analysis), mostly dialkyl disulfides with alkyl chain lengths no greater than C4.

1.2 Physical-Chemical Properties

The physical-chemical properties of the sponsored substance and supporting chemicals are summarized in Table 1. Structures of the supporting chemicals for the sponsored substance are provided in the Appendix. Disulfide oil and the supporting chemicals exist as liquids at room temperature with moderate to high water solubility and moderate to high vapor pressure.

Table 1. Physical-Chemical Properties of Dialkyl and di-Ph Disulfides, Naphtha Sweetening and Certain Individual Constituents[1]					
Table 1. Physical-Chemical Properties of Disulfides, dialkyl and di-Ph, Naphtha Sweetening and its Individual Constituents[1]					
Property	**SPONSORED CHEMICAL** **Dialkyl and di-Ph disulfides, naphtha sweetening**	**SUPPORTING CHEMICAL** **Dimethyl Disulfide**	**SUPPORTING CHEMICAL** **Dipropyl Disulfide**	**SUPPORTING CHEMICAL** **Diisopropyl Disulfide**	**SUPPORTING CHEMICAL** **Diethyl Disulfide**
CASRN	68955-96-4	624-92-0	629-19-6	4253-89-8	110-81-6
Molecular Weight	Complex mixture	94.19	150.31	150.31	122.25
Physical State	Yellow liquid	Liquid	Liquid	Liquid	Liquid
Melting Point	-54°C (measured)	-85°C (measured)[2]	-85.6°C (measured)[3]	-69°C (measured)[3]	-101.5°C (measured)[3]
Boiling Point	111–174°C (measured)	109.6°C (measured)[2]	193.5°C (measured)[3]	177°C (measured)[3]	154.1°C (measured)[3]
Vapor Pressure	57 mm Hg at 25°C (measured)	22.0 mm Hg at 20°C (measured); 28.6 mm Hg at 25°C (measured)[3]	0.512 mm Hg at 25°C (measured)[3]	1.12 mm Hg at 25°C (estimated)[2]	4.28 at 25°C (measured)[3]
Dissociation Constant (pK_a)	Not applicable				
Henry's Law Constant	0.00121–0.0038 atm-m^3/mole at 25°C (calcd from meas. data/estim)[3,4,5]	0.00121 atm-m^3/mole at 20°C (Calcd from meas. data)[3]	0.0038 atm-m^3/mole at 25°C (estimated)[2]	0.0038 atm-m^3/mole at 25°C (estimated)[2]	0.0022 atm-m^3/mole at 25°C (Calcd from meas.data)[3]
Water Solubility	<100 mg/L at 25°C (measured)	2,500 mg/L at 20°C (measured)[2]	51.7 mg/L at 25°C (estimated)[2]	71.6 mg/L at 25°C (estimated)[2]	300 mg/L at 25°C (measured)[3]
Log K_{ow}	1.77–3.84 (estimated)[4,5]	1.77 (measured)[2]	3.84 (estimated)[2]	3.69 (estimated)[2]	2.86 (estimated)[4]

[1] Petroleum HPV Testing Group. 2010. Revised Test Plan and Robust Summary for Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (aka Disulfide Oil) (CASRN 68955-96-4). Available online at http://www.epa.gov/chemrtk/pubs/summaries/disuloil/c16767tc.htm as of April 18, 2011.

[2] ATOFINA Chemicals, Inc. 2011. Test Revised Plan and Robust Summary for Dimethyl Disulfide. Available online at http://www.epa.gov/oppt/chemrtk/pubs/summaries/dimthdsl/c16161tc.htm as of April 13, 2011.

[3] SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available online at http://www.syrres.com/esc/physprop.htm as of April 13, 2011.

[4] U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of April 13, 2011.

[5] Data range is based upon read across data from supporting chemicals; see Appendix for detailed information on the supporting chemicals.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 624-92-0 had an aggregated production and/or import volume in the United States between 1 million pounds and 10 million pounds during calendar year 2005.

No industrial processing and uses, and commercial and consumer uses were reported for this chemical.

2.2 Environmental Exposure and Fate

The environmental fate properties are provided in Tables 2.

Disulfide oil and the supporting chemicals are expected to have moderate to high mobility in soil. Biodegradation data exists for one member of this mixture. Dimethyl disulfide, which on average constitutes 12% w/w of the disulfide oil mixture, degraded <10% after 28 days in the closed bottle tests (OECD 301D) and is considered not readily biodegradable. It was also not readily biodegradable using a modified MITI (OECD 301C) test designed for volatile substances. Volatilization from water is expected to be high based on the Henry's Law constants for the sponsored and supporting chemicals. The components of this complex mixture are not subject to hydrolysis because they lack water-sensitive functional groups. The rate of atmospheric photooxidation is considered rapid for the sponsored mixture and supporting chemicals. The overall weight of experimental evidence and data from structurally similar compounds suggests that the sponsored mixture and its supporting constituent chemicals will have moderate persistence (P2) and low (B1) bioaccumulation potential.

