201-16767

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December 19, 2008

The Honorable Stephen L. Johnson, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know
HPV Challenge Program, AR-201
HPV CONSORTIUM

RE: Data Review and Assessment for Reclaimed Substances: Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (aka Disulfide Oil) CAS # 68955-96-4

Dear Administrator Johnson:

On December 15, 2003, API submitted on behalf of the Petroleum HPV Testing Group (TG) a test plan entitled "Test Plan for Reclaimed Substances: Streams Containing Naphthenic Acids, Phenolics, Disulfides, Acids or Caustics". The plan included a technical discussion for four disulfide substances that concluded none of them should be evaluated in the HPV program. In response to EPA and public comments the TG revised this conclusion and modified the test plan such that the four separate categories of reclaimed substances were created.

The subject document covers one member of the original disulfide category. After a thorough investigation of the manufacturing status of the category members, the Testing Group withdrew sponsorship of three disulfide substances[1] and determined that a separate assessment on the one remaining substance, diethyl and diphenyl disulfide, naptha sweetening (CAS 68955-96-4), was warranted.

With this letter API is submitting on behalf of the TG the subject report including its four appendices:

- Appendix I - Analytical Results Composition of Disulfide Oil
- Appendix II - Dimethyl Disulfide Test Plan

[1] Letter from Lorraine Twerdok, API, to USEPA Administrator, Reclaimed Substances Test Plan - Withdrawal of Sponsorship in Reclaimed Substances Naphthenic Acids (1 CASRN) and Disulfides (2 CASRN) Categories, May 4, 2005. Letter from Thomas Gray, API, to Stephen L. Johnson, USEPA, Notification of Sponsorship Withdrawal of CASRN 68920-64-9, January 24, 2006.

- Appendix III - Dimethyl Disulfide Robust Summaries
- Appendix IV - IUCLID 5 Report for Disulfide Oil

For the possible convenience of your staff, API is also submitting an export IUCLID file containing the contents of Appendix IV.

The TG believes that it has completed with this submission its obligation under the HPV Challenge Program for the substance "Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (aka Disulfide Oil)" CAS # 68955-96-4.

Please contact me with any comments or questions you may have regarding this submission.

Sincerely,

Thomas M. Gray, M.S., D.A.B.T.®

Attachment

cc (via email): chem.rtk@epa.gov
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Gloria Drayton-Miller, USEPA
Oscar Hernandez, USEPA
Diane Sheridan, USEPA
Mark Townsend, USEPA
Petroleum HPV Testing Group Oversight Committee and Technical Workgroup

Appendix II

Dimethyl Disulfide Test Plan

High Production Volume (HPV) Challenge Program

DIMETHYL DISULFIDE
(CAS# 624-92-0)
Test Plan

Arkema Inc.
2000 Market Street
19103 Philadelphia, PA

December 2005

EXECUTIVE SUMMARY

Arkema Inc has volunteered to sponsor dimethyl disulfide (DMDS, CAS# 624-92-0) in the USEPA HPV program. The DMDS Test Plan is being submitted to fulfill the United States Environmental Protection Agency (USEPA) High Production Volume (HPV) Challenge Program commitment for DMDS.

Data from company proprietary files, peer-reviewed literature, and/or calculated endpoints using widely accepted computer modeling programs have been identified for purposes of this program. Robust summaries of the available data are included in the attached IUCLID. The following table summarizes the available data and proposed testing for DMDS.

Table 1: Matrix of Available and Adequate Data on DMDS

"SIDS ENDPOINT"	Data Available Y/N	Testing Planned? Y/N
Physical and Chemical Data		
Melting Point	Y	N
Boiling Point	Y	N
Vapor Pressure	Y	N
Partition Coefficient	Y	N
Water Solubility	Y	N
Environmental Fate		
Photodegradation	Y	N
Stability in Water (Hydrolysis)	N	Y
Transport/Distribution	Y	N
Biodegradation	Y	N
Ecotoxicity		
Acute/Prolonged Toxicity to Fish	N	Y
Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	Y	N
Acute Toxicity to Aquatic Plants (Algae)	Y	N
Toxicity		
Acute Toxicity (Oral)	Y	N
Acute Toxicity (Dermal)	Y	N
Acute Toxicity (Inhalation)	Y	N
Repeated Dose	Y	N
GeneticToxicity *in vitro* – Gene Mutation	Y	N
Genetic Toxicity *in vitro* – Chromosomal Aberration	Y	N
Reproductive Toxicity Developmental Toxicity	Y	N

Note: **The data used to characterize the OECD SIDS endpoints for substances in this Test Plan were identified either in company proprietary files, peer-reviewed literature, and/or calculated using widely accepted computer modelling programs. All data were evaluated for study reliability in accordance with criteria outlined by the USEPA (1999a). Only studies that met the reliability criteria of "1" (reliable without restrictions) or "2" (reliable with restrictions) were used. Additional data are also included in the IUCLID (International Uniform Chemical Information Dataset) attached in Annex I. A more detailed discussion of the data quality and reliability assessment process used to develop this test plan is provided in Annex II.**

1.1 Physico-Chemical properties

DMDS is a pale yellow liquid with a strong garlic like odor. Experimental data for the physical chemical parameters are available and reported in EPIWIN© (USEPA, 2004) and are provided in the following table.

Table 2. Physicochemical Data

Parameter	***Value***
Melting Point	-85ºC [1]
Boiling Point	110ºC [1]
Vapor Pressure	29.3 hPa
Kow Partition Coefficient	1.77[1]
Water Solubility (mg/l)	2500[1]

[1]EPIWIN v3.12 – Syspro database

Conclusion

Adequate data are available for the HPV physical/chemical property endpoints. No additional testing for the HPV program is proposed.

GENERAL INFORMATION ON EXPOSURE

1.2 Production Volumes and Use Pattern

DMDS is on EPA's high production volume list indicating it is manufactured and/or imported at greater than 1 million pounds per year according to the toxic inventory update rule (IUR).

1.2.1 Use Pattern:

DMDS has several industrial uses. It is used in the oil industry as a sulfiding/presulfiding agent to activate catalysts of hydrotreating units, to reduce the number of decoking operations in the petrochemical industry, as a chemical intermediate in the fine chemical industry, and as an anti-corrosive in metallurgy.

1.3 Environmental Exposure and Fate

1.3.1 Photodegradation

The photodegradation of DMDS was evaluated using EPIWIN 3.12. The half life of DMDS was calculated to be 0.565 hours based on the experimental rate constant of 227 x E-12 cm3/molecule-sec.

Conclusion

Adequate data are available to assess the photodegradation of DMDS. No additional studies are proposed for the HPV program.

1.3.2 Stability in Water

EPIWIN was unable to calculate a hydrolysis rate for DMDS. A hydrolysis study is proposed for DMDS.

1.3.3 Transport between Environmental Compartments

The transport of DMDS between environmental compartments was assessed by fugacity modeling using EPIWIN (v3.12). Results are listed in the table below:

Table 3. Fugacity Results for DMDS

Compartment	Mass amount (%)	Estimated half life (hr)
Air	1.01	1.13
Water	58.1	360
Soil	40.8	360
Sediment	0.168	3.24x e003

1.3.4 Biodegradation

DMDS was not readily biodegradable when evaluated according to OECD 301D. The degradation was less than 10% following 28 days exposure.

Conclusion

Adequate data are available to assess the biodegradation of DMDS. No additional studies are proposed for the HPV program.

2 HUMAN HEALTH HAZARDS

2.1.1 Acute Toxicity

Single exposure (acute) studies indicate DMDS is moderately toxic if swallowed (rat; 290 mg/kg < LD50 < 500 mg/kg), no more then slightly toxic if absorbed through skin (rabbit LD50 >2,000 mg/kg), and slightly toxic if inhaled (rat 4-hr LC50 805 ppm).

Conclusion

Adequate data are available to assess the acute toxicity of DMDS and no additional studies are proposed.

2.1.2 Repeated Dose Toxicity

DMDS was evaluated in a 90-day repeated dose study on rats according to OECD guidelines. This study featured inhalation dosing, measurement of mortality, body weight changes, food consumption, hematological and blood biochemical examinations, urinalysis, organ weights, histopathology and a functional observational battery. Rats were exposed whole body to 0, 10, 50, 150, and 250 ppm DMDS for 6 hours per day for 90 days. Satellite groups were evaluated

following a 2-week recovery period. Results from this study showed decreased body weights, food consumption, hypoactivity, changes in white blood cell counts, reduced thymus gland weight and increased liver weight. Reversible microscopic changes were noted in the nasal mucosa.

Conclusion

Adequate data are available to assess the reproductive toxicity of DMDS. No additional testing is proposed for purposes of the HPV program.

2.1.3 Mutagenicity

Several reliable genetic toxicity studies are available for DMDS. Predominantly negative results were obtained with DMDS when tested *in vitro* (negative bacterial and mammalian mutagenicity assays, negative DNA damage and repair, ambiguous positive in vitro chromosome aberration study using human lymphocytes). Negative results were obtained when DMDS was evaluated *in vivo* (mouse micronucleus, unscheduled DNA synthesis).

Conclusion

Adequate data are available to assess the genetic toxicity of DMDS. No additional testing is proposed for purposes of the HPV program.

2.1.4 Toxicity for Reproductive/Developmental Toxicity

Reproductive Toxicity

The 90 day repeated dose toxicity study will be used to assess the reproductive toxicity of DMDS. Reproductive organs examined in this study included the epididymus, prostate, and testes in males and ovaries and uterus in females. No lesions were reported.

Developmental Toxicity

A Developmental Toxicity test was completed for DMDS in Sprague-Dawley rats following OECD Guideline 414 "Teratogenicity." DMDS was administered by inhalation to 0, 5, 15, and 50 ppm on gestation days 6 to 15. Maternal toxicity was noted at 15 and 50 ppm. No evidence of developmental toxicity was observed. No additional studies are proposed.

Conclusion

Adequate data are available to assess the reproductive and developmental toxicity of DMDS. No additional testing is proposed for the HPB program.

3 HAZARDS TO AQUATIC ORGANISMS

DMDS has been evaluated in an acute daphnia immobilization and algal growth inhibition studies. DMDS is moderately toxic to daphnia with a 48 hour EC50 value of 7 mg/l. DMDS is slightly toxic to *Selenastrum capricornutum* alga with a 72 hour EC50 of 35 mg/l. No data are available for acute fish and alga. No data are available to assess the acute fish toxicity and an acute fish toxicity (OECD guideline 203) is proposed for DMDS.

Conclusion

Adequate data are available to assess the aquatic toxicity of DMDS to daphnia and alga but not fish. An acute fish toxicity study is proposed (OECD guideline 203) for DMDS.

References

Atofina, 2005. IUCLID Data Set, CAS No. 624-92-0 dimethyldisulfide. Atofina, Paris, France.

Klimisch, H.J., E. Andreae, and U. Tillmann. 1997. A systematic approach for evaluating the quality of experimental and ecotoxicological data. *Reg. Tox. and Pharm*. 25: 1-5.

Organisation for Economic Co-operation and Development (OECD) Secretariat. 2002. *Manual for Investigation of HPV Chemicals* (November 2002).

U.S. Environmental Protection Agency (USEPA), Office of Pollution Prevention and Toxics. 1998. Guidance for Meeting the SIDS Requirements: Chemical Right-to-Know Initiative.

USEPA, Office of Pollution Prevention and Toxics. 1999b. Draft Determining the Adequacy of Existing Data.

USEPA, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. 2004. EPI Suite v 3.12.

ANNEX I: DIMETHYL DISULFIDE IUCLID

See attached IUCLID documents.

ANNEX II: DATA QUALITY ASSESSMENT

Available environmental, ecotoxicity, and mammalian toxicity studies were reviewed and assessed for reliability according to standards specified by Klimisch et al., (1997), as recommended by the USEPA (1999a) and the OECD (OECD, 2002). The following reliability classification (Klimisch rating) has been applied to each study assessed:

- *1 = Reliable without Restriction* – Includes studies that comply with USEPA- and/or OECD-accepted testing guidelines and were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented;

- *2 = Reliable with Restriction* – Includes studies that were conducted according to national/international testing guidance and are well documented. May include studies that were conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters that are well documented and scientifically valid but vary slightly from current testing guidance. Also included in this category were physical-chemical property data obtained from reference handbooks, as well as environmental endpoint values obtained from an accepted method of estimation (e.g., USEPA's EPIWIN estimation program);

- *3 = Not Reliable* – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or in which documentation is insufficient; and,

- *4 = Not Assignable* – This designation is used in this dossier for studies that appear scientifically valid but for which insufficient information is available to adequately judge robustness.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this dossier. Those key studies selected for inclusion are considered typical of the endpoint responses observed in other studies of a similar nature and design that were identified during our search of the literature.

U.S. EPA HPV Challenge Program

Data Review and Assessment for

Reclaimed Substances:
Disulfides, Diethyl and Diphenyl, Naphtha Sweetening

(aka Disulfide Oil)

CAS # 68955-96-4

Submitted by:

Petroleum HPV Testing Group

American Petroleum Institute
1220 L Street NW
Washington, DC 20005

December 19, 2008

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Appendices

Appendix I. Analytical Results: Composition of Disulfide Oil

Appendix II. Dimethyl Disulfide Test Plan

Appendix III. Dimethyl Disulfide Robust Summaries

Appendix IV. IUCLID 5 Report for Disulfide Oil

Background

An initial data assessment containing reference to disulfide oils, "Test Plan for Reclaimed Substances: Streams Containing Naphthenic Acids, Phenolics, Disulfides, Acids or Caustics", was posted to EPA's website on January 20, 2004. This assessment has been revised in response to the EPA and public comment and has been modified so that individual categories or streams of reclaimed substances are addressed separately.

This data review and assessment document examines one member of the originally proposed disulfide category. Originally, it was thought that the disulfide category could be addressed as a technical letter. After more investigation and review of the manufacturing status of the original category members, the Testing Group withdrew sponsorship of three of the substances in the category and determined that a separate assessment on the remaining substance, diethyl and diphenyl disulfide, naptha sweetening (CAS 68955-96-4) was warranted.

Executive Summary

Diethyl and diphenyl disulfide, naphtha sweetening (CAS# 68955-96-4) is primarily composed of low molecular weight dialkyl disulfides that are extracted from C_4 to C_5 light hydrocarbon streams during the refining of petroleum. The disulfide substance, commonly known as disulfide oil or DSO, can be composed of up to 17 different dialkyl disulfides with alkyl chain lengths no greater than C_4. Although the exact composition and concentrations vary depending upon the type of organo-sulfur compounds being extracted, ten disulfides tend to predominate the substance and are representative of the types and amounts of disulfides in DSO.

On the whole, the dialkyl disulfides in DSO constitute a homologous series of chemicals that are perfectly suited for examination using structure-activity analyses (SAR). Although some data are available for DSO, the majority of the testing needs for this substance have been satisfied using SAR and the read across of information available for dimethyl disulfide (DMDS), which is present in DSO in high amounts and is the lowest member of the homologous series. Use of DMDS as a surrogate for DSO in a

"read across" manner is supported by a common mechanism of action that all disulfides exhibit when eliciting harmful systemic effects. This mechanism, which involves the generation of free radical intermediates and the initiation of a redox cycle after an initial disulfide bond cleavage, has been shown to be less active in disulfides that are more highly substituted. Consequently, the toxic potency of dialkyl disulfides decreases as the chain length increases, and the effects observed with DMDS provide a good worst case estimate of the toxicity associated with the remaining members of the series.