Table 2. Environmental Properties of Dialkyl and Di-Ph Disulfides, Naphtha Sweetening and Certain Individual Constituents[1]					
Property	**SPONSORED CHEMICAL** **Dialkyl and di-Ph disulfides, naphtha sweetening**	**SUPPORTING CHEMICAL** **Dimethyl Disulfide**	**SUPPORTING CHEMICAL** **Diisopropyl disulfide**	**SUPPORTING CHEMICAL** **Dipropyl Disulfide**	**SUPPORTING CHEMICAL** **Diethyl Disulfide**
CASRN	68955-96-4	624-92-0	4253-89-8	629-19-6	110-81-6
Photodegradation Half-life	0.5–0.6 hours (estimated)[2,3]	0.6 hours (estimated)[2]; 4.6 hours (direct photolysis)[4]; 1.1 hours (estimated photooxidation with nitrate radicals)[4]	0.5 hours (estimated)[2]	0.5 hours (estimated)[2]	0.5 hours (estimated)[2]
Hydrolysis Half-life	Stable				
Biodegradation	No data	<10% after 28 days (not readily biodegradable); 0–4% after 28 days (not readily biodegradable)[5]	No data	No data	No data
Bioaccumulation Factor	BAF = 6.1–220 (estimated)[2,3]	BAF = 6.1 (estimated)[2]	BAF = 178 (estimated)[2]	BAF = 210 (estimated)[2]	BAF = 50.1 (estimated)[2]
Log K_{oc}	1.6–2.6 (estimated)[2,3]	1.6 (estimated)[2]	2.5 (estimated)[2]	2.6 (estimated)[2]	2.1 (estimated)[2]
Fugacity (Level III Model)[2]					
Air (%)	0.5–1.0	1.0	0.6	0.5	0.7
Water (%)	31.3–58.1	58.1	36	31.3	40.9
Soil (%)	40.8–67.7	40.8	62.9	67.7	58.1
Sediment (%)	0.2–0.6	0.2	0.5	0.6	0.3
Persistence[6]	P2 (moderate)	P2 (moderate)	P2 (moderate)	P2 (moderate)	P2 (moderate)
Bioaccumulation[6]	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)

[1] Petroleum HPV Testing Group. 2010. Revised Test Plan and Robust Summary for Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (aka Disulfide Oil) (CASRN 68955-96-4). Available online at http://www.epa.gov/chemrtk/pubs/summaries/disuloil/c16767tc.htm as of April 18, 2011.

[2] U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of April 13, 2011.

[3] Data range is based upon read across data from supporting chemicals; see Appendix for detailed information on the supporting chemicals.

[4] Hazardous Substance Databank. 2011. Methyl disulfide CASRN 624-92-0. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB as of April 15, 2011.

[5] National Institute of Technology and Evaluation. 2002. Biodegradation and bioaccumulation of the existing

[6] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. Federal Register 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: Disulfide oil is a complex mixture consisting primarily of 10 dialkyl disulfide components. At ambient temperatures, disulfide oil and the supporting chemicals exist as liquids with moderate to high water solubility and moderate to high vapor pressure. They are expected to have moderate to high mobility in soil. Volatilization is expected to be high based on the Henry's Law constants of the components. The components are not subject to hydrolysis because they lack water-sensitive functional groups. The rate of atmospheric photooxidation is considered rapid. Data for dimethyl disulfide suggest that the chemicals in this complex mixture are not readily biodegradable. The overall weight of experimental evidence including data from structurally similar compounds suggests that the sponsored mixture and its supporting constituent chemicals will have moderate persistence (P2) and low (B1) bioaccumulation potential.

3. Human Health Hazard

A summary of the human health toxicity data submitted for SIDS endpoint is provided in Table 3. The table also indicates where data for the supporting chemical are read-across (RA) to the sponsored chemical.

Acute Oral Toxicity

Diethyl and Diphenyl Disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Male and female rats (number and strain not specified) were administered disulfide oil via oral gavage. Doses and detailed methods were not provided.
LD_{50} (males) = 1700 mg/kg
LD_{50} (females) = 1590 mg/kg

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
(1) Sprague-Dawley rats (5/sex/dose) were administered a single dose of dimethyl disulfide undiluted at 5 mL/kg or a suspension at 10 mL/kg in polyethylene glycol 300 via oral gavage at 0, 100, 290, 350, 500 or 5300 mg/kg and observed for 14 days following dosing. Mortalities were observed at 290 (30%) and 500 (100%) mg/kg.
LD_{50} = 290 - 500 mg/kg

(2) Wistar rats (5/sex/dose) were administered dimethyl disulfide as a suspension in 3% carboxymethyl cellulose via oral gavage at 0, 125, 188, 250, 375 or 500 mg/kg and observed for 14 days following dosing. Male rat mortalities were observed at 125(0/5), 188(5/5), 250(3/5) 375 (5/5) and 500(5/5). Female mortalities were observed at 125(1/5), 188(1/5), 250(4/5), 375(5/5), 500(5/5).
LD_{50} > 188 < 250 mg/kg

Dipropyl disulfide (CASRN 629-19-6, supporting chemical)
Rats (sex, number and strain not specified) were administered dipropyl disulfide via the oral route. No other details were provided.
LD_{50} > 2000 mg/kg

Acute Dermal Toxicity

Diethyl and diphenyl disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Rabbits (sex, number and strain not specified) were administered disulfide oil via the dermal route. No other details were provided.
LD_{50} > 1800 mg/kg