In the HPV guidance, the EPA included a provision for the use of SAR to reduce testing needs (USEPA, 1999a). In the guidance, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity" (USEPA, 1999b). The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing. It is believed that this analysis provides a good example of how SAR can be effectively used to identify the health hazards associated with structurally similar substances. The advantages afforded by the use of SAR and a read-across extrapolation from DMDS to DSO eliminates the need for redundant testing of a substance that is not released to the environment nor found in the marketplace.

As summarized in Table 1, adequate data are believed to exist for DSO in eighteen of the twenty test categories examined. These testing needs were filled either by actual testing of DSO, by the use of SAR programs and techniques, or by analogy with DMDS, which has previously been reviewed under the HPV Challenge Program. As such, the robust summary for DMDS has been included with this submission. The test areas where DMDS, and by analogy DSO, lack adequate information (water stability and chronic fish toxicity) are scheduled to be filled under voluntary agreement with the HPV sponsor for DMDS. In conclusion, evidence is available showing that the health and environmental hazards associated with DSO has been sufficiently evaluated and no further testing is deemed necessary for this material.

Table 1. Data Availability, Type, and Acceptability for Disulfide Oil

DSO Category	Information Available	OECD Study	GLP Study	Other Study	Estimated Value	Results Acceptable	Testing Necessary
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physiochemical							
melting point	Y	N	N	Y	N	Y	N
boiling point	Y	N	N	Y	N	Y	N
vapor pressure	Y	N	N	Y	N	Y	N
partition coefficient	Y	N	N	N	Y	Y	N
water solubility	Y	N	N	Y	N	Y	N
Environmental Fate							
photooxidation	Y	N	N	N	Y	Y	N
water stability	N	N	N	N	N	N	N
biodegradation	Y	N	N	N	Y	Y	N
distribution	Y	N	N	N	Y	Y	N
Ecotoxicity							
acute fish	Y	N	N	N	Y	Y	N
chronic fish	N	N	N	N	Y	N	N
acute invertebrate	Y	N	N	N	Y	Y	N
acute algae	Y	N	N	N	Y	Y	N
terrestrial	Y	N	N	N	Y	Y	N
Toxicity							
acute (oral)	Y	N	Y	N	N	Y	N
acute (dermal)	Y	N	Y	N	N	Y	N
acute (inhalation)	Y	N	Y	N	N	Y	N
repeated dose	Y	Y	N	N	Y	Y	N
mutagenicity	Y	Y	N	N	Y	Y	N
reproductive/developmental	Y	Y	N	N	Y	Y	N

1. Introduction

The High Production Volume Challenge Program has identified diethyl and diphenyl disulfides, naphtha sweetening (CAS# 68955-96-4) as a candidate category based on production volume estimates obtained through the TSCA Inventory Update Rule.

Commonly known as disulfide oil or DSO, this substance is produced by a single company as a byproduct of the petroleum refining process. The substance is not sold commercially nor is it used directly in any downstream products. DSO is a product of mercaptan removal from selected C_4 to C_5 light hydrocarbon streams by a process known as sweetening, since it removes the sour smelling sulfides from 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 including liquefied petroleum gas (LPG), naphtha, or any other hydrocarbon fraction (see Figure 1).

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 initial step in the extraction sequence is depicted by the following reaction equation, with R representing a short chain alkyl group:

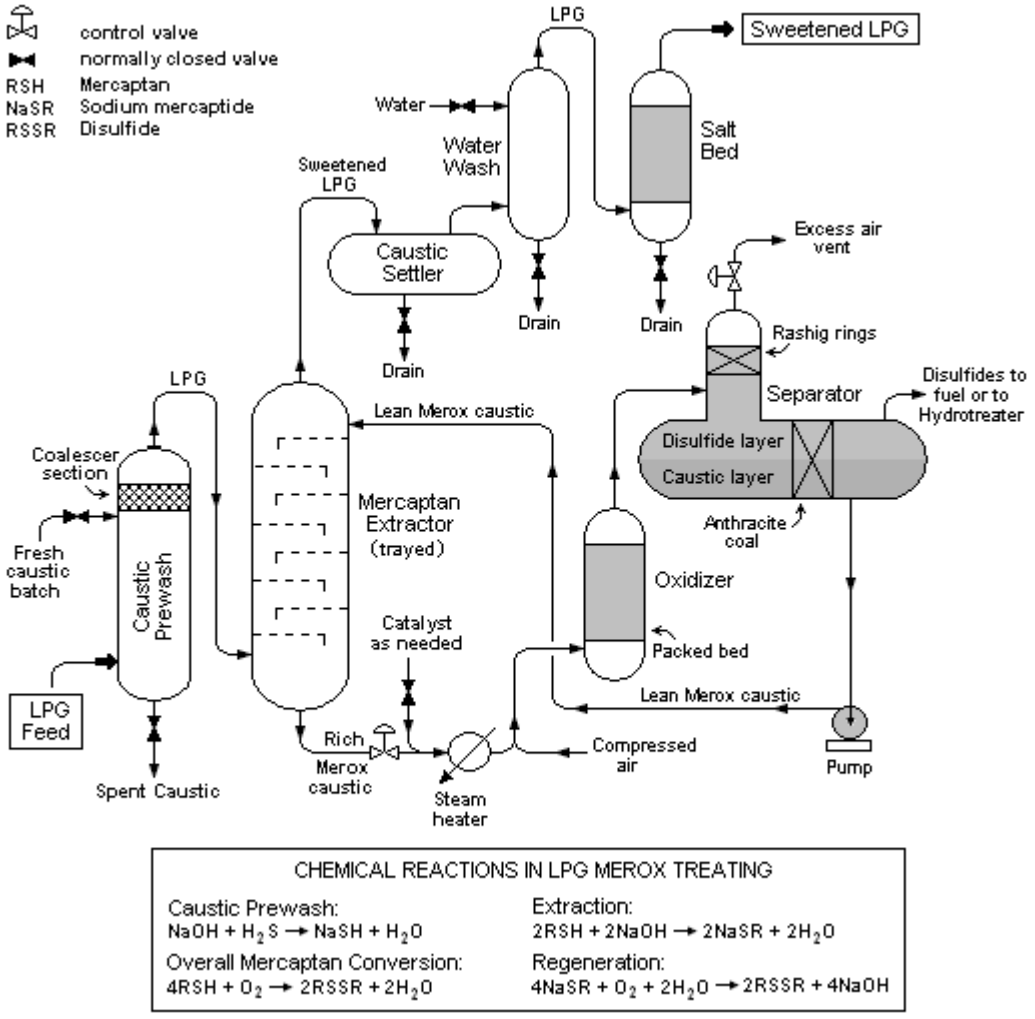
$$\mathbf{RSH + NaOH \rightarrow NaSR + H_2O}$$

The second step is referred to as regeneration and it involves heating and oxidizing the caustic solution leaving the extractor. The oxidation converts the extracted alkyl mercaptans (RSH) to organic disulfides (RSSR), which are less water soluble than

the initial mono-sulfides thereby facilitating separation and removal from the aqueous caustic solution. The reaction that takes place in the regeneration step is:

$$4\ NaSR\ +\ O_2\ +\ 2\ H_2O\ \rightarrow\ 2\ RSSR\ +\ 4\ NaOH$$

Figure 1. Flow Diagram for a Merox® Unit Producing Disulfide Oil from LPG



The net overall Merox reaction covering the extraction and regeneration steps may be expressed as:

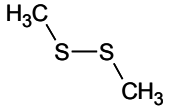
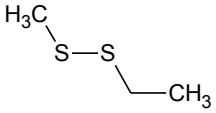
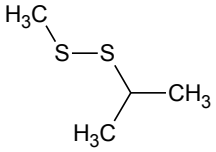
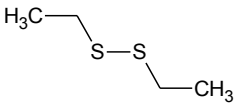
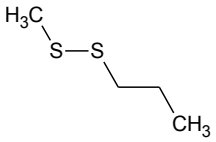
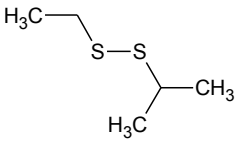
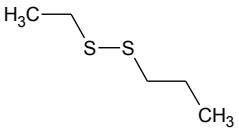
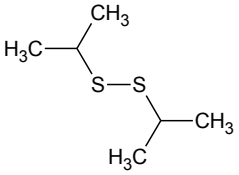
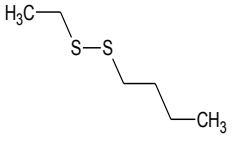
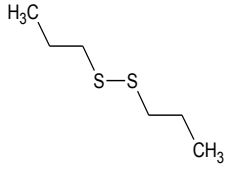
$$4\ RSH + O_2 \rightarrow 2\ RSSR + 2\ H_2O$$

After decantation of the disulfide oil, the regenerated caustic solution is recirculated back to the top of the extractor in a continuous loop to extract additional mercaptans. Extraction equilibrium is favored by lower molecular weight mercaptans

and by lower temperatures. Consequently, the disulfide oil is generally rich in alkyl disulfides with small chain lengths, but the exact chemical composition can vary depending on types of sulfur contaminants in the treated feedstock.

The compositional information in Table 2 was extracted from a recently completed chemical analysis of DSO (Appendix I) and is representative of the types of disulfides found in DSO. The analysis reveals that ten dialkyl disulfides comprise approximately 87% of the total weight in disulfide oil. These disulfides range in molecular weight from 94 to 150 amu and are remarkably similar in chemical structure with each possessing a characteristic disulfide linkage attached to a C_1 to C_4 alkyl group. Despite the official nomenclature, DSO does not contain appreciable amounts of diphenyl disulfides. The full analytical report presented in Appendix I shows that less than 0.5% of the oil is composed of hydrocarbon solvents and that the balance is composed of low molecular weight mono and trisulfides that generally comprise less than 2% of the total weight percentage. The exception is diisopropyl sulfone, which is present at levels of about 5% by weight. Because sulfones of this type have been shown to lie in the metabolic pathways for dialkyl disulfides (see Health Effects, section 5), its presence in DSO at relatively high amounts does not pose any particular toxicological concern and it can be assumed to act in the same fashion as the disulfide from which it is derived. The benzene levels in DSO have been reduced in recent years and are currently present at concentrations less than 0.1%. Past samples used in the acute toxicity testing performed over fifteen years ago contained benzene levels up to 1.0%.

Table 2. Identity and Concentration of the Individual Disulfides in 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
methyl ethyl disulfide		20333-39-5	$C_3H_8S_2$	108.25	18.2
methyl isopropyl disulfide		40136-65-0	$C_4H_{10}S_2$	122.28	14.4
diethyl disulfide		110-81-6	$C_4H_{10}S_2$	122.28	11.2
methyl n-propyl disulfide		2179-60-4	$C_4H_{10}S_2$	122.28	7.7
ethyl isopropyl disulfide		53966-36-2	$C_5H_{12}S_2$	136.31	11.6
ethyl n-propyl disulfide		30453-31-7	$C_5H_{12}S_2$	136.31	7.0
diisopropyl disulfide		4253-89-8	$C_6H_{14}S_2$	150.34	2.0
ethyl n-butyl disulfide		63986-03-8	$C_6H_{14}S_2$	150.34	0.5
dipropyl disulfide		629-19-6	$C_6H_{14}S_2$	150.34	2.5
				Total	**87.1**

Consistent with published guidelines for identifying and establishing a categorical approach for a chemical mixture, DSO is deemed to meet all of the requirements for consideration as a chemical category. The hallmarks of the DSO series are: i) the regular and predictable fashion in which the alkyl groups affect physical properties and environmental attributes and ii) the pivotal role played by the disulfide bridge in eliciting a toxic response. As such, to the extent possible, information has been assembled for all ten of the disulfide constituents. When information was unavailable, however a surrogate approach has been applied. Since the DSO is essentially a homologous series of chemicals with dimethyl disulfide (DMDS) occupying the lowest position, structure-activity methods provide an acceptable approach for evaluating the properties and fulfilling the testing needs of the entire category.

DSO is also well suited for the application of a "read across" approach for predicting the health and environmental impacts of DSO, where modeling might not meet data needs. To the extent possible, information has been assembled for the primary disulfide constituents of DSO. When, structure-activity data is absent or missing, the effects of DMDS are offered as a reasonable alternative to testing the entire category. This is a well-reasoned decision that was heavily influenced by a common mechanism of action for the environmental and mammalian toxicity of dialkyl disulfides and by systematic knowledge of the impact of carbon chain length on the toxic potency of disulfides. Because DMDS is a well studied chemical that has previously been examined under the HPV Challenge Program, the available test data provide a source of surrogate information for DSO. An examination of the test plan (Appendix II) and robust summary for DMDS (Appendix III) reveal that it has few data deficiencies and those gaps that exist are scheduled to be addressed under a voluntary agreement recently approved and accepted by the US EPA (USEPA, 2008). The data presented in this data assessment for DSO and DMDS were identified either in company proprietary files, peer-reviewed literature, the DMDS IUCLID data set, and/or calculated using accepted computer modeling programs. A robust summary has been prepared in IUCLID 5 format (Appendix IV) that describes the data used in support of this submission on DSO. All data were evaluated for study reliability in accordance with criteria outlined by Klimisch

et al., (1997) and recognized by the USEPA. Only studies that met the reliability criteria of "1" (reliable without restrictions) or "2" (reliable with restrictions) are presented. In some cases, test data has been extracted from MSDSs because the original reports were either inaccessible or unavailable. These data were judged to be reliable with restriction for the purposes of this data review based on their plausibility and recent release.

2. Physical Chemical Properties

DSO is an extremely flammable substance with a relatively high vapor pressure and low water solubility. At room temperature, the material exists as a yellow liquid with an extremely foul and obnoxious odor. The physical and environmental properties for the individual DSO disulfides have been estimated using EPA's EPI Suite software package and are presented in Table 3 (USEPA, 2007). To assess their validity, the physical property estimates for the individual disulfides were averaged using the additivity rule for ideal mixtures, which provided a rough but effective approximation for comparing the actual measured values for DSO with a calculated estimate. Experimental data was located in the published literature for three of the ten component disulfides in DSO. As shown in Table 1, approximately 64% of DSO is composed of five dialkyl disulfides with an alkyl carbon number of C_4 or less. Consequently, the chemical and physical properties associated with these disulfides will exert a disproportionate impact on the properties of the substance.

A. Melting Point

Estimated melting points for the disulfides in DSO were derived using the MPBPWIN (v 1.42) module in the EPI Suite program. Table 3 shows that the estimated values follow a regular progression as a function of carbon number, with the melting points increasing as the carbon content rises. Actual experimental values were located for three chemicals: DMDS, diethyl disulfide (DEDS), and dipropyl disulfide (DPDS). A comparison of the actual measurements against the predicted values for these three chemicals show reasonable agreement with some tendency for the estimation routine to over predict the actual value (predicted values of -69.7, -45.2, and -21.8 °C for DMDS, DEDS, and DPDS, respectively). A fractionally-weighted compositional average was

calculated using the estimated values for all ten disulfides, which were then compared to the actual value for DSO. The fractionally-weighted average of -44.3 °C compares well with actual DSO value of -54 °C (-65 °F) (ST Laboratories, 2008).