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
New Zealand White rabbits (5/sex/dose) were administered dimethyl disulfide via the dermal route at 2000 mg/kg under occluded conditions for 24 hours and observed for 14 days following dosing. No mortalities were observed.
LD_{50} > 2000 mg/kg

Acute Inhalation Toxicity

Diethyl and diphenyl disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Rats (male and female; number and strain not specified) were exposed to disulfide oil via inhalation for 4 hours. No other details were provided.
LC_{50} > 4.84 mg/L

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
Sprague-Dawley rats (5/sex/dose) were exposed whole-body to dimethyl disulfide via inhalation at 0, 500, 700, 775, 800, 840, 875, 950, 1100 or 1581 ppm (approximately 0, 1.93, 2.70, 3.00, 3.08, 3.24, 3.37, 3.66, 4.24 and 6.09 mg/L, respectively) for 4 hours and observed for 14 days following dosing. Mortalities were observed at exposure concentrations ≥ 3.00 mg/L (specific mortalities at each concentration were not stated).
LC_{50} = 3.10 mg/L

Diethyl disulfide (CASRN 110-81-6, supporting chemical)
Male Sprague-Dawley rats (6/dose) were exposed to diethyl disulfide via vapor inhalation at 2156 or 4390 ppm (10.78 and 21.95 mg/L, respectively) for 7 hours and then observed for 14 days. Five male rats were maintained as controls under ambient conditions or until death of all six animals. Mortality was observed in all rats exposed to 21.95 mg/L within 5 hours of exposure and in one rat exposed to 10.78 mg/L within 24 hours. Signs of toxicity included rapid and shallow breathing, weight loss and congestion of the lungs, liver and kidneys. Pathologic examination two weeks after exposure revealed testicular atrophy in 3 of 4 of the survivors exposed to 10.78 mg/L [TSCATS OTS0544443 (88-920005660S) and OTS0544426 (88-920005643)].
LC_{50} = 10.78 – 21.95 mg/L

Repeated-Dose Toxicity

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)

(1) In a 90-day study, Sprague-Dawley rats (20/sex/dose) were exposed to dimethyl disulfide (99.88% pure) via whole-body inhalation at 0, 10, 50, 150 or 250 ppm (approximately 0, 0.039, 0.19, 0.578 and 0.963 mg/L/day, respectively) for 6 hours/day, 5 days/week. Ten rats/sex/dose were assigned as the recovery group animals and allowed to recover 4 weeks after termination of the main study animals for groups 1 (control), 2 (0.39 mg/kg-day), 3 (0.19 mg/kg-day) and 5 (0.963 mg/kg-day). The exposure of group 4 (0.578 mg/kg-day) was terminated after 6 weeks; its recovery group subgroup was necropsied 2 weeks later. Clinical observations included morbidity and mortality, clinical signs, functional observation tests, body weight food consumption and opthalmoscopy. Laboratory investigations included an evaluation of hematological and clinical chemistry parameters. Pathology consisted of a full internal and external examination at sacrifice, evaluation of organ weights (organs not specified) and histological evaluation. No mortalities were observed. No treatment-related effects were observed with respect to signs of neurotoxicity, opthalmoscopy, organ weights or macroscopic observations at necropsy. Treatment-related clinical signs included dyspnea, salivation, lacrimation and reduced activity during the initial (first and second) exposures at 0.578 (dose discontinued for the remainder of the study) and 0.963 mg/L/day. A dose-related decrease in body weight gain was paralleled by comparable changes in food consumption in all treated groups. The decrease in food consumption was not statistically significant in 0.19 mg/L/day males or 0.039 mg/L/day groups. Treatment-related effects on hematology were limited to a small reduction in hemoglobin, erythrocytes and packed cell volume in the 0.963 mg/L/day females only. Treatment-related effects on blood chemistry included unspecified changes in alanine aminotransferase, alkaline phosphatase and bilirubin (at an unspecified concentration). No changes in organ weights were noted. Microscopic evaluation revealed dose-related unspecified changes in the nasal mucosa at 0.039, 0.19 and 0.963 mg/L/day.
LOAEC ~ 0.039 mg/L/day (microscopic dose-related changes in the nasal mucosa)
NOAEC= not established

(2) In a 13-week study, Fischer 344 rats (10/sex/group) were exposed whole-body to dimethyl disulfide via inhalation at 0, 5, 25 or 125 ppm (~ 0, 0.019, 0.096 and 0.48 mg/L/day, respectively) for 6 hours/day, 5 days/week. Clinical observations included mortality, clinical signs, body weight, food consumption and ophthalmoscopy. Laboratory investigations included an evaluation of hematological, clinical chemistry parameters and urinalysis. Pathology consisted of macroscopic examination at sacrifice, evaluation of organ weights and histological evaluation. Treatment-related effects at 0.096 mg/L/day include decreases in body weight gain and food consumption, AST, ALT and BUN in males, but not females. At 0.48 mg/L/day, treatment-related effects include decreases in body weight gain and food consumption in both sexes. The only effect on clinical chemistry that was considered to be treatment-related was an increase in serum glucose in males at 0.48 mg/L/day. Treatment-related effects on organ weights included increased relative adrenal weight in males and reduced absolute thymus weight in females at 0.48 mg/L/day. No treatment-related histopathological effects were observed at any dose. No treatment-related effects were observed at 0.019 mg/L/day (Kim et al., 2006).
$LOAEC_m$ ~ 0.096 mg/L/day (based on decreased mean body weight gain)
$NOAEC_m$ ~ 0.019 mg/L/day