B. Boiling Point

Boiling points were estimated using the same software module used to estimate melting points. The predicted values ranged from 100 to 200 °C and increased in a direct relationship to molecular weight. Estimated values for DMDS, DEDS, and DPDS show good agreement with the actual measurements (109.8, 154.1, and 193.5 °C for DMDS, DEDS, and DPDS, respectively), differing by only a few degrees. The weighted average for the estimated boiling points of all ten disulfides was 131.3 °C, which is consistent with the reported boiling point range of 111-174 °C for DSO (ST Laboratories, 2008).

C. Vapor Pressure

The ten disulfides in DSO display a considerable range in volatility. Using the MPBPWIN (v 1.42) module, the vapor pressure was estimated to range from 24.5 mmHg for DMDS to 0.50 mmHg for DPDS. These values are in excellent agreement with the actual measured values for these two compounds. The Reid vapor pressure of DSO was determined to be 1.1 psia at 100 °F (37.7 °C) (ST Laboratories, 2008). This pressure is approximately equal to a true vapor pressure of about 1.1 psi or 57 mmHg at 25 °C. By comparison, the fractionally-weighted vapor pressure for the disulfides in DSO was calculated to be 5.87 mmHg at 25 °C. The difference between the two values is likely due to the relatively high volatility of the non-disulfide chemicals in DSO and their disproportionate contribution to the overall volatility of the substance.

D. Partition Coefficient

Octanol/water partition coefficients were estimated using the KOWIN (v 1.67) module within EPI Suite. The values in Table 3 are generally similar for all ten disulfides and show no more than a two-fold range in variation from the lowest (DMDS) to highest (DPDS) members of the series. The estimated log Kow value of 1.87 for DMDS agrees well with the actual measured value of 1.77. The fractionally-weighted average value of 2.40 for all ten disulfides was not appreciably different from the value for DMDS, which supports the use of this chemical as a surrogate for the entire blend.

E. Water Solubility

The disulfides in DSO show a relatively large range in water solubility. Using the WSKOW (v 1.41) subroutine in EPI Suite, water solubility estimates of 3.74 g/L (DMDS) to 0.04 g/L (DPDS) were calculated. The actual experimental value of 2.5 g/L for DMDS shows good agreement with the estimated value of 2.9 g/L. The fractionally-weighted average of 0.80 g/L for the ten disulfides is also reasonably close to a measured value that was less than 0.01% by weight (<0.1 g/L) for the solubility of DSO in water (ST Laboratories, 2008).

Table 3. Estimated Physiochemical Constants from EPI Suite

Disulfide	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mmHg 25 °C)	Octanol/Water Partition Coeff. (log K_{ow})	Water Solubility (g/L)
dimethyl disulfide	-69.7 (-85*)	113.6 (109.8*)	24.5 (21.98*)	1.87 (1.77*)	3.7 (2.5*)
methyl ethyl disulfide	-57.3	136.7	7.40	2.36	1.06
methyl isopropyl disulfide	-56.6	145.6	4.92	2.78	0.41
diethyl disulfide	-45.2 (-102†)	158.8 (154.1†)	3.31 (4.28†)	2.86	0.36
methyl n-propyl disulfide	-45.2	158.8	2.65	2.86	0.36
ethyl isopropyl disulfide	-44.6	167.4	1.77	3.27	0.14
ethyl n-propyl disulfide	-33.4	180.1	0.96	3.35	0.12
diisopropyl disulfide	-32.9	188.2	0.64	3.76	0.05
ethyl n-butyl disulfide	-21.8	200.4	0.35	3.84	0.04
dipropyl disulfide	-21.8 (-86†)	200.4 (193.5†)	0.50 (0.51†)	3.84	0.04
DSO	-65Δ	111-174Δ	57Δ	1.77#	<0.1Δ

* Actual measured value taken from DMDS test plan (2005).
† Actual measured value taken from EPIWIN Suite v 3.20 (USEPA 2007).
Δ Actual reported or converted value taken from a certificate of analysis (ST Laboratories, 2008).
Estimated value.

3. Environmental Fate

The environmental fate of DSO has not been examined; however, structure-activity information and suggestive anecdotal test data is available for DMDS and the remaining disulfides in the mix. Many of the disulfides in DSO are naturally found in the environment either as ingredients in vegetables, especially garlic and onions, or as products of the microbial oxidation of assimilated mercaptans (TGSC, 2008). Preliminary studies with DMDS and DPDS have shown that these two disulfides are relatively stable in soil and water (Arnault *et al*., 2004). DMDS, in particular, has been found in many environmental compartments and is considered to have an integral role in the global sulfur cycle (Caron and Kramer, 1994). Natural background concentrations of DMDS have been measured in a wide variety of media including air, surface waters, sediment, wastewater effluent, vegetation, and expired human air (HSDB, 2005). Interestingly, DMDS has been shown to be absorbed from air into moist and dry soils at a rate that was influenced by the presence of soil microbes, which facilitated the uptake into moist soil only (Bremner and Banwart, 1976). This may be an important environmental process for the disulfides in DSO because of their tendency to partition into the soil compartment.

A. Photooxidation

The atmospheric photodegradation of the disulfides in DSO was estimated using the AopWIN (v 1.92) subroutine in the EPI Suite program. As shown in Table 4, the rate of tropospheric photooxidation by reaction with hydroxyl radicals is nearly identical for the ten disulfides in DSO. The atmospheric half-life of each disulfide is approximately 30 min, which meets the definition of a rapidly removed VOC. The estimated rates of DMDS hydroxyl radical reactivity also compared well with the actual value (0.56 versus 1.2 hr).

B. Water Stability

None of the disulfides could be evaluated for aqueous stability because the HYDROWIN algorithm has only been validated for use with a limited number of chemical classes. Available information for DMDS indicates, however, that aqueous hydrolysis at ambient temperature is too slow to be an important environmental fate

process when the pH is less than 12 (Bentvelzen *et al*., 1975). This conclusion is consistent with the relative stability of the disulfide bridge to acid base hydrolysis and reported claims that DMDS slowly hydrolyzes to non-volatile methane sulfinic acid in water at pH 11-12. In addition, voluntary testing of the aqueous stability of DMDS has been agreed to in a previously submitted test plan for this chemical and the information will provide a reasonable surrogate for the water stability of DSO.

C. Biodegradation

The biodegradability of the ten DSO disulfides was examined using the BIOWIN (v 4.00) subroutine in the EPI Suite program. The BIOWIN routine uses eight different methods to evaluate the biological degradation of a target chemical under either aerobic or anaerobic conditions. Although several of the methods suggest that the probability of disulfide biodegradation is relatively high, it is believed that the most reliable information comes from the results for DMDS itself and from those models indicating a lack of ready biodegradability (see Table 4). A closed bottle ready biodegradability test performed with DMDS indicated that less than 10% of the material was degraded over a 28-day period (ELF ATOCHEM, 1995). Ready biodegradability, as defined in accordance with OECD guidelines, only occurs when at least 70% of a chemical is biologically removed from the environment within the 28-day period. Accordingly, DSO is expected to fail the biodegradability test and these conclusions are in agreement with actual test data for DMDS.

Table 4. Estimated Environmental Fate Parameters from EPI Suite

Disulfide	Photo-oxidation (K_{OH} $t_{½}$ hrs)	Water Stability	Ready Biodegradation Probability		Readily Biodegradable
			linear	non-linear	
dimethyl disulfide	0.56 (1.2*)	ND$^{\Delta}$	0.43	0.46	no (no†)
methyl ethyl disulfide	0.55	ND$^{\Delta}$	0.44	0.47	no
methyl isopropyl disulfide	0.53	ND$^{\Delta}$	0.30	0.26	no
diethyl disulfide	0.54	ND$^{\Delta}$	0.45	0.47	no
methyl n-propyl disulfide	0.54	ND$^{\Delta}$	0.45	0.47	no
ethyl isopropyl disulfide	0.52	ND$^{\Delta}$	0.31	0.26	no
ethyl n-propyl disulfide	0.53	ND$^{\Delta}$	0.46	0.48	no
diisopropyl disulfide	0.51	ND$^{\Delta}$	0.31	0.27	no
ethyl n-butyl disulfide	0.53	ND$^{\Delta}$	0.46	0.49	no
dipropyl disulfide	0.52	ND$^{\Delta}$	0.46	0.49	no
DSO	1.2$^{\#}$	ND$^{\Delta}$	0.43$^{\#}$	0.46$^{\#}$	no$^{\#}$

* Actual measured value taken from Finlayson-Pitts and Pitts (2000).
† Actual measured degradation of 10% over 28-days (DMDS test plan, 2005).
$^{\Delta}$ Not determined.
$^{\#}$ Estimated value.

D. Environmental Distribution

The environmental distribution of the composite disulfides in DSO is presented in Table 5. The estimated percent distribution in the four environmental media were determined using a Level III multi-media media fugacity model (LEV3EPI) imbedded within the EPI Suite software package and based on the work of Mackay *et al*. (1996). A level 1 fugacity analysis performed using the EQC (Equilibrium Criterion Model, v2.02) revealed that virtually 100% of each disulfide distributed to the air compartment, which is inconsistent with known partitioning behavior of DMDS in the environment (Farwell *et al*., 1979; Richards *et al*., 1991). All ten disulfides show a preference for water or soil with the distribution shifting from water to soil as the dialkyl carbon number increases

from C_2 to C_6. The tendency for the disulfides to concentrate in soil warranted an evaluation of terrestrial effects in the following ecotoxicity section of the document.

The estimated half-life for all ten disulfides was identical with values of 1.1 hr, 360 hr, 720 hr, and 135 days for air, water, soil, and sediment, respectively. Except for sediment, which was not identified as a major disulfide reservoir, these half-life estimates do not indicate environmental persistence in any media. The overall persistence in the environment ranged from 119 to 350 hrs and the fractionally-weighted additive contribution for all ten disulfides in DSO was calculated to be 184 days.

Table 5. Estimated Environmental Distribution from EPI Suite

Disulfide	Environmental Distribution (%)				Overall Persistence (hrs)
	air	water	soil	sediment	
dimethyl disulfide	1.0	58.1	40.8	0.2	119
methyl ethyl disulfide	0.7	41.9	57.2	0.2	160
methyl isopropyl disulfide	0.5	31.9	67.3	0.4	206
diethyl disulfide	0.5	29.7	69.4	0.4	220
methyl n-propyl disulfide	0.5	29.7	69.5	0.4	221
ethyl isopropyl disulfide	0.3	23.3	75.7	0.7	275
ethyl n-propyl disulfide	0.3	22.1	76.9	0.7	290
diisopropyl disulfide	0.2	18.7	79.6	1.4	338
ethyl n-butyl disulfide	0.2	18.1	80.0	1.6	350
dipropyl disulfide	0.2	18.1	80.0	1.6	350
DSO	0.2-1.0[#]	18.1-58.1[#]	40.8-80.0[#]	0.2-1.6[#]	119-350[#]

[#] Estimated value.

4. Ecotoxicity

Evidence suggests that the aquatic and terrestrial toxicity of DSO mimics the effects observed with DMDS. Initial modeling of DMDS and the remaining disulfide constituents of DSO using EPA's ECOSAR software package (Meylan and Howard, 1998) reveled that the ecotoxicity of the disulfides increased as a function of alkyl chain length. Although this finding is consistent with the observed increase in octanol/water partition coefficients for these disulfides, the results are inconsistent with available test data and knowledge of disulfide metabolism. The modeling results, therefore, have not been utilized since the assumed mode of action, non-polar narcosis, is most likely incorrect, a condition that often occurs when this endpoint is invoked indiscriminately (de Roode *et al*., 2006).

The underpinnings for the SAR routines used in the ECOSAR program assume that non-polar narcosis is the operant mode of action for the disulfides; but this class of chemicals is not explicitly represented in the training sets used to develop the mathematical relationships. In fact, disulfides are more likely to operate in terrestrial and aquatic organisms by the same mode of action observed in mammals, which involves disulfide bond cleavage and redox cycling of the free radical intermediates (Münchberg *et al*., 2007; Lesser, 2006). The reactive oxygen species produced in this reaction can lead to oxidative stress and protein interactions that are typically more severe and less consistent across species than those elicited by narcotic chemicals (Jager *et al*., 2007). This lack of applicability is evident when test data for DMDS are compared to the estimates obtained using ECOSAR (see Table 6). The toxicity of DMDS is generally under predicted by a factor 10-200 fold, which signals that a mode of action other than narcosis is in effect.

Table 6. A Comparison of Actual and Estimated Ecotoxicity Values for DMDS

Ecotoxicity Endpoint	Estimated Toxicity (mg/L)	Actual Toxicity (mg/L)
Acute Fish 96-hr LC_{50}	92.51	0.97*
Chronic Fish 30-day	11.67	--
Acute Invertebrate 48-hr EC_{50}	98.24	7†
Acute Plant 96-hr EC_{50}	60.96	35#
Earthworm 14-day LC_{50}	635.4	32*

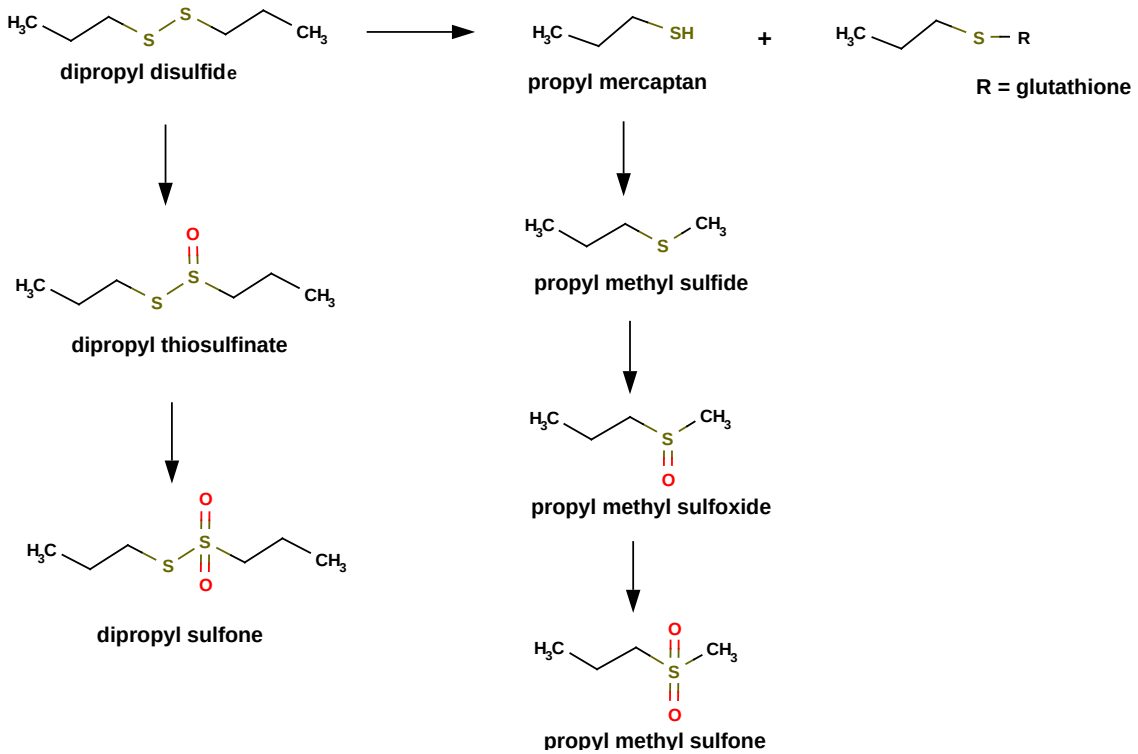
* Actual measured value taken from Arkema, Inc. (2007).
† Actual measured value taken from ELF ATOCHEM (1996).
# Additional test results for algae (ErC_{50}, EbC_{50}, NOECr, and NOECb) are available (ELF ATOCHEM, 2000).

Additional support for the use of DMDS as a surrogate for the disulfides in DSO comes from available test data for higher homologs in the series. When the acute toxicity of DMDS to fish (0.97 mg/L) is compared to the LC_{50} results obtained with DEDS (7.43 mg/L), DPDS (2.62 mg/L), and diisopropyl disulfide (8.31 mg/L), there is no apparent increase in toxicity as a function of chain length (NITE, 2003; Chevron Phillips Chemical Company, 2005; Russom *et al*., 1997). In addition, the 24-hr EC_{50} value for DEDS (14.5 mg/L) in *Daphnia magna* is nearly 2-fold greater than the 48-hr value for DMDS (7 mg/L) (Gälli *et al*., 1994). Taken together, these data are consistent with the expected change in potency for the oxidative stress caused by disulfide bond cleavage (see section 5), and confirms that DMDS is the most toxic member of the disulfide series in DSO. Additional testing with DSO is not expected to result in effect concentrations less than those observed DMDS, and therefore no further testing can be justified for the endpoints listed. Despite the lack of DMDS test data for chronic fish toxicity, testing will not be performed within the context of this submission because it will be completed in conjunction with the previously submitted test plan for DMDS. When this voluntary testing is completed, a full complement of ecotoxicity data will be available for DMDS and by analogy DSO.

5. Health Effects

Sufficient information is available to make reliable and sensible determinations of the health effects of DSO. Whereas some test data is available on the oil itself, the majority of information can be extracted from the robust summary and test plan for DMDS (DMDS Robust Summary, 2005). The rationale and justification for using the health effects data of DMDS as a substitute for the disulfides in DSO are based on sound scientific principles and a plethora of mechanistic information showing that all of the dialkyl disulfides in DSO operate through a common toxic mechanism. This mechanism, which has been well studied and clearly elucidated in the published literature, focuses on the unique characteristics of the disulfide bridge and the ease with which free radical intermediates can be formed once the bridge is cleaved.

Figure 2. Typical Pathways for the *In Vivo* Metabolism of Dialkyl Disulfides



The metabolism of many, if not all, disulfides is initiated by a thiol-disulfide exchange reaction that substitutes the sulfhydral group of glutathione for a mercaptide

fragment within the disulfide molecule. This reaction is depicted in Figure 2 for DPDS, whose *in vivo* metabolism has been examined in the greatest detail of the ten DSO disulfides (Germain *et al*., 2008; Teyssier and Siess, 2000). Evidence shows that this same initial glutathione exchange reaction also takes place for a host of alkyl, alkenyl, phenyl, and branched chain disulfides (Bach *et al*., 2008; Munday and Manns, 1994; Munday, 1989; Nishikawa *et al*., 1987). Using an expert knowledge based system for predicting the metabolic reactions that take place *in vivo* (Meteor, v 9.0.0), the disulfides in DSO were all predicted to undergo reductive cleavage of the disulfide bond with a high degree of probability (Greene *et al*., 1999).

The exchange reaction with glutathione is catalyzed by a thioltransferase, also known as glutaredoxin, which is widely distributed in nature and shows high levels of activity in the tissues and organs affected by alkyl disulfide toxicity (Lillig and Holmgren, 2007). This reaction is the key step in the toxic mechanism for dialkyl disulfides. The activation mechanism has been associated with the initiation of a redox cycle that generates excessive quantities of highly reactive free radical intermediates that are capable of interacting with tissue macromolecules at or near the site where they are formed. In some cases this site has been the red blood cell and in other cases the liver depending on the species examined (Munday, 1989). The sequence of reactions in the redox cycling of alkyl disulfide is depicted generically in Figure 3. The first product of the initial thioltansferase exchange reaction is an alkyl mercaptan that undergoes a one-electron oxidation to a free radical intermediate following ionization. This intermediate is the proximal toxicant, responsible for producing a continuous supply of hydroxyl radicals and other reactive oxygen species that can sustain the redox cycling, cause oxidative stress, and precipitate tissue injury at sites where it is formed.

Importantly, the reactivity of the mercaptans formed in the exchange reaction is directly affected by the length and branching pattern of the attached alkyl substitutents, with longer chain lengths leading to reduced radical stabilization and lower oxidation rates (Munday, 1989). In addition, the reactivity and toxicity of alkyl disulfides has been shown to decrease in the following order *n* > *sec* > *tert* due to the influence of steric

factors on thioltransferase activity. These data indicate that DMDS will be the most reactive member of the series with the longer chain lengths and higher branching patterns of the remaining homologs ameliorating the toxicity by affecting the rate of formation and ultimate stabilization of the free radical intermediates. This fact provides strong justification for the use of DMDS as a surrogate for the higher chain length disulfides in DSO and validates its use in a "read across" transfer to other disulfides in the category. The test data for DMDS is therefore offered as a reasonable and mechanistically supportable substitute for DSO, since it represents the most toxic member of the disulfide series. As such, the existing information on DSO and the disulfide category is deemed sufficient, and no further testing is needed nor required to assess the health hazards associated with this category of reclaimed substances.

Figure 3. Mechanism of Redox Cycling and Free Radical Formation from Alkyl Disulfide Metabolism (Munday and Manna, 1994)

$$2\ GSH + RSSR \leftrightarrow GSSG + 2\ RSH$$

$$RSH \leftrightarrow RS^- + H^+$$

$$(Hb)Fe^3O_2^{\bullet -} + RS^- + 2H^+ \rightarrow (Hb)Fe^3 + RS^{\bullet} + H_2O_2$$

$$RS^{\bullet} + RS^- \leftrightarrow (RSSR)^{\bullet -}$$

$$(RSSR)^{\bullet -} + 0_2 \rightarrow RSSR + 0_2^{\bullet -}$$

$$RSH + 0_2^{\bullet -} + - H^+ \rightarrow RS^{\bullet} + H_2O_2$$

A. Acute Toxicity

Oral, dermal, and inhalation studies have all been performed with DSO and the results are described in detail in the robust summaries presented in Appendix IV. The oral LD_{50} value was 1590 mg/kg in female rats and 1700 mg/kg in males (Furedi-Machacek, 1991a). Gross necropsy on dead and moribund animals revealed intestines filled with red fluid and tan-colored lungs. Darkly colored spleens were noted upon sacrifice of all female rats, with all animals displaying enlarged spleens. In an initial acute oral screening LD_{50} study on the same material, both female and male rats were

administered 5000 mg/kg, after which all the animals died (Furedi-Machacek, 1991b). The 4-hr inhalation LC_{50} value was found to be greater than 4.84 mg/L in male and female rats (Drummond, 1991). The dermal LD_{50} value was greater than 1800 mg/kg in rabbits (Furedi-Machacek, 1991c). Mild to moderate irritation was observed in a Draize rabbit skin test and the same material was determined to be minimally irritating in rabbit eyes (Furedi-Machacek, 1991d,e). It was negative in a guinea pig sensitization test (Furedi-Machacek, 1991f).

Comparable studies with DMDS revealed an oral LD_{50} value for rats of 190 mg/kg (Penwalt, 1985a), a dermal LD_{50} value for rabbits that was greater than 2,000 mg/kg (Penwalt, 1985b), and a 4-hr inhalation LC_{50} value for rats of 805 ppm (3.10 mg/L) (Tansy *et al*., 1981). These data suggest that DMDS is more toxic than DSO. By comparison, a single rat oral LD_{50} value of greater than 2000 mg/kg has been reported for DPDS (Chevron Phillips Chemical Company, 2005). Some disulfides, in particular DMDS and DPDS have been shown to cause mild to severe red blood cell hemolysis in cats, dogs, and a variety of livestock animals following oral ingestion (Gruhzit, 1931; Munday, 1989). Interestingly, vegetables containing relatively high amounts of these and other disulfides have long been associated with hemolytic anemia following accidental or intentional ingestion by dogs and farm animals (Munday and Manns, 1994; Yamato, *et al*., 2005). Rats, however, are more resistant to dialkyl, but not diaryl, disulfide induced hemolytic damage (Munday and Munday, 2003).

B. Repeated Dose Toxicity

No studies have been reported on the repeat dose effects of disulfide oil, but studies are available for both DMDS and DPDS. DMDS was examined in five separate, well-designed, oral, dermal, or inhalation studies. In the first inhalation study, summarized in the IUCLID dataset for DMDS, male and female rats were exposed to 10, 50, 150, and 250 ppm (0.04, 0.19, 0.58, and 0.96 mg/L) DMDS for 6 hr/day for 90 days (ELF ATOCHEM, 1992). Findings included decreases in body weight and food consumption, reduced thymus gland weights, and increased liver weights. Possible reductions hemoglobin, red blood cell count, and packed cell volume were observed at the highest concentration. Histopathological changes were noted in the nose and spleen.

Treatment-related changes in alanine aminotransferase, alkaline phosphatase and total bilirubin indicated some degree of liver involvement. The NOAEL for this study was 10 ppm (0.04 mg/L). In the second inhalation study, rats were exposed for 13 weeks to 5, 25, or 125 ppm (0.02, 0.10, or 0.48 mg/L) DMDS for 6 hr/day (Kim *et al*., 2006). A treatment-related decrease in body weight gain, food consumption, and thymus weight were observed along with an increase in adrenal gland weight. Histopatholgy did not reveal any increase in the incidence or severity of abnormal tissue alterations relative to controls. Statistically significant decreases were also noted in serum aspartate aminotransferase, blood urea nitrogen, and creatine phosphokinase levels. The NOAEL was 5 ppm (0.02 mg/L) for male rats and 25 ppm (0.10 mg/L) for female rats.

The two dermal studies were performed in male and female New Zealand rabbits treated with DMDS for 6 hr/day by applying the neat material under an occlusive bandage (DMDS Robust Summary, 2005). In the first range-finding study, animals treated with DMDS levels of 0.1, 0.5, or 1 mL/kg/day (106, 505, or 1063 mg/kg/day) for 14 days caused dose-related lethargy or unconsciousness in all treatment groups that dissipated by the end of the day (ELF ATOCHEM, 1989). Severe treatment-related skin lesions were also observed in all three treatment groups. The NOAEL and LOAEL for this study were determined to be less than 106 mg/kg/day and 106 mg/kg/day, respectively. In the second study, the rabbits were treated dermally at levels of 0.01, 0.1, or 1 mL/kg/day (10.6, 106.3, or 1063 mg/kg/day) for 28 days (ATOCHEM, 1989a). Consistent with the range-finding studies, dose-related changes in lethargy and skin irritation were also observed in the more prolonged study. After 13 days, mortality was observed in the rabbits in the high dose group and treatment was terminated in this dose group. The male rabbits in the high dose group also displayed some abnormal changes in hematology and clinical chemistry measurements that were not observed in the female rabbits. Histopathologic examination and organ-weight measurements failed to reveal any treatment-related changes in the adrenals, brain, heart, kidneys, liver, lungs, ovaries, testis, thyroid, or thymus. The NOAEL for systemic effects was 10.6 mg/kg/day and the NOAEL for localized dermal irritation was less than 10.6 mg/kg/day.

Finally, a 90-day oral feeding study with DPDS failed to show any toxic effects following the dietary administration of 7.3 mg/kg/day or 8.2 mg/kg/day to male or female rats, respectively (Posternak *et al*., 1969). Food consumption and body weights were recorded weekly and hematological examinations and blood urea nitrogen measurements were performed on half the animals at 7 weeks and on all animals at 13 weeks. A slight non-statistical increase in blood urea nitrogen was observed at end of the study. The organ weight measurements, gross examinations, tissue histopathology performed at necropsy failed to show any treatment-related effects. The dietary NOAELs for DPDS can be roughly equated to inhalation values of 3.1 and 4.6 ppm using standard route-to-route extrapolation techniques that assume 100% absorption by both routes (Rennen *et al*., 2004). Recognizing that only a single dose was administered in the DPDS study, the route conversion still provides a consistency check for the toxic potency of the lowest and highest disulfide members of the DSO category. Since the threshold for DPDS toxicity is essentially equal to, and quite possibly higher than, the threshold value DMDS, the data are consistent with the argument that DMDS is the most toxic member dialkyl disulfide series. In fact, the World Health Organization has determined that the information on DPDS oral toxicity was sufficient for use as a surrogate for evaluating the food safety of a host of related alkyl and allyl disulfides (WHO, 2000).

C. Mutagenicity

Although there are no results available for DSO, DMDS has been examined in a variety of *in vivo* and *in vitro* genetic toxicology screening assays (DMDS Robust Summary, 2005). The test results revealed that DMDS was negative in bacterial mutagenicity assays (Penwalt, 1985c), negative in mammalian mutagenicity tests (ELF ATOCHEM, 1990a), negative for DNA damage and repair (ELF ATOCHEM, 1990b), and ambiguously positive in a chromosomal aberration study using human lymphocytes (ELF ATOCHEM, 1990c). Except for the DNA damage and repair assay, these tests were all performed in the presence and absence of metabolic activation. Similarly, negative results were obtained when DMDS was evaluated *in vivo* in a mouse micronucleus assay at inhalation concentrations of 250 and 500 ppm (ATOCHEM, 1989b), and did not cause unscheduled DNA synthesis in the hepatocytes of rats exposed to 500 ppm (ATOCHEM, 1990). By comparison, DPDS did not cause any reverse

mutations in an Ames *S. typhimurium* assay using strain TA98 (Tsai *et al*., 1996). None of the disulfides in DSO were judged to be genotoxic by an expert knowledge based system used to predict the health effects of untested chemical substances (Derek, v 9.0.0) (Greene *et al*., 1999).

D. Reproductive and Developmental Toxicity

Although no studies have been reported on the reproductive or developmental toxicity of disulfide oil, studies performed with DMDS are offered as a reasonable surrogate for the disulfides in DSO. An evaluation of developmental effects was examined in a series of inhalation exposure studies performed in rats with DMDS (DMDS Robust Summary, 2005). In an initial range finding study, pregnant dams were exposed for 6 hr/day on days 6 through 15 of gestation to DMDS concentrations of 10, 50, or 250 ppm (0.04, 0.19, or 0.96 mg/L) (ATOCHEM, 1991a). Treatment-related reductions in body weight gain and food consumption were observed in all treatment groups, but pregnancy incidence, intrauterine death incidence, pre-implantation loss, litter size, sex ratio, and the incidence of malformations were all within the expected range. Mean fetal weights showed an exposure-related reduction in all treatment groups that was considered to be an equivocal finding. The maternal NOAEL was determined to be less than 10 ppm (0.04 mg/L).