$LOAEC_f$ ~ 0.48 mg/L/day (based on decreased mean body weight gain)
$NOAEC_f$ ~ 0.096 mg/L/day

(3) In a 4-week study, New Zealand White rabbits (5 – 10/sex/dose) were administered dimethyl disulfide (99.88% pure) via dermal occlusive application at 0, 10.63, 106.3 or 1063 mg/kg-day for 6 hours/day, 5 days/week. The control and 1063 mg/kg-day groups were comprised of 10 rabbits per sex/dose, while the 10.63 and 106.3 mg/kg-day groups included 5 rabbits per sex/dose. The experimental doses selected in this study were based on a preliminary range-finding study. Clinical observations included clinical signs, mortality, dermal reactions, body weight, food consumption and evaluation of clinical chemistry and hematology parameters. Organ weights were taken. There was no indication of a microscopic examination of organs. Treatment-related mortalities were observed in males and females at 1063 mg/kg-day, which led to a premature termination of this group after 13 days of treatment. Treatment-related clinical signs included lethargy in the 106.3 and 1063 mg/kg-day exposure groups. Severe, dose-dependent skin irritation occurred in all exposure groups. Unspecified differences in hematological and clinical chemistry parameters were observed in males exposed to 1063 mg/kg-day. No effects of treatment were seen on organ weights or upon macroscopic observation at autopsy.
NOAEL (systemic toxicity) = 106.3 mg/kg-day (highest dose tested)

Reproductive Toxicity

Dimethyl disulfide (CASRN 624-92-0, supporting chemical)
In the 90-day inhalation repeated-dose toxicity study in Sprague-Dawley rats described above, no effects were noted upon examination of the epididymis, prostate and testes in males and ovaries and uterus in females exposed to dimethyl disulfide at concentrations up to 0.963 mg/L/day.

Developmental Toxicity

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
In a prenatal developmental toxicity study, Crl:CD(SD)BR rats (25 – 30 females/concentration) were exposed to dimethyl disulfide (99.88% pure) via whole-body inhalation at 0, 5, 15 or 50 ppm (0, ~ 0.019, 0.058 and 0.19 mg/L/day, respectively) for 6 hours/day on days 6 – 15 of gestation. At gestation day 20, measured endpoints included maternal body weight and food consumption, numbers of corpora lutea and implantations, numbers of live and dead fetuses, numbers of early and late intrauterine deaths, fetal body weight and sex ratio. Fetuses were examined for gross, visceral and skeletal abnormalities and variations. Effects in the dams included dose-related reductions in maternal body weight gain were observed at $\geq$ 0.058 mg/L/day; and a higher incidence of rough hair coat and reduced food consumption at 0.19 mg/L/day. No treatment-related effects were reported for post-implantation loss. Effects in offspring included reduced litter and fetal weights and a slightly higher incidence of retarded ossification in fetuses at 0.19 mg/L. No fetal malformations were reported at any dose. No effects were reported for litter size or sex ratio. No unusual lesions were observed at necropsy in either dams or fetuses.

LOAEC (maternal toxicity) ~ 0.058 mg/L/day (based on reduced weight gain)
NOAEC (maternal toxicity) ~ 0.019 mg/L/day
LOAEC (developmental toxicity) ~ 0.19 mg/L/day (based on decreased litter weight and fetal weights and increased incidence of retarded ossification)
NOAEC (developmental toxicity) ~ 0.058 mg/L/day

Genetic Toxicity – Gene Mutation

In vitro

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
(1) In a reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to dimethyl disulfide (98.98% pure) at 0, 5, 50, 500 or 5000 µg/plate with and without metabolic activation and at 50, 150, 500, 1500 or 5000 µg/plate with and without metabolic activation for a mutation assay. Positive, negative and solvent (dimethyl sulfoxide) controls were included. The positive control responded appropriately. The cytotoxic concentration was observed to be ≥ 5000 µg/plate. There was no increase in the revertant frequency in any of the tested strains at any concentrations.
Dimethyl disulfide was not mutagenic in this assay.

(2) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to dimethyl disulfide at 50, 166, 500, 1666 or 5000 µg/plate with and without metabolic activation. The cytotoxic concentration was 5000 µg/plate. Positive and solvent (dimethyl sulfoxide) controls were included, but their responses were not indicated. There was no increase in the revertant frequency in any of the tested strains at any concentrations.
Dimethyl disulfide was not mutagenic in this assay.

(3) In a study conducted by the National Toxicology Program (Study ID: 390409), *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 were exposed to dimethyl disulfide at 0, 10, 33, 100, 333, 1000, 3333 or 10,000 µg/plate with and without activation. Toxicity was observed at 3333 µg/plate in strain TA100 without activation and at 10,000 µg/plate in strain TA97 with activation. Positive and negative controls were included and responded appropriately. There was no increase in the revertant frequency in any of the tested strains at any concentrations. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.overallresults&cas_no=624-92-0&endpointlist=SA
Dimethyl disulfide was not mutagenic in this assay.