In a more detailed study, three groups of 30 mated female rats were exposed to DMDS by whole body exposure at 5, 15 or 50 ppm (0.02, 0.06, or 0.19 mg/L) for 6 hours daily from day 6 to day 15 of gestation (ATOCHEM, 1991b). A similar group of 30 rats, exposed to filtered air only over the same period, served as controls. All animals were maintained until day 20 of gestation, and then sacrificed. No deaths were observed or unusual lesions were observed, but a higher incidence of rough hair coat was seen at 50 ppm (0.19 mg/L). Clinical condition at 5 and 15 ppm (0.02 and 0.06 mg/L) did not differ from controls. Treatment-related reductions in weight gain were observed at 15 and 50 ppm (0.06 and 0.19 mg/L). Food intake was lower than controls at 50 ppm (0.19 mg/L), but comparable at 5 or 15 ppm (0.02 and 0.06 mg/L). There was no effect of treatment on pre or post-implantation loss, litter size or sex ratio. Maternal toxicity was noted at 15 and 50 ppm (0.06 and 0.19 mg/L), but there was no evidence of developmental effects.

Litter and fetal weights were reduced at 50 ppm (0.19 mg/L). At 5 and 15 ppm (0.02 and 0.06 mg/L) these parameters were comparable to controls. No malformations were observed in fetuses from the treated groups. A slightly higher incidence of retarded ossification was observed at 50 ppm (0.19 mg/L), which indicated delayed maturation as a result of the lower fetal weight, rather than teratogenicity. The NOAELs for maternal toxicity, teratogenicity, and fetotoxicity were 5, 50, and 15 ppm (0.02, 0.06, and 0.19 mg/L), respectively.

The effects of DMDS on reproductive organs were assessed in male and female rats exposed to 10, 50, 150, or 250 ppm (0.04, 0.19, 0.58, or 0.96 mg/L) DMDS for 6 hr/day for 90 days (ELF ATOCHEM, 1992). Tissue histopathology did not reveal any lesions or damage to the epididymus, prostrate, or testes of the male rats, nor ovaries or uterus of female rats.

6. Conclusions

The preceding examination of the physical properties, health effects, and mode of action of the disulfides in DSO demonstrates that DMDS can be used as reasonable worst case surrogate for this substance. The analysis provides strong and consistent mechanistic evidence that DMDS is the most potent member of the alkyl disulfide series, and that the higher molecular weight members found in DSO do not pose a greater health threat or environmental hazard. Accordingly, the available test data for DMDS, a chemical previously reviewed under the HPV Challenge Program, are offered as a justifiable substitute for DSO. The summary of available findings for DMDS and DSO presented in Table 7 show that all of the testing requirements have met or will be met once the DMDS testing is completed for water stability and chronic fish toxicity. Testing for these endpoints will be completed under a voluntary agreement recently approved and accepted by the US EPA. In conclusion, the data review indicates that DMDS can be used a surrogate for DSO and that all of the necessary testing requirements under the HPV Challenge Program have been satisfied.

Table 7. Data Matrix for Disulfide Oil

Endpoint	Sponsored Substance Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (68955-96-4)	Supporting Chemical Dimethyl Disulfide (624-92-0)	Supporting Chemical Diethyl Disulfide (110-81-6)	Supporting Chemical Dipropyl Disulfide (629-19-6)
Summary of Physical and Chemical Properties				
Melting Point (°C)	**-54** -102 – -21.8 (est)	**-85** -69.7 (est)	**-102** -45.2 (est)	**-86** -21.8 (est)
Boiling Point (°C)	**111 – 174** 109.8 – 200.4 (est)	**109.8** 113.6 (est)	**154.1** 158.8 (est)	**193.5** 200.4 (est)
Vapor Pressure (mmHg at 25°C)	**57** 0.35 – 24.5 (est)	**21.98** 24.5 (est)	**4.28** 3.31 (est)	**0.51** 0.50 (est)
Log Kow	1.77 (Read Across)	**1.77** 1.87 (est)	**-** 2.86 (est)	**-** 3.84 (est)
Water Solubility (mg/L at 25°C)	**< 100** 40 – 3740 (est)	**2500** 3740 (est)	- 360 (est)	- 40 (est)

Table 7. Data Matrix for Disulfide Oil (cont'd)

Endpoint	Sponsored Substance Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (68955-96-4)	Supporting Chemical Dimethyl Disulfide (624-92-0)	Supporting Chemical Diethyl Disulfide (110-81-6)	Supporting Chemical Dipropyl Disulfide (629-19-6)
Summary of Environmental Fate Data				
Indirect (OH^-) Photodegradation Half-life ($t_{1/2}$)	1.2 (Read Across)	**1.2** 0.56 h (est)	- 0.54	- 0.52
Stability in Water (Hydrolysis) Half-life ($t_{1/2}$)	Read Across	**TBD**	-	-
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	 0.2 – 1.0 (est) 18.1 – 58.1 (est) 40.8 – 80 (est) 0.2 – 1.6 (est)	 1.0 (est) 58.1 (est) 40.8 (est) 0.2 (est)	 0.5 (est) 29.7 (est) 69.4 (est) 0.4 (est)	 0.2 (est) 18.1 (est) 80.0 (est) 1.6 (est)
Biodegradation at 28 days (%)	< 10 (Read Across)	**< 10**	-	-
Summary of Environmental Effects – Aquatic and Terrestrial Toxicity Data				
Fish (acute) 96-h LC_{50} (mg/L)	0.97 (Read Across)	**0.97**	**7.43**	**2.62**
Fish (chronic) ChV 30-day (mg/L)	Read Across	**TBD**	-	-
Aquatic Invertebrates 48-h EC_{50} (mg/L)	7 (Read Across)	**7**	**14.5 (24-hr)**	-
Aquatic Plants 72-h EC_{50} (mg/L) (growth)	35 (Read Across)	**35**	-	-
Earthworm 14-day LC_{50} (mg/kg)	32 (Read Across)	**32**	-	-

Table 7. Data Matrix for Disulfide Oil (cont'd)

Endpoint	Sponsored Substance Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (68955-96-4)	Supporting Chemical Dimethyl Disulfide (624-92-0)	Supporting Chemical Diethyl Disulfide (110-81-6)	Supporting Chemical Dipropyl Disulfide (629-19-6)
Summary of Human Health Data				
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	(rat) **1590 – 1700**	(rat) **190**	-	(rat) **> 2000** hdt
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	(rabbit) **> 1800** hdt	(rabbit) **> 2000** hdt	-	**-**
Acute Inhalation Toxicity **LC_{50} (mg/L)**	(rat) **> 4.84** hdt	(rat) **3.1**	-	**-**
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	-	-	-	(rat) **NOAEL = 7.3 - 8.2** (hdt)
Repeated-Dose Toxicity **NOAEL/LOAEL** **Dermal (mg/kg-bw/day)**	(rabbit) NOAEL = 10 (Read Across) LOAEL = 100 (Read Across)	(rabbit) **NOAEL = 10** **LOAEL = 100)**	-	-
Repeated-Dose Toxicity **NOAEC/LOAEC** **Inhalation (mg/L/day)**	(rat) NOAEC = 0.019 - 0.096 (Read Across) LOAEC = 0.096 – 0.482 (Read Across)	(rat) **NOAEC = 0.019 - 0.096** **LOAEC = 0.096 – 0.482**	-	-
Reproductive Toxicity **NOAEC/LOAEC** **Inhalation (ppm)**	No effects were seen following evaluation of reproductive organs in the two 13-week inhalation repeated dose toxicity studies in rats (Read Across)	**No effects were seen following evaluation of reproductive organs in the two 13-week inhalation repeated dose toxicity studies in rats**	-	-

Table 7. Data Matrix for Disulfide Oil (cont'd)

Endpoint	Sponsored Substance Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (68955-96-4)	Supporting Chemical Dimethyl Disulfide (624-92-0)	Supporting Chemical Diethyl Disulfide (110-81-6)	Supporting Chemical Dipropyl Disulfide (629-19-6)
Summary of Human Health Data				
Developmental Toxicity NOAEC/LOAEC **Inhalation (mg/L/day)** **Maternal Toxicity**	(rat) NOAEC = 0.019 (Read Across) LOAEC = 0.058 (Read Across)	(rat) **NOAEC = 0.019** **LOAEC = 0.058**	-	-
Developmental Toxicity	NOAEC = 0.058 (Read Across) LOAEC = 0.193 (Read Across)	**NOAEC = 0.058** **LOAEC = 0.193**		
Genetic Toxicity – Gene Mutation ***In vitro (bacterial)*** ***In vitro (mammalian)***	Negative (Read Across) Negative (Read Across)	**Negative** **Negative**	-	**Negative** -
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Ambiguous (Read Across)	**Ambiguous**	-	-
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	(mouse) Negative (Read Across)	(mouse) **Negative**	-	-
Genetic Toxicity – Other ***In vitro*** **Unscheduled DNA synthesis**	Negative (Read Across)	**Negative**	-	-
Genetic Toxicity – Other ***In vivo*** **Unscheduled DNA synthesis**	(male rat) Negative (Read Across)	(male rat) **Negative**	-	-

Table 7. Data Matrix for Disulfide Oil (cont'd)

Endpoint	Sponsored Substance Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (68955-96-4)	Supporting Chemical Dimethyl Disulfide (624-92-0)	Supporting Chemical Diethyl Disulfide (110-81-6)	Supporting Chemical Dipropyl Disulfide (629-19-6)
Summary of Human Health Data				
Other Information Dermal irritation	**Mildly to moderately irritating**	**Slightly irritating**	-	-
Other Information Eye irritation	**Minimally irritating**	**Slightly irritating**	-	-
Other Information Sensitization	**Negative**	**Negative**	-	-

[1] This table includes measured and predicted SIDS values for the sponsored substance and three of its components for which measured data were identified and used to meet or support the sponsored substance data requirements. Predicted physical-chemical and environmental fate values for seven other disulfide components also used to support the sponsored substance requirements are presented elsewhere in the document.

(-) Indicates that endpoint was not addressed for this chemical.
(est) indicates estimated.
(TBD) indicates data to be developed.
(hdt) indicates highest dose tested.
Bold values represent measured data.

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Appendix I

Analytical Results
Composition of Disulfide Oil

Composition of Disulfide Oil

Client: Houston Refining LP **Lab #: P622737708**

Sample ID: V207 Sample #1167453 04/12/07 0842 **Date: 11/28/07**

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**

Appendix II

Dimethyl Disulfide Test Plan

201-16161A

High Production Volume (HPV) Challenge Program

DIMETHYL DISULFIDE

(CAS# 624-92-0)

Test Plan

Arkema Inc.
2000 Market Street
19103 Philadelphia, PA

December 2005

EXECUTIVE SUMMARY

Arkema Inc has volunteered to sponsor dimethyl disulfide (DMDS, CAS# 624-92-0) in the USEPA HPV program. The DMDS Test Plan is being submitted to fulfill the United States Environmental Protection Agency (USEPA) High Production Volume (HPV) Challenge Program commitment for DMDS.

Data from company proprietary files, peer-reviewed literature, and/or calculated endpoints using widely accepted computer modeling programs have been identified for purposes of this program. Robust summaries of the available data are included in the attached IUCLID. The following table summarizes the available data and proposed testing for DMDS.

Table 1: Matrix of Available and Adequate Data on DMDS

"SIDS ENDPOINT"	Data Available Y/N	Testing Planned? Y/N
Physical and Chemical Data		
Melting Point	Y	N
Boiling Point	Y	N
Vapor Pressure	Y	N
Partition Coefficient	Y	N
Water Solubility	Y	N
Environmental Fate		
Photodegradation	Y	N
Stability in Water (Hydrolysis)	N	Y
Transport/Distribution	Y	N
Biodegradation	Y	N
Ecotoxicity		
Acute/Prolonged Toxicity to Fish	N	Y
Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	Y	N
Acute Toxicity to Aquatic Plants (Algae)	Y	N
Toxicity		
Acute Toxicity (Oral)	Y	N
Acute Toxicity (Dermal)	Y	N
Acute Toxicity (Inhalation)	Y	N
Repeated Dose	Y	N
GeneticToxicity *in vitro* – Gene Mutation	Y	N
Genetic Toxicity *in vitro* – Chromosomal Aberration	Y	N
Reproductive Toxicity Developmental Toxicity	Y	N

Note: **The data used to characterize the OECD SIDS endpoints for substances in this Test Plan were identified either in company proprietary files, peer-reviewed literature, and/or calculated using widely accepted computer modelling programs. All data were evaluated for study reliability in accordance with criteria outlined by the USEPA (1999a). Only studies that met the reliability criteria of "1" (reliable without restrictions) or "2" (reliable with restrictions) were used. Additional data are also included in the IUCLID (International Uniform Chemical Information Dataset) attached in Annex I. A more detailed discussion of the data quality and reliability assessment process used to develop this test plan is provided in Annex II.**

1.1 Physico-Chemical properties

DMDS is a pale yellow liquid with a strong garlic like odor. Experimental data for the physical chemical parameters are available and reported in EPIWIN© (USEPA, 2004) and are provided in the following table.

Table 2. Physicochemical Data

Parameter	***Value***
Melting Point	-85ºC [1]
Boiling Point	110ºC [1]
Vapor Pressure	29.3 hPa
Kow Partition Coefficient	1.77[1]
Water Solubility (mg/l)	2500[1]

[1]EPIWIN v3.12 – Syspro database

Conclusion

Adequate data are available for the HPV physical/chemical property endpoints. No additional testing for the HPV program is proposed.

GENERAL INFORMATION ON EXPOSURE

1.2 Production Volumes and Use Pattern

DMDS is on EPA's high production volume list indicating it is manufactured and/or imported at greater than 1 million pounds per year according to the toxic inventory update rule (IUR).

1.2.1 Use Pattern:

DMDS has several industrial uses. It is used in the oil industry as a sulfiding/presulfiding agent to activate catalysts of hydrotreating units, to reduce the number of decoking operations in the petrochemical industry, as a chemical intermediate in the fine chemical industry, and as an anti-corrosive in metallurgy.

1.3 Environmental Exposure and Fate

1.3.1 Photodegradation

The photodegradation of DMDS was evaluated using EPIWIN 3.12. The half life of DMDS was calculated to be 0.565 hours based on the experimental rate constant of 227 x E-12 cm3/molecule-sec.

Conclusion

Adequate data are available to assess the photodegradation of DMDS. No additional studies are proposed for the HPV program.

1.3.2 Stability in Water

EPIWIN was unable to calculate a hydrolysis rate for DMDS. A hydrolysis study is proposed for DMDS.

1.3.3 Transport between Environmental Compartments

The transport of DMDS between environmental compartments was assessed by fugacity modeling using EPIWIN (v3.12). Results are listed in the table below:

Table 3. Fugacity Results for DMDS

Compartment	Mass amount (%)	Estimated half life (hr)
Air	1.01	1.13
Water	58.1	360
Soil	40.8	360
Sediment	0.168	3.24x e003

1.3.4 Biodegradation

DMDS was not readily biodegradable when evaluated according to OECD 301D. The degradation was less than 10% following 28 days exposure.

Conclusion

Adequate data are available to assess the biodegradation of DMDS. No additional studies are proposed for the HPV program.

2 HUMAN HEALTH HAZARDS

2.1.1 Acute Toxicity

Single exposure (acute) studies indicate DMDS is moderately toxic if swallowed (rat; 290 mg/kg < LD50 < 500 mg/kg), no more then slightly toxic if absorbed through skin (rabbit LD50 >2,000 mg/kg), and slightly toxic if inhaled (rat 4-hr LC50 805 ppm).

Conclusion

Adequate data are available to assess the acute toxicity of DMDS and no additional studies are proposed.

2.1.2 Repeated Dose Toxicity

DMDS was evaluated in a 90-day repeated dose study on rats according to OECD guidelines. This study featured inhalation dosing, measurement of mortality, body weight changes, food consumption, hematological and blood biochemical examinations, urinalysis, organ weights, histopathology and a functional observational battery. Rats were exposed whole body to 0, 10, 50, 150, and 250 ppm DMDS for 6 hours per day for 90 days. Satellite groups were evaluated

following a 2-week recovery period. Results from this study showed decreased body weights, food consumption, hypoactivity, changes in white blood cell counts, reduced thymus gland weight and increased liver weight. Reversible microscopic changes were noted in the nasal mucosa.

Conclusion

Adequate data are available to assess the reproductive toxicity of DMDS. No additional testing is proposed for purposes of the HPV program.

2.1.3 Mutagenicity

Several reliable genetic toxicity studies are available for DMDS. Predominantly negative results were obtained with DMDS when tested *in vitro* (negative bacterial and mammalian mutagenicity assays, negative DNA damage and repair, ambiguous positive in vitro chromosome aberration study using human lymphocytes). Negative results were obtained when DMDS was evaluated *in vivo* (mouse micronucleus, unscheduled DNA synthesis).

Conclusion

Adequate data are available to assess the genetic toxicity of DMDS. No additional testing is proposed for purposes of the HPV program.

2.1.4 Toxicity for Reproductive/Developmental Toxicity

Reproductive Toxicity

The 90 day repeated dose toxicity study will be used to assess the reproductive toxicity of DMDS. Reproductive organs examined in this study included the epididymus, prostate, and testes in males and ovaries and uterus in females. No lesions were reported.

Developmental Toxicity

A Developmental Toxicity test was completed for DMDS in Sprague-Dawley rats following OECD Guideline 414 "Teratogenicity." DMDS was administered by inhalation to 0, 5, 15, and 50 ppm on gestation days 6 to 15. Maternal toxicity was noted at 15 and 50 ppm. No evidence of developmental toxicity was observed. No additional studies are proposed.

Conclusion

Adequate data are available to assess the reproductive and developmental toxicity of DMDS. No additional testing is proposed for the HPB program.

3 HAZARDS TO AQUATIC ORGANISMS

DMDS has been evaluated in an acute daphnia immobilization and algal growth inhibition studies. DMDS is moderately toxic to daphnia with a 48 hour EC50 value of 7 mg/l. DMDS is slightly toxic to *Selenastrum capricornutum* alga with a 72 hour EC50 of 35 mg/l. No data are available for acute fish and alga. No data are available to assess the acute fish toxicity and an acute fish toxicity (OECD guideline 203) is proposed for DMDS.

Conclusion

Adequate data are available to assess the aquatic toxicity of DMDS to daphnia and alga but not fish. An acute fish toxicity study is proposed (OECD guideline 203) for DMDS.

References

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ANNEX I: DIMETHYL DISULFIDE IUCLID

See attached IUCLID documents.

ANNEX II: DATA QUALITY ASSESSMENT

Available environmental, ecotoxicity, and mammalian toxicity studies were reviewed and assessed for reliability according to standards specified by Klimisch et al., (1997), as recommended by the USEPA (1999a) and the OECD (OECD, 2002). The following reliability classification (Klimisch rating) has been applied to each study assessed:

- *1 = Reliable without Restriction* – Includes studies that comply with USEPA- and/or OECD-accepted testing guidelines and were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented;

- *2 = Reliable with Restriction* – Includes studies that were conducted according to national/international testing guidance and are well documented. May include studies that were conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters that are well documented and scientifically valid but vary slightly from current testing guidance. Also included in this category were physical-chemical property data obtained from reference handbooks, as well as environmental endpoint values obtained from an accepted method of estimation (e.g., USEPA's EPIWIN estimation program);

- *3 = Not Reliable* – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or in which documentation is insufficient; and,

- *4 = Not Assignable* – This designation is used in this dossier for studies that appear scientifically valid but for which insufficient information is available to adequately judge robustness.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this dossier. Those key studies selected for inclusion are considered typical of the endpoint responses observed in other studies of a similar nature and design that were identified during our search of the literature.

Appendix III

Dimethyl Disulfide Robust Summaries

IUCLID

Data Set

Existing Chemical	:	ID: 624-92-0
CAS No.	:	624-92-0
EINECS Name	:	dimethyl disulphide
EC No.	:	210-871-0
TSCA Name	:	Disulfide, dimethyl
Molecular Formula	:	C2H6S2
Producer related part		
Company	:	ATOFINA Chemicals Inc.
Creation date	:	27.12.2005
Substance related part		
Company	:	ATOFINA Chemicals Inc.
Creation date	:	27.12.2005
Status	:	
Memo	:	
Printing date	:	31.12.2005
Revision date	:	
Date of last update	:	31.12.2005
Number of pages	:	51
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	ARKEMA
Contact person	:	
Date	:	
Street	:	4-8, cours Michelet La Défense 10
Town	:	95091 Paris La Défense Cedex
Country	:	France
Phone	:	+33 1 49 00 80 80
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	Atofina Paris La Défense Cedex

14.12.2005

Type	:	importer of product
Name	:	ARKEMA Chemicals Inc.
Contact person	:	
Date	:	
Street	:	2000 Market Street
Town	:	Philadelphia
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Remark	:	formerly ATOFINA Inc.
Source	:	Atofina Paris La Défense Cedex

31.12.2005

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	
Molecular formula	:	C2-H6-S2
Molecular weight	:	94.2
Petrol class	:	
Source	:	Atofina Paris La Défense Cedex

23.12.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	> 99.5 % w/w
Colour	:	Light yellow
Odour	:	Strong garlic odour
Source	:	ARKEMA, Paris-la-Défense, France (JFR) Atofina Paris La Défense Cedex

23.12.2005

1.1.2 SPECTRA

1.2 SYNONYMS AND TR ADENAMES

DMDS
2,3-Dithiabutane
Dimethyl disulfide
Dimethyldisulfide
Disulfide, dimethyl
Methyldisulfide
Methyldithiomethane

Source	:	ARKEMA, Paris-la-Défense, France Atofina Paris La Défense Cedex

27.12.2005

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use	:	industrial
Category	:	Chemical industry: used in synthesis

Source : Atofina Paris La Défense Cedex
23.12.2005

Type of use : industrial
Category : other: Sulphurization agent (Petrochemical)

Source : ARKEMA, Paris-la-Défense, France (JFR)
Atofina Paris La Défense Cedex
23.12.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information : 210-871-0

Source : Atofina Paris La Défense Cedex
23.12.2005

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 23.12.2005

Source : ARKEMA, Paris-la-Défense, France (JFR)
Atofina Paris La Défense Cedex

23.12.2005

1.13 REVIEWS

2.1 MELTING POINT

Value : -85 °C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
27.12.2005 (18)

Value : = -84.7 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance :

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex
15.11.1993 (28)

2.2 BOILING POINT

Value : = 109.6 °C at 1013 hPa
Decomposition : yes
Method :
Year :
GLP : no data
Test substance :

Remark : Start of Decomposition: 390 degree C
Decomposition products: Hydrogen sulphide, Dimethyl sulphide and methanethiol
Similar result (109.6C) reported in Epiwin 3.12 syspro experimental database
Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.12.2005 (28)

2.3 DENSITY

Type : density
Value : = 1.063 g/cm³ at 20 °C
Method :
Year :
GLP : no data
Test substance :

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex
15.11.1993 (28)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 29.3 hPa at 20 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.12.2005 (32)

Value	:	= 38 hPa at 25 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex

15.11.1993 (28)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 1.77 at °C
pH value	:	
Method	:	other (measured)
Year	:	
GLP	:	
Test substance	:	no data
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

31.12.2005 (20)

Partition coefficient	:	octanol-water
Log pow	:	= 1.87 at °C
pH value	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex

04.12.2001 (31)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water

Value	:	= 2500 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Unit of water solubility: ppm Similar data (3000 mg/l) reported in EPIWIN v3.12 experimental database
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

31.12.2005 (32)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 16 °C
Type	:	closed cup
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Method: ASTM D 93
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex

15.11.1993 (28)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result	:	flammable
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex

15.11.1993 (28)

2.10 EXPLOSIVE PROPERTIES

Result	:	other
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Explosive limits of vapours: 1.1 to 16.1 %v/v in air
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex

15.11.1993 (28)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	= .000000000227 cm³/(molecule*sec)
Degradation	:	= 50 % after .6 hour(s)
Result	:	AOP Program (v1.91) Results: ========== SMILES : S(SC)C CHEM : Disulfide, dimethyl MOL FOR: C2 H6 S2 MOL WT : 94.19 ---------- SUMMARY (AOP v1.91): HYDROXYL RADICALS ---------- Hydrogen Abstraction = 2.1216 E-12 cm3/molecule-sec Reaction with N, S and -OH = 225.0000 E-12 cm3/molecule-sec Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec Addition to Aromatic Rings = 0.0000 E-12 cm3/molecule-sec Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec OVERALL OH Rate Constant = 227.1216 E-12 cm3/molecule-sec HALF-LIFE = 0.047 Days (12-hr day; 1.5E6 OH/cm3) HALF-LIFE = 0.565 Hrs ---------- SUMMARY (AOP v1.91): OZONE REACTION ---------- ****** NO OZONE REACTION ESTIMATION ****** (ONLY Olefins and Acetylenes are Estimated) Experimental Database Structure Match: Chem Name : Dimethyl disufide CAS Number: 000624-92-0 Exper OH rate constant : 227 E-12 cm3/molecule-sec Exper OH Reference: KWOK,ESC & ATKINSON,R (1994) Exper Ozone rate constant: --- cm3/molecule-sec Exper NO3 rate constant : 7 E-13 cm3/molecule-sec
Reliability	:	(2) valid with restrictions Acceptable calculation method based on experimental rate constant.
Flag	:	Critical study for SIDS endpoint

31.12.2005

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Remark	:	Hydrolysis at ambient temperature and pH<12 is too slow to be an important environmental fate process.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
27.12.2005 (7)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : 1.01 % (Fugacity Model Level I)
Water : 58.1 % (Fugacity Model Level I)
Soil : 40.8 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : .165 % (Fugacity Model Level II/III)
Method : other: model
Year :

Result : Level III Fugacity Model (Full-Output):

==========

Chem Name : Disulfide, dimethyl
Molecular Wt: 94.19
Henry's LC : 0.00121 atm-m3/mole (Henry database)
Vapor Press : 24.5 mm Hg (Mpbpwin program)
Log Kow : 1.77 (Kowwin program)
Soil Koc : 24.1 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.01	1.13	1000
Water	58.1	360	1000
Soil	40.8	720	1000
Sediment	0.165	3.24e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	9.37e-012	2.21e+003	36.1	73.8	1.2
Water	1.34e-008	400	208	13.3	6.93
Soil	1.17e-007	141	0	4.69	0
Sediment	1.2e-008	0.126	0.0118	0.00421	0.000394

Persistence Time: 119 hr
Reaction Time: 130 hr
Advection Time: 1.47e+003 hr
Percent Reacted: 91.9
Percent Advected: 8.14

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 1.131

Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 2.991 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.12.2005 (19)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Contact time :
Degradation : < 10 (±) % after 28 day(s)
Result : other: not readily biodegradable
Kinetic of testsubst. : 7 day(s) = .3 %
14 day(s) = 1.1 %
20 day(s) = 1.9 %
28 day(s) < 0 %
%
Control substance : Benzoic acid, sodium salt
Kinetic : 14 day(s) = 86.1 %
28 day(s) = 84.5 %
Deg. product : not measured
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1992
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : O2 dissolved (mg/l)

	0 d	7 d	14 d	20 d	28 d
1- Medium + inoculum					
mean	8.41	8.26	8.12	7.64	7.32
2- Medium + inoculum + test substance					
mean	8.42	8.24	8.05	7.51	7.44
3- Medium + inoculum + test substance + reference substance					
mean	8.37	5.55	5.43	4.79	4.74
4- Medium + inoculum + reference substance					
mean	8.41	2.61	2.37	2.09	1.68

BOD (O2 mg/mg substance)

	0 d	7 d	14 d	20 d	28 d
serie 2 (substance)	0.00	0.01	0.02	0.04	-0.04
serie 3 (inhibition control)	0.00	0.76	0.76	0.80	0.73
serie 4 (reference)	0.00	1.41	1.44	1.39	1.41

BIODEGRADATION (%)

	0 d	7 d	14 d	20 d	28 d
serie 2 (substance)	0	0.3	1.1	1.9	-1.8
serie 3 (inhibition control)	0	40.1	39.9	42.2	38.2
serie 4 (reference)	0	84.5	86.1	83.1	84.5

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
Guideline study without detailed documentation.

Flag : Critical study for SIDS endpoint
31.12.2005 (8)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 7
EC50, 24 h : > 13.4
Analytical monitoring : yes
Method : OECD Guide-line 202
Year : 1996
GLP : yes
Test substance : other TS: DMDS, Atofina, 98.93% purity

Result : - Biological observations
20 daphnia per concentration

mg/l nominal	%Immo	1	2	3	4	total
13.4	85	1	1	0	1	3
10.6	75	1	2	1	1	5
9.5	70	2	2	1	1	6
7.8	60	3	2	2	1	8
6.3	50	3	2	3	2	10
5.5	45	3	3	3	2	11
4.7	20	4	4	4	4	16
3.8	10	4	5	4	5	18
3.3	10	5	5	4	4	18
0 témoin	10	5		4	5	4	18

- EC50, 48h : 7 mg/l ; 95% CI : 6.5 - 7.6 mg/l

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : - Test organisms
Daphnia magna Straus Clone A from INERIS, France. Breeding colony realized in the laboratory in an Elendt M7 medium, supplemented with algal based feed. Organisms are selected by sieving.
Age at study initiation : < 24h old, laboratory bred

- A stock solution is prepared before the beginning of the test, by mixing 100 mg of the substance with 1 liter of dilution water.
Test temperature range : 20-21°C
Exposure vessel type :
Closed flasks (120 ml) as test glassware entirely filled with test solutions and stoppered with PTFE bungs and sealed with aluminum caps.