(4) In an HGPRT assay, Chinese hamster ovary cells were exposed to dimethyl disulfide at 0.46, 1.37, 4.12, 12.3, 37.0, 74.0, 111, 333, 667 or 1000 µg/mL with and without metabolic activation. The range of cytotoxic concentrations was observed to be 74 – 1000 µg/mL. Positive and negative (dimethyl sulfoxide) controls were included. The positive controls responded appropriately. Dimethyl disulfide (dissolved in dimethyl sulfoxide) was soluble in the culture medium at a maximum concentration of 1 mg/mL. A slight increase in mutant frequency was observed at several concentrations with metabolic activation, but the increase was not concentration-related.

Dimethyl disulfide was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
Ina cytogenetic assay, human lymphocytes were exposed to dimethyl disulfide (99.98% pure) at 3.7, 11.1, 33.3, 100 or 300 µg/mL with and without metabolic activation. The cytotoxic concentration was observed to be ≥ 300 µg/mL. Positive and negative (dimethylsulfoxide) controls were included. An appropriate response was observed in the positive control. A Statistically significant induction of chromosome aberrations was observed only at the toxic concentration of 300 µg/mL. Dimethyl disulfide (dissolved in DMSO) was soluble in culture medium at a maximum concentration of 1 mg/mL. The sponsor concluded the results of the assay to be inconclusive.

In vivo

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
In a micronucleus assay, Swiss mice (5 – 10/sex/dose) were exposed to dimethyl disulfide (99.88% pure) via inhalation at 0, 250 or 500 ppm (0, ~ 0.963 and 1.93 mg/L/day, respectively) for 6 hours/day for 4 days. Ten mice per sex were included in the high-dose group, while the remaining exposure and control groups included five mice per sex. A positive control group was administered an intraperitoneal injection of 1.5 mg/kg-bw Mitomycin C 24 hours before sacrifice; the positive control responded appropriately. Mortality was observed in the high-dose group. Male and female body weight loss was observed in both exposure groups. Mean numbers of polychromatic erythrocytes were slightly lower in high-dose mice ($0.001 < p < 0.01$), indicating slight cytotoxic effects on bone marrow cells.
Dimethyl disulfide did not induce micronuclei in this assay.

Genetic Toxicity – Other

In vitro

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
In a DNA damage and repair assay, rat hepatocytes in primary culture were exposed to dimethyl disulfide (99.88% pure) at 1, 5, 10, 50, 100, 200 or 300 µg/mL without metabolic activation. The cytotoxic concentration was observed to be ≥ 100 µg/mL. Positive, negative and solvent (DMSO) controls were included. The positive controls responded appropriately. Dimethyl disulfide was soluble in culture medium at a maximum concentration of 100 µg/mL.
Dimethyl disulfide did not induce unscheduled DNA synthesis in this assay.

In vivo

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
In an unscheduled DNA synthesis assay, male Wistar rats were exposed to dimethyl disulfide (99.88% pure) via inhalation at 500 ppm (~1.93 mg/L) for 4 hours and sacrificed for isolation of hepatocytes immediately after exposure or after subsequent non-exposure periods of 16 and 24 hours. Positive and negative controls were included and responded appropriately.
Dimethyl disulfide did not induce unscheduled DNA synthesis in this assay.

Additional Information

Skin Irritation

Diethyl and diphenyl disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Rabbits (sex, number and strain not specified) were given an ocular administration of disulfide oil. Minimal irritation was observed. No other details were provided.
Disulfide oil was minimally irritating to rabbit eyes in this study.

Dimethyl Disulfide (CASRN 624-92-0, supporting chemical)
(1) Rabbits (four males, two females; strain not specified) were exposed to dimethyl disulfide undiluted via the dermal route at unspecified dose under semi-occlusive conditions for 4 hours. The Primary Skin Irritation score was 2.02 after 48 hours and an average score of 1.10 was observed after 14 days.
Dimethyl disulfide was irritating to the skin of rabbits in this study.

(2) Undiluted dimethyl disulfide (amount not specified) was applied on to the skin of six rabbits (sex and strain not specified) for 4 hours under semi-occlusive conditions. The test substance was slightly irritating to the rabbit skin.
Dimethyl disulfide was irritating to the skin of rabbits in this study.

(3) In the two repeated-dose dermal toxicity studies described previously, a severe dose-dependent skin irritation was observed following dermal occlusive application of dimethyl disulfide to rabbits.
Dimethyl disulfide was irritating to the skin of rabbits in these studies.

Eye Irritation

Diethyl and diphenyl disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Rabbits (sex, number and strain not specified) were instilled disulfide oil into the eyes. Minimal irritation was observed. No other details were provided.
Disulfide oil was irritating to rabbit eyes in this study.

Sensitization

Diethyl and diphenyl disulfides, Naphtha Sweetening (CASRN 68955-96-4)
Guinea pigs (sex, number and strain not specified) were exposed to CASRN 68955-96-4 in a dermal sensitization test. No other details were provided.
Disulfide oil was not sensitizing to guinea pig skin in this study.