-Dilution water is prepared in the laboratory using pure water and salts according to ISO 6341.
25 ml/l of the below solutions , aerated up to oxygen

saturated
11.76 g CaCl2, 2 H2O /l ultrapure water
4.93 g MgSO4, 7 H2O /l ultrapure water
2.59 g NaHCO3 /l ultrapure water
0.23 g KCl /l ultrapure water

- Dilution water chemistry
According to ISO 6341
Ca+Mg ions = 2.5 mmol/l.
Ca/Mg = 4
Na/K = 10
pH 7.8 ± 0.2

- incubation of test flasks in darkness.

- Water chemistry in test :

C nominal
(mg/l) 0 3.3 4.0 4.8 5.8 6.9 8.3 10.0 12.0 14.4

02 at 48h (mg/l)
8.3 8.2 8.2 8.3 8.3 8.3 8.3 8.4 8.3 8.3
pH at 48 h
7.89 7.90 7.88 7.88 7.95 7.93 7.96 8.01 8.03 8.00

- Test design

Concentration			
Nominal	Measured		
	Initial mg/l	Final mg/l	Final/Initial %
3.3	3.3	3.6	109.1
4.0	3.8	4.1	107.9
4.8	4.7	5.2	110.6
5.8	5.5	5.3	96.4
6.9	6.3	6.6	104.8
8.3	7.8	8.2	105.1
10	9.5	9.9	104.2
12	10.6	11.8	111.3
14.4	13.4	13.7	102.2

- Analytical monitoring Gas chromatography/FID
- 5 individuals per replicate

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.12.2005 (10)

Type : static
Species : Daphnia pulex (Crustacea)
Exposure period : 4 hour(s)
Unit : mg/l
EC50 : = 21.4
Analytical monitoring : no
Method : other
Year : 1963
GLP : no
Test substance : no data

Method : Groups of 3-5 daphnia were dispensed into glass sample vials, each of which containing 5.0 ml of a biological harmless "culture water" at 21°C.

15.0 ml of toxic solution were added.
The vials were transported in the darkness of a covered , thermostatically controlled water-bath (21+-0.05°C).
The vials were set up in triplicate.
There were 6 concentrations per chemical.
The concentration series was progressively adjusted so as to approach the 50% mortality.
Controls were included in each experiments to give an estimate of control-mortality.

Source : Atochem Paris la Defense
Atofina Paris La Défense Cedex

04.12.2001 (33)

Type : static
Species : Daphnia pulex (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 4
EC50, 24h : = 15
Analytical monitoring : no
Method : other
Year : 1970
GLP : no
Test substance : no data

Remark : Method according to: WERNER, A.E.: Sulphur compounds in kraft pulp mill effluents.Can. Pulp paper Ind., 1963, 16, 3, 35-43.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Atofina Paris La Défense Cedex
Test condition : The test was made in glass cylinder of 110 ml capacity.The volume of the test solution was 100 ml.The temperature was about 20°C.

04.12.2001 (29)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/l
NOEC : = 10.43 measured/nominal
EC10 : = 9.3 measured/nominal
EC50 : = 35 measured/nominal
Limit test :
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2000
GLP : yes
Test substance : other TS: DMDS, Atofina, 99.65% purity

Result : - Values (mg/l)
ErC50, 72h = 35
ErC10, 72h = 9.3
EbC50, 72h = 11
EbC10, 72h = 10.43

NOECb : 10.43
NOECr : 10.43

- control response satisfactory : yes

- BIOLOGICAL OBSERVATIONS

+Cell density at each flask at each measuring point

Sample N°	Replicat	algal conc. (Cell/ml) T0	T24h	T48h	T72h
mg/l nom					
0	mean	1.00E+04	5.00E+04	2.34E+05	3.28E+06
100	mean	1.00E+04	8.33E+03	2.00E+04	4.23E+04
55.56	mean	1,00E+04	9.00E+03	3.57E+04	2.00E+05
30.86	mean	1.00E+04	1.80E+04	1.08E+05	6.97E+05
17.15	mean	1.00E+04	3.30E+04	2.32E+05	1.68E+06
9.53	mean	1.00E+04	1.60E+04	2.63E+05	1.91E+06
5.29	mean	1.00E+04	4.50E+04	2.87E+07	2.35E+06

+Percent biomass/growth rate inhibition per concentration

sample	mean Inhibition % integral blomass	growth rate
nominal (mg/l)	IAI (%)	Iμi (%)
0	0.00	0.00
5.29	22.03	5.78
9.53	35.27	9.36
17.15	40.10	11.55
30.86	76.32	26.74
55.56	93.70	48.29
100	98.71	75.09

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : - Static test
· Test temperature range : 24 ± 1 °C
· Growth/test medium chemistry
Prepared according to § 1.6.1.2 of C.3. method (Annex 5 of 92/69/EEC Directive)
pH 8
· Dilution water source
See above

· Exposure vessel type
120 ml glass bottles completely filled with test solution and stoppered with PTFE bungs and sealed with aluminum caps

· Water chemistry in test (pH and O2 dissolved mg/l))

C% vol	T0	T72h	T0	T72h
0	7.31	7.67	7.7	11.2
5.29	7.03	7.46	7.4	10.0
9.53	7.01	7.46	7.5	11.1
17.15	7.00	7.43	7.8	10.7
30.86	7.00	7.36	7.5	9.6
55.56	7.00	7.27	7.6	9.4
100	7.09	7.18	8.1	8.4

· Stock solutions preparation

Ultrapure water (ultrafiltration, active carbon, ions exchange, 0.22 µm filter)
Stock solution prepared 1 h before the beginning of the test, by adding 94µl of substance in 1 l of dilution water, stirred during 1h.

· Light levels and quality during exposure
Constantly illuminated between 6000 to 10000 lx.

- Test design
3 replicates at each test concentration
7 concentrations (nominal) :
0, 5.29, 9.53, 17.15, 30.86, 55.56,100 mg/l

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
31.12.2005 (9)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	290 - 500 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	60
Vehicle	:	other: polyethylene glycol 300
Doses	:	0, 100, 290, 350, 500 and 5300 mg/kg
Method	:	Directive 84/449/EEC, B.1 "Acute toxicity (oral)"
Year	:	1986
GLP	:	yes
Test substance	:	other TS
Method	:	DIMETHYL DISULFIDE was administered undiluted at a volume of 5 ml/kg bw, or as a suspension (10 ml/kg) in polyethylene glycol 300 at the dose levels of 100, 170, 290, 350 and 500 mg/kg. Clinical signs, mortality and body weight gain were checked for a period of up to 14 days following the single administration of the test item. All animals were subjected to necropsy.
Result	:	Mortality: - 100 and 170 mg/kg : none - 290 mg/kg : 30 % - 350 mg/kg : none - 500 mg/kg : 100 % Clinical signs: Sedation, hypotonia, dyspnea, piloerection and coma, appeared just after the administration and disappeared after 24 hours. Body weight: No effect was noted on the body weight gain of the surviving rats. Macroscopic examination: Haemorragic stomachs was observed at the macroscopic examination of the rats dead on the first day (290 and 500 mg/kg).
Source	:	ARKEMA, Paris-la-Défense, France (JFR). Atofina Paris La Défense Cedex
Test condition	:	TEST ORGANISMS: - Adaptation period: 7 days - Number of animals: 5 males + 5 females / dose - Controls: no HOUSING The animals were housed 5 of the same sex per polycarbonate cages ADMINISTRATION: - Exposure route: gavage - Volume administered: see freetext ME - Post dose observation period: 14 days

EXAMINATIONS: clinical observations, body weight, mortality and necropsy

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Purity: no data

Conclusion : The oral LD50 of DIMETHYL DISULFURE in rats is lower than 500 mg/kg but higher than 290 mg/kg.

Reliability : (1) valid without restriction

Flag : Material Safety Dataset, Directive 67/548/EEC, Critical study for SIDS endpoint

31.12.2005 (30)

Type : LD50
Value : = 190 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 50
Vehicle : CMC
Doses : 125, 188, 250, 375 and 500 mg/kg
Method : other: EPA 40 CFR 163.81-1
Year :
GLP : yes
Test substance : other TS

Method : DIMETHYL DISULFIDE was administered as a suspension in 3% carboxymethyl cellulose at the dose levels of 125, 188, 250, 375 and 500 mg/kg.
Clinical signs, mortality and body weight gain were checked for a period of up to 14 days following the single administration of the test item. All animals were subjected to necropsy.

Result :

Group	Dose g/kg	Mortality Male	Mortality Female	Mortality %
1	0.125	0/5	1/5	10
2	0.188	5/5	1/5	60
3	0.250	3/5	4/5	70
4	0.375	5/5	5/5	100
5	0.50	5/5	5/5	100

LD50 = 0.19 (0.15-0.24) g/kg

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : TEST ORGANISMS:
- Adaptation period: 14 days
- Number of animals: 5 males + 5 females / dose
- Controls: no

ADMINISTRATION:
- Exposure route: gavage
- Volume administered: no data
- Post dose observation period: 14 days

EXAMINATIONS: clinical observations, body weight, mortality and necropsy

STATISTICAL DETERMINATION OF THE LD50:
- Litchfield-Wilcoxon method of probit analysis.

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0

Purity: no data

Conclusion : Acute Oral Defined LD50: 0.19 g/kg
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
31.12.2005 (26)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : = 805 ppm
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 100
Vehicle :
Doses : 0, 500, 700, 775, 800, 840, 875, 950, 1100 and 1581 ppm
Exposure time : 4 hour(s)
Method : other: comparable to OECD Guide-line 403
Year :
GLP : no
Test substance : other TS

Result : MORTALITY:
See the attached table

CLINICAL SIGNS:
No data

MACROSCOPIC OBSERVATION:

No data

LC50 = 805 (776-835) ppm

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Aldrich
Batch: no data
Purity: no data

Test substance : TEST ORGANISMS:
- Adaptation period: >= 7 days
- Number of animals: 5 males + 5 females
- Controls: no

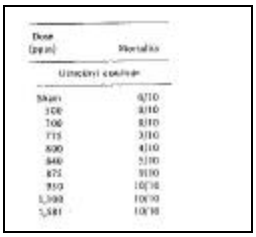
HOUSING
The animals of the same sex were housed 5 per cage

ADMINISTRATION:
- Exposure : whole-boby inhalation
- Analytical control of the concentration: no data

EXAMINATIONS:
- Clinical observations, mortality and necropsy
- Post dose observation period: 14 days

STATISTICAL DETERMINATION OF THE LC50:
- Litchfield-Wilcoxon method of probit analysis.

Attached document : Tansy table.bmp



Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.12.2005 (21)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD0
Value : >= 2000 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 10
Vehicle : other: none
Doses : 2000 mg/kg
Method : other: EPA 40 CFR 163.81-2
Year :
GLP : yes
Test substance : other TS

Method : Adaptation period of at least 7 days,
five male and five female rabbits.
A non-permeable patch containing 2 g/kg body weight of the test material (applied neat) was placed over a 4 -5 cm2 area on each rabbit.
After 24 hours exposure to the test material, the patches were removed and the exposed surface was wiped clean of any residual test material using a damp cloth. The rabbits were observed for gross toxicity and mortality at least twice daily for a period of 14 days. Since there were no mortalities, gross necropsies were performed on all survivors at terminal sacrifice. The body weights were recorded on the day of dosing and at 7 and 14 days.

Result : All rabbits appeared active and healthy throughout the test period. There were no overt signs of gross toxicity nor was there any evidence of severe skin lesions. Eight rabbits gained weight over the 14 day observation period and two remained the same.

Gross necropsies were unrevealing. All organs and tissues appeared normal.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : TEST ORGANISMS:
- Adaptation period: at least 7 days
- Number of animals: 5 males + 5 females
- Controls: no

ADMINISTRATION:
- Exposure route: dermal, under a non-permeable patch, over 10% of the body surface
- Volume administered: no data

		EXAMINATIONS: - Clinical observations, body weight, mortality and necropsy - Post dose observati on period: 14 days
Test substance	:	Test substance: Dimethyl disulfide C AS no.: 624-92-0 Source: Pennwalt Corp. Batch: no data Purity: no data
Conclusion	:	The acute dermal toxicity of Dimethyl Disulfide is > 2.0 g/kg body weight.
Reliability	:	(1) valid without restriction
Flag	:	Material Safety Dataset, Directive 67/548/EEC, Critical study for SIDS endpoint

31.12.2005 (25)

Type	:	LD0
Value	:	>= 2000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	2000 mg/kg
Method	:	other: Directive 79/831/EEC Annexe V
Year	:	
GLP	:	no
Test substance	:	
Result	:	No mortality was observed. Apathy and prostration were noted in most of the animals between 15 minutes and 3 hours after the application of the product. An increase in the spontaneous activity was noted for some animals the first day of treatment. The behavior of the animals during the remainder of the period of observation was considered normal. No macroscopic lesion was observed.
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test condition	:	TEST ORGANISMS: - Acclimatation period: no data - Number of animals: 5 males + 5 females - Controls: no ADMINISTRATION: - Exposure route: dermal, under a non-permeable patch, over 10% of the body surface - Volume administered: no data
		EXAMINATIONS: - Clinical observations, body weight, mortality and necropsy - Post dose observation period: 15 days
Test substance	:	Test substance: Dimethyl disulfide C AS no.: 624-92-0 Source: SNEA(P) Batch: A1 Purity: no data
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

31.12.2005 (12)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1982
GLP	:	no
Test substance	:	other TS
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test substance	:	DMDS, purity 98.98%.
Reliability	:	(2) valid with restrictions
Flag	:	Material Safety Dataset, Directive 67/548/EEC

31.12.2005 (15)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	1.1
Result	:	slightly irritating
Classification	:	not irritating
Method	:	other: EPA 40 CFR 163.81-5
Year	:	
GLP	:	yes
Test substance	:	
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test condition	:	TEST ORGANISMS: - Adaptation period: 8 weeks - Number of animals: 4 males + 2 females - Controls: no
Test substance	:	Test substance: Dimethyl disulfide CAS no.: 624-92-0 Source: Pennwalt Corp. Batch: no data Purity: no data
Conclusion	:	Based on the average Primary Skin Irritation Score at 48 hours (2.02) and the average score over 14 days (1.10), Dimethyl Disulfide is considered to be a mild primary skin irritant.
Reliability	:	(1) valid without restriction

31.12.2005 (23)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	
Result	:	irritating
Classification	:	irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1982
GLP	:	no
Test substance	:	other TS
Result	:	Mean scores (24+48+72 hours) for the 6 rabbits: - Chemosis: 1.89 - Enanthema: 1.33 - Iris: 1.0. - Cornea: 0.83
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test substance	:	DMDS, purity 98.98%.
Reliability	:	(2) valid with restrictions
Flag	:	Material Safety Dataset, Directive 67/548/EEC

31.12.2005 (15)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	other: not rinsed for 6 rabbits, rinsed after 20-30 sec. for 3 rabbits
Number of animals	:	9
Vehicle	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	other: EPA-40 CFR 163-81-4
Year	:	
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The average 24 hour maximum mean total score (MMTS) for the unwashed eyes was 14.8 (minimally irritating.). For the washed eyes the 24 hour MMTS was 6 (minimally irritating).
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test condition	:	TEST ORGANISMS: - Adaptation period: 7 days - Number of animals: 4 males + 5 females - Controls: no
Conclusion	:	Dimethyl Disulfide is considered to be minimally irritating to both the unwashed and the washed eye.
Reliability	:	(1) valid without restriction

31.12.2005 (22)

5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Concentration	:	1st: Induction undiluted occlusive epicutaneous 2nd: Challenge undiluted occlusive epicutaneous 3rd:
Number of animals	:	20
Vehicle	:	
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: EPA-40 CFR 163-81-6
Year	:	1985
GLP	:	yes
Test substance	:	
Result	:	In the preliminary screen, no erythema was observed at any of the concentrations of test material applied to the skin over a 48 hour period. The test material was therefore tested neat in the full scale sensitization study. After the initial and second challenge applications, the guinea pigs did not exhibit any erythema and were considered non-sensitized. Expected responsed were noted in the positive control animals. The data validates the responsiveness of the guinea pigs to DNCB.
Source	:	Atofina, Paris-la-Défense, France. Atofina Paris La Défense Cedex
Test condition	:	TEST ORGANISMS: - guinea pigs - Weight at study initiation: 256-424 g - Adaptation period: 10 days - Number of animals: 10 males for the test substance 10 males for the positive control (DNCB 0.3%) METHOD - Induction: 10 applications every 2 days (excluding week-end) - duration of the application: 6 hours/day - Challenge test: 10 days after the last induction application - Scoring local reaction: 24 and 48 hours after each induction application and after the challege application
Test substance	:	Test substance: Dimethyl disulfide CAS no.: 624-92-0 Source: Pennwalt Corp. Batch: no data Purity: no data
Conclusion	:	Dimethyl Disulfide is a non (contact) sensitizer.
Reliability	:	(1) valid without restriction
Flag	:	Material Safety Dataset, Directive 67/548/EEC

30.12.2005 (24)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation

Exposure period	:	90 days
Frequency of treatm.	:	6 h/day; 5 d/week
Post exposure period	:	4 weeks
Doses	:	10, 50, 150, 250 ppm
Control group	:	yes, concurrent vehicle
NOAEL	:	ca. 10 ppm
LOAEL	:	= 50 ppm
Method	:	OECD Guide-line 413 "Subchronic Inhalation Toxicity: 90-day Study"
Year	:	1981
GLP	:	yes
Test substance	:	

Method : Four groups of 20 male and 20 female Sprague-Dawley were exposed 6 hours/day, 5 days/week to 0, 10, 50, 150, or 250 ppm DMDS. The exposure of the 150 ppm group was terminated after 6 weeks and its treatment-free subgroup necropsied 2 weeks later. The remaining groups received a 13 week exposure period followed by four weeks for the treatment-free subgroups.

Result : MORTALITY
There was no treatment-related mortality.

CLINICAL SIGNS
The only clinical signs attributable to treatment were salivation, lacrimation or reduced activity during exposure 1 and 2 of the 150 and 250 ppm groups and a low incidence of dyspnoea or wheezing in the early part of the study, particularly in the 250 ppm animals at week 1.

FOB
Functional observation tests indicated no evidence of neurotoxicity.

BOBY WEIGHT
There was a dosage-related decrease in body weight gain over the treatment period in treated groups compared with controls.

FOOD CONSUMPTION
Differences in food consumption paralleled those of body weight gain and werenot statistically significant in the 50 ppm males or the 10 ppm groups.

OPHTHALMOSCOPY
The eyes of the animals were unremarkable.

H AEMATOLOGY
Haematological profiles suggested a possible small reduction in Hb, RBC and PCV in the 250 ppm female group only.

BOOLD CHEMISTRY
Blood chemistry examinations showed treatment-related changes in ALT, alkaline phosphatase and bilirubin.

ORGAN WEIGHTS
There were no changes in organ weights that were considered to be treatment-related.

MACROSCOPIC OBSERVATIONS
There were no treatment-related macroscopic abnormalities at necropsy.

MICROSCOPIC OBSERVATIONS

In the 10, 50 and 250 ppm animals examined microscopically there was a dose-related effect on nasal mucosa.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : TEST ORGANISMS:

- Number of animals: 100 rats : 20 males + 20 females / dose group (4 dose groups + 1 control group)
- Aclimatation period: 14 days

ADMINISTRATION:
- Type of inhalation study: whole body
- Production of test atmospheres:
Five horizontal flow, recirculating exposure chambers were used.
- Vehicle: filtered air
- Exposure chamber test article concentration
* Measured concentration
Samples for analysis were withdrawn from the exposure chambers twice hourly.

SATELLITE GROUPS: none

RECOVERY GROUPS
10 rats/sex/group were allowed to recover for 4 weeks after termination of the main study animals in groups 1, 2, 3 and 5 and for 2 weeks for group 4 animals.

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical observations
* Morbidity and mortality
* Clinical signs
* Functional observation tests
* Body weight
* Food consumption
* Ophthalmoscopy

- Laboratory investigations

* Haematology:
Haemoglobin, mean cell volume, red blood cell count and indices: mean cell haemoglobin, mean cell haemoglobin concentration packed cell volume, total and differential white blood cell count platelet count.
* Clinical chemistry:
aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, potassium, chloride, calcium inorganic phosphorus, glucose, urea, total bilirubin, creatinine, total protein, albumin, albumin/globulin ratio total cholesterol.

- Pathology
* Necropsy
Full internal and external examination at sacrifice
* Organ weights
* Histology

- Statistical evaluation
* ANOVA, T-test
Body weight: week 0
* ANOVA, Regression and Dunnett's

* ANCOVA, Dunnett's
* Kruskal-Wallis, Terpstra-Jonckheere, Wilcoxon

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : Clear treatment-related effects were seen at 50 and 250 ppm and were present to a marginal degree at 10 ppm. It was concluded that the effect level was 50 ppm. The no-effect level was in the region of, but less than, 10 ppm due to the reversible changes in the nasal mucosa

Reliability : (1) valid without restriction

Flag : Material Safety Dataset, Critical study for SIDS endpoint

31.12.2005 (11)

Type :
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 28 days
Frequency of treatm. : 6 h/day
Post exposure period : no
Doses : 0.01, 0.1, 1 ml/kg/day (10.63, 106.3 and 1063 mg/kg bw/d)
Control group : other: sham treated with the occlusive dressing
NOAEL : = 10.63 mg/kg bw
LOAEL : = 106.3 mg/kg bw
Method : OECD Guide-line 410 "Repeated Dose Dermal Toxicity: 21/28-day Study"
Year : 1981
GLP : yes
Test substance :

Method : DMDS was administered daily, by dermal occlusive application (6 hours daily) to four groups of albino rabbits. The dose levels equivalent to 0, 10.63, 106.3, and 1063 mg/kg body weight/day, respectively. The control and 1.0 ml/kg/d group consisting of 10 males and 10 females, and the 0.01 and 0.1 ml/kg/d group consisting of 5 males and 5 females. The animals of the 0.01 and 0.1 ml/kg/d group were treated five days a week during a four-week period, whereas animals of the 1 ml/kg/d group were treated with DMDS for 2 1/2 weeks (i.e. 13 days of treatment).

Result : CLINICAL SIGNS:
During daily treatment with DMDS, lethargy was observed in a dose related manner in the mid and high dose group. No treatment-related clinical signs were observed in the animals of the low dose group or in the controls.

MORTALITY:
During the second and third week of the study treatment-related mortality occurred in males and females of high dose group and treatment was suspended after 13 days of treatment.

SKIN REACTIONS:
Repeated dermal administration of DMDS caused severe, dose-dependent skin irritation in all dose groups.

BLOOD EXAMINATIONS:
Haematology and clinical chemistry examinations revealed differences in some blood paremeters and clinical chemistry in the high dose group males. No treatment related changes were observed in females.

PATHOLOGY:
The absolute and relative organ weights measured at autopsy did not show statistically significant differences. Macroscopic examination

at autopsy did not reveal any treatment-related changes other than the dermal lesions induced during the treatment with DMDS.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : TEST ORGANISMS:
- Number of animals: The control and top-dose group comprised 10 males and 10 females, whereas the low - and mid-dose group comprised 5 males and 5 females.
- Aclimatation period: 13 days

ADMINISTRATION:
- Route: dermal
Doses were applied by volume. The respective amounts of the test substance were applied topically to the intact, shaven skin. The test site was covered with porous gauze
dressing fixed onto a non-irritating tape. The entire trunk
was wrapped to maintain the gauze dressing in position and to retard evaporation of volatile substances.
The animals of the control group were sham-treated with the patches only.

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: twice a day on exposure days and once a day on non-exposure days.
- Mortality: twice a day.
- Dermal reactions:
At the start of the study and prior to each daily administration.
- Body weight:
- Food consumption:
- Blood examinations:
haematology and clinical chemistry determinations were conducted in blood or plasma of the animals
* Haematology:
Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential leukocyte count, platelet count, mean cell volume, mean cell haemoglobin concentration, mean cell haemoglobin
* Biochemistry:
. Electrolytes: calcium, chloride, phosphorous, potassium, sodium,
. Enzymes: alkaline phosphatase, alanine-aminotransferase, aspartate-aminotransferase, gamma-glutamyl-transferase
. Other: albumin, blood creatinine, blood urea nitrogen, albumin/globulin, glucose, total bilirubin, total cholesterol, total serum protein, bile acids

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Weighed organs: adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thyroid and thymus.
- Microscopic examinations:

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : The NOAEL of DMDS for systemic toxicity is 10.63 mg/kg bw/d. For local skin effects, the NOAEL is lower than 10.63 mg/kg bw/d.

Reliability : (1) valid without restriction

Flag : Material Safety Dataset, Critical study for SIDS endpoint

31.12.2005 (6)

Type	:	
Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	14 days
Frequency of treatm.	:	6 h/day
Post exposure period	:	no
Doses	:	0.1, 0.5 and 1 ml/kg/day (106, 503 and 1063 mg/kg/day)
Control group	:	other: sham treated with the occlusive dressing
NOAEL	:	< .1 mg/kg
LOAEL	:	= .1 mg/kg
Method	:	other: range finding study
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : In this range-finding study, DMDS was administered to a restricted number of albino rabbits by dermal occlusive application, daily, during a two-week period. The dose levels applied were 106.3, 531.5, and 1063 mg DMDS/kg body weight/day, repectively, and the daily exposure period was 6 hours. The control group was sham treated with the occlusive dressing only.

Result : During exposure temporary signs slight lethargy in the low-dose group, distinct lethargy in the mid-dose group, and unconscinousness in the high-dose group. At the end of each daily exposure, these effects were no longer observed.
During the entire test period of the study, the controls did not show any signs of abnormal behaviour after treatment with the patches only. Repeated dermal administration of DMDS caused severe skin lesions in all three dose groups.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Reliability : (1) valid without restriction
31.12.2005 (17)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	Strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100
Test concentration	:	0, 5, 50, 150, 500, 1500, and 5000 µg/plate
Cycotoxic concentr.	:	>= 5000 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1983
GLP	:	yes
Test substance	:	

Method : PRELIMINARY TOXICITY ASSAY
The preliminary toxicity assay was used to establish the dose range over which the test article would be assayed.

MUTAGENICITY ASSAY

- Five dose levels of test article along with appropriate vehicle control and positive controls were plated with overnight cultures of TA98, TA100, TA1535, TA1537 and TA1538 on selective agar in the presence and absence of Aroclor induced rat liver S9. All dose levels of test article, vehicle control and positive controls were plated in triplicate.
- Second mutation test
The procedure was repeated at a later date.

EVALUATION OF RESULTS
The mean number of revertant colonies for all treatment groups is compared with those obtained for negative and positive control groups. The effect of metabolic activation is assessed by comparing the results obtained both in the presence and absence of the liver microsomal fraction for each treatment group.
A compound is deemed to provide evidence of mutagenic potential if (1) a statistically significant dose-related increase in the number of revertant colonies is obtained in two separate experiments, and (2) the increase in the number of revertant colonies is at least twice the concurrent solvent control value.

Remark : The positive controls responded as expected.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : CONTROL MATERIALS
- Negative: culture medium
- Solvent: Dimethylsulphoxide
- Positive:
* With S-9 mix
2-Aminoanthracene at 2 µg/plate for strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.
* Without S-9 mix
2-Nitrofluorene at 10 µg/plate for strains TA 1538 and TA 98.
9-Aminoacridine at 20 µg/plate for strain TA 1537. Sodium azide at 5 µg/plate for strains TA 1535 and TA 100.

ACTIVATION
- S9 derived from Sprague-Dawley rats induced with a single intraperitoneal injection of Aroclor 1254, 500 mg/kg, five days prior to sacrifice.

- S9 mix composition:

Component	Concentration
S9	10% (v/v)
Sodium phosphate buffer (pH 7.4)	100 mM
glucose 6 -phosphate	5 mM
NADP	4 mM
KCl	33 mM
MgCl2	8 mM

TEST ORGANISMS
- Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537 and a 1538
- test organisms were properly maintained and were checked for appropriate genetic markers (rfa mutation, R factor)

TEST CONCENTRATIONS
(a) Preliminary cytotoxicity assay:
Plate incorporation assay: 0, 5, 50, 500 and 5000 µg per

plate were evaluated with and without S9 activation in all strains. A single plate was used, per dose, per condition.

(b)Mutation assays:
Plate incorporation assay: 50, 150, 500, 1500 and 5000 µg per plate were evaluated in triplicate in the presence and absence of S9 activation; all test strains were used.

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Purity 98.98%

Reliability : (1) valid without restriction
Flag : Material Safety Dataset, Critical study for SIDS endpoint
30.12.2005 (1)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100
Test concentration : 50, 166, 500, 1666, 5000 µg/plate
Cycotoxic concentr. : 5000 µg/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year : 1983
GLP : yes
Test substance :

Method : PRELIMINARY TOXICITY ASSAY
The preliminary toxicity assay was used to establish the dose range over which the test article would be assayed.

MUTAGENICITY ASSAY
- Five dose levels of test article along with appropriate vehicle control and positive controls were plated with overnight cultures of TA98, TA100, TA1535, TA1537 and TA1538 on selective agar in the presence and absence of Aroclor induced rat liver S9. All dose levels of test article, vehicle control and positive controls were plated in triplicate.
- Second mutation test
The procedure was repeated at a later date.

TEST PROCEDURE
- Without metabolic activation
0.1 ml aliquots of bacterial suspension is added to each of one set of sterile tubes.
0.1 ml of the test compound is added to cultures at five concentrations. The negative control is the chosen solvent. The appropriate positive control is also included.
- With metabolic activation
Methodology is as described above except that 0.5 ml of liver homogenate S-9 mix is added to the tubes in place of sterile buffer.

EVALUATION OF RESULTS
The mean number of revertant colonies for all treatment groups is compared with those obtained for negative and positive control groups. The effect of metabolic activation is assessed by comparing the results obtained both in the presence and absence of the liver microsomal fraction for each treatment group.
A compound is deemed to provide evidence