Conclusions:
The acute oral toxicity of disulfide oil and supporting chemical dipropyl disulfide is low in rats. The acute oral toxicity of supporting chemical dimethyl disulfide is moderate in rats. The acute dermal toxicity of disulfide oil and dimethyl disulfide is moderate and low, respectively, in rabbits. The acute inhalation toxicity of disulfide oil and supporting chemicals dimethyl disulfide and diethyl disulfide is moderate in rats. In a 90-day inhalation repeated-dose toxicity study in rats with dimethyl disulfide, microscopic changes in the nasal mucosa were observed at 0.039 mg/L/day; the NOAEC for systemic toxicity was not established. A 90-day inhalation repeated-dose toxicity study with dimethyl disulfide showed a decrease in mean body weight gain in females at 0.096 and in males at 0.048 mg/L/day; the NOAEC for systemic toxicity is 0.019 and 0.096 mg/L/day in female and male rats respectively. A 4-week dermal repeated-dose toxicity study in rabbits with dimethyl disulfide showed no treatment-related effects at 106.3 mg/kg/day (highest dose tested). Supporting chemical dipropyl disulfide showed no treatment-related effects in rats in a 90-day dietary repeated-dose toxicity study at 7.3 mg/kg-bw/day in males and 8.2 mg/kg-bw/day in females (highest doses tested). No specific reproductive toxicity data are available; however, in the 90-day inhalation repeated-dose toxicity study with dimethyl disulfide, no treatment-related effects were observed on reproductive organs. In an inhalation prenatal developmental toxicity study in rats with dimethyl disulfide a decrease in body weight gain was observed in dams at 0.058 mg/L/day; the NOAEC for maternal toxicity is 0.019 mg/L/day. In the same study, a decrease in litter size, fetal weights and increased retarded fetal ossification were observed at 0.19 mg/L/day; the NOAEC for developmental toxicity is 0.058 mg/L/day. Dimethyl disulfide is not mutagenic in bacteria and Chinese Hampster Ovary (CHO) cells *in vitro*. Dimethyl disulfide did not induce chromosomal aberrations in human lymphocytes *in vitro* and did not induce micronuclei in mice *in vivo* or induce unscheduled DNA synthesis in rat hepatocytes *in vitro* or *in vivo*. Disulfide oil is irritating to the rabbit eye and skin and is not a skin sensitizer in guinea pigs. Dimethyl disulfide is irritating to the rabbit eye and skin and is not a sensitizer to guinea pig skin. Diethyl disulfide is irritating to the rat eye.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data				
Endpoints	**SPONSORED CHEMICAL** **Diethyl and diphenyl disulfides, Naphtha Sweetening** **68955-96-4**	**SUPPORTING CHEMICAL** **Dimethyl Disulfide** **624-92-0**	**SUPPORTING CHEMICAL** **Dipropyl Disulfide** **629-19-6**	**SUPPORTING CHEMICAL** **Diethyl Disulfide**
Acute Oral Toxicity LD_{50} (mg/kg)	**1700 (m)** **1590 (f)** **(rat)**	**< 125 (m)** **> 188 < 250 (f)** **(rat)**	**> 2000** **(rat)**	–
Acute Dermal Toxicity LD_{50} (mg/kg)	**> 1800** **(rabbit)**	**> 2000** **(rabbit)**	–	–
Acute Inhalation Toxicity LC_{50} (mg/L)	**> 4.84** **(rat)**	**3.10** **(whole-body)** **(rat)**		**10.78 – 21.95** **(vapor)** **(rat)**
Repeated-Dose Toxicity NOAEC/LOAEC Inhalation (mg/L/day)	90-Day LOAEC ~ 0.039 NOAEC = NE (RA) LOAEC ~ 0.096(f) NOAEC ~0.019(f) LOAEC ~ 0.48(m) NOAEC ~ 0.096(m) (RA)	**90-Day** **LOAEC ~ 0.039** **NOAEC = NE** **(SD rat)** **LOAEC ~ 0.096(f)** **NOAEC ~0.019(f)** **LOAEC ~ 0.48(m)** **NOAEC ~ 0.096(m)** **(F344 rat)**	–	–
Repeated-Dose Toxicity NOAEL/LOAEL Dietary (mg/kg-bw/day)	90-Day NOAEL = 7.3 (m) NOAEL = 8.2 (f) (hdt) (RA)		**90-Day** **NOAEL = 7.3 (m)** **NOAEL = 8.2 (f)** **(hdt)** **(rat)**	–

Repeated-Dose Toxicity **NOAEL/LOAEL** **Dermal (mg/kg/day)**	4-weeks LOAEL = 106.3 NOAEL = 10.6 (RA)	**4-weeks** **NOAEL = 106.3** **(hdt)** **(rabbit)**	–	–
Reproductive Toxicity **NOAEC/LOAEC** **Inhalation (mg/L/day)** **Reproductive Toxicity**	No effects were observed during the evaluation of reproductive organs in a 90-day repeated-dose toxicity study in rats. (RA)	**No effects were observed during the evaluation of reproductive organs in a 90-day repeated-dose toxicity study in rats.**	–	–
Developmental Toxicity **NOAEC/LOAEC** **Inhalation (mg/L/day)** **Maternal Toxicity** **Developmental Toxicity**	No Data LOAEC = 0.058 NOAEC = 0.019 LOAEC = 0.19 NOAEC = 0.058 (RA)	 **LOAEC = 0.058** **NOAEC = 0.019** **LOAEC = 0.19** **NOAEC = 0.058** **(rats)**	–	–
Genetic Toxicity – Gene Mutation ***In vitro***	Negative (RA)	**Negative**	–	–
Genetic Toxicity – Chromosomal Aberrations ***In vivo*** ***In vitro***	Negative Negative (RA)	**Negative** **Negative**	–	–
Genetic Toxicity – Other (UDS Assay) Synthesis) ***In vivo*** ***In vitro***	Negative Negative (RA)	**Negative** **Negative**	–	–

Additional Information			–	
Eye Irritation	**Irritating**	**Irritating**		**Irritating**
Skin Irritation	**Irritating**	**Irritating**		
Dermal Sensitization	**Not Sensitizing**	**Not Sensitizing**		

m = males; f = females; hdt = highest dose tested; (RA) = Read across; − the endpoint was not addressed for this substance.

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDs endpoints is provided in Table 4. The table also indicates where data for the supporting chemical are read-across (RA) to the sponsored chemical.

Acute Toxicity to Fish

Dimethyl disulfide (CASRN 624-92-0, supporting chemical)
(1) Rainbow trout (*Oncorhynchus mykiss*; 10/concentration) were exposed to dimethyl disulfide at nominal concentrations of 0, 1.25, 2.5, 5.0 or 10 mg/L under static renewal conditions for 96 hours. The corresponding mean measured concentrations were 0, 0.227, 0.541, 1.26, 3.07 and 6.90 mg/L, respectively.
96-h LC_{50} = 0.97 mg/L

(2) Zebrafish (*Brachydanio rerio*; 10/concentration) were exposed to dimethyl disulfide at nominal concentrations of 0, 6.25, 12.5, 25, 50 or 100 mg/L under static renewal conditions for 96 hours. The corresponding mean measured concentrations were 3.3, 7.59, 19.0, 33.4 and 71.0 mg/L, respectively.
96-h LC_{50} = 5.01 mg/L

Diisopropyl disulfide (CASRN 4253-89-8, supporting chemical)
Fathead minnows (*Pimephales promelas*) were exposed to diisopropyl disulfide at unspecified concentrations under flow-through conditions for 96 hours. The toxicity value was calculated based on measured concentrations.
96-h LC_{50} = 8.31 mg/L

Dipropyl disulfide (CASRN 629-19-6, supporting chemical)
Fathead minnows (*Pimephales promelas*) were exposed to dipropyl disulfide at unspecified concentrations under flow-through conditions for 96 hours. The toxicity value was calculated based on measured concentrations.
96-h LC_{50} = 2.62 mg/L

Acute Toxicity to Aquatic Invertebrates

Dimethyl disulfide (CASRN 624-92-0, supporting chemical)
(1) *Daphnia magna* (20/concentration) were exposed to dimethyl disulfide at nominal concentrations of 0, 0.97, 2.13, 4.7, 10.3, 22.7 or 50 mg/L under static renewal conditions in sealed test vessels with minimal headspace for 96 hours. The corresponding mean measured concentrations were 0, 0.618, 1.79, 3.69, 8.25, 17.4 and 45.1 mg/L, respectively.
48-h EC_{50} = 1.82 mg/L

(2) *Daphnia magna* (20/concentration) were exposed to dimethyl disulfide (98.93% pure) at nominal concentrations of 0, 3.3, 4.0, 4.8, 5.8, 6.9, 8.3, 10, 12 or 14.4 mg/L under static conditions in sealed test vessels with minimal headspace for 48 hours. The corresponding initial

measured concentrations were 0, 3.3, 3.8, 4.7, 5.5, 6.3, 7.8, 9.5, 10.6 and 13.4 mg/L, respectively; final measured concentrations were 0, 3.6, 4.1, 5.2, 5.3, 6.6, 8.2, 9.9, 11.8 and 13.7 mg/L, respectively.
48-h EC_{50} = 7 mg/L

Toxicity to Aquatic Plants

Dimethyl disulfide (CASRN 624-92-0, supporting chemical)
(1) Green algae (*Pseudokirchneriella subcapitata*) were exposed to dimethyl disulfide at initial concentrations of 0, 5.73, 11.6, 21.9, 44 or 86.7 mg/L under static conditions in sealed test vessels with minimal headspace for 72 hours. The mean measured concentrations were 9.4, 20.6, 41.9 and 82.8 mg/L for initial test concentrations of 11.6, 21.9, 44 and 86.7 mg/L, respectively. Control response was appropriate.
72-h EC_{50} (biomass) = 14.3 mg/L
72-h EC_{50} (growth) =25.6 mg/L

(2) Green algae (*Pseudokirchneriella subcapitata*; 3 replicates/concentration) were exposed to dimethyl disulfide (99.65% pure) at nominal concentrations of 0, 5.29, 9.53, 17.15, 30.86, 55.56 or 100 mg/L under static conditions in sealed test vessels with minimal headspace for 72 hours. Control response was appropriate.
72-h EC_{50} (biomass) = 11 mg/L
72-h EC_{50} (growth) = 35 mg/L

Conclusions: For disulfide oil, based on data for dimethyl disulfide, diisopropyl disulfide and dipropyl disulfide, the 96-h LC_{50} for fish ranges from 0.97 to 8.3 mg/L. Based on dimethyl disulfide data, the 48-h EC_{50} for aquatic invertebrates is 1.82 mg/L, and the 96-h EC_{50} for aquatic plants is 14.3 mg/L for biomass and 25.6 mg/L for growth rate, respectively.

Table 4. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program - Aquatic Toxicity Data				
Endpoints	**SPONSORED CHEMICAL Diethyl and diphenyl disulfides, Naphtha Sweetening (68955-96-4)**	**SUPPORTING CHEMICAL Dimethyl disulfide (624-92-0)**	**SUPPORTING CHEMICAL Diisopropyl disulfide (4523-89-8)**	**SUPPORTING CHEMICAL Dipropyl disulfide (629-19-6)**
Fish 96-h LC_{50} (mg/L)	No Data 0.97 – 8.3 (RA)	**0.97**	**8.3**	**2.62**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No Data 1.82 (RA)	**1.82**	–	–
Aquatic Plants 72-h EC_{50}				
(mg/L)	No Data	**14.3**	–	–
(biomass)	14.3	**25.6**	–	–
(growth)	25.6 (RA)			

Bold= measured data (i.e., derived from experiment); (RA) = Read Across; indicates that the endpoint was not addressed for this substance.

5. References

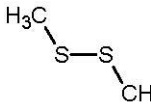
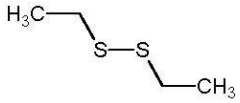
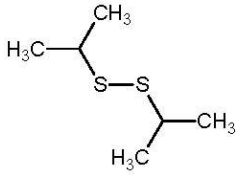
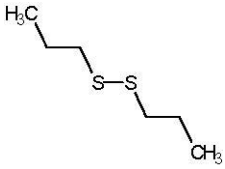
Kim et al., 2006. Evaluation of subchronic inhalation toxicity of dimethyl disulfide in rats. Inhalation Toxicology 18(5): 395-403).

Posternak et al., 1969 (Summaries of toxicological data: Toxicological tests on flavouring matters. Food and Cosmetics Toxicology 7: 405-407).

APPENDIX

Disulfide oil is produced by mercaptan extraction from C4 to C5 light hydrocarbon streams during the refining of petroleum by a process known as sweetening. The mercaptans are extracted from the feedstock in a closed system and then oxidized to disulfides. Disulfide oil is a complex mixture of dialkyl disulfides with alkyl chain lengths no greater than C4. Although the exact composition and concentrations depend on the type of organosulfur compounds being extracted, ten dialkyl disulfides tend to predominate in the substance and are representative of the types and amounts of disulfides in disulfide oil. The ten dialkyl disulfides comprise approximately 87% of the total weight. In addition to dialkyl disulfides, a small but measurable amount of four dialkyl trisulfides have been shown to be present in the mixture at levels ranging from 0.4 to 1.6%. The second table below shows 44 compounds quantified in a sample of disulfide oil.

Identity and Concentration of Supporting Chemicals and Composition of Disulfide Oil

Disulfide Constituent	Chemical Structure	CAS Number	Chemical Formula	Mol. Wt.	Conc. DSO (% w/w)
dimethyl disulfide		624-92-0	$C_2H_6S_2$	94.22	12.0
diethyl disulfide		110-81-6	$C_4H_{10}S_2$	122.28	11.2
diisopropyl disulfide		4253-89-8	$C_6H_{14}S_2$	150.34	2.0
dipropyl disulfide		629-19-6	$C_6H_{14}S_2$	150.34	2.5
				Total	**27.7**

Method	Compounds	Concentration, Wt-%
GC/MS	n-Butane	0.04
	3-Methyl Butene-1	0.02
	Acetone	0.04
	Isopentane	0.03
	2-Thiopropane	0.01
	1,2-Dimethylcyclopropane	0.01
	Propionitrile	0.01
	2,3-Dimethylbutane	0.02
	Methyl Ethyl Ketone	0.11
	2-Methyl Pentane	0.01
	n-Hexane	0.01
	Methyl Ethyl Sulfide	0.06
	Benzene	0.02
	3-Methylthiolpropane	0.06
	Diethyl Sulfide	0.04
	Isooctane	0.11
	Dimethylhexane	0.03
	Dimethyl Disulfide	11.97
	Ethyl Isopropyl Sulfide	0.02
	Propyl Ethyl Sulfide	0.03
	n-Octane	0.02
	Methyl Ethyl Disulfide	18.23
	Methyl Isopropyl Disulfide	14.38
	1,3-Dithiane	0.17
	Diethyl Disulfide	11.23
	Methyl Propyl Disulfide	7.66
	Dimethyl Trisulfide	1.62
	Ethyl 1-Methylethyl Disulfide	11.63
	Diisopropyl Disulfide	2.05
	Methyl n-Butyl Disulfide	0.14
	Thieno-(3,2b) Thiophene	1.71
	Diisopropyl Sulfone	4.99
	Ethyl Butyl Disulfide	0.51
	Ethyl n-Propyl Disulfide	6.96
	Propyl Disulfide	2.46
	Methyl (Methylthio) Methyl Disulfide	0.36
	Diethyl Trisulfide	0.69
	Methyl Propyl Trisulfide	0.51
	n-Propyl sec-Butyl Disulfide	0.18
	1,1 bis (Methyl Mercaptan)	0.22
	Ethyl 2-Mercaptan Propionic Acid	0.77
	1,1 bis (Ethyl Mercaptan)	0.20
	Diisopropyl Trisulfide	0.44
	Unidentified Sulfide Components	0.22
	Total	**100.00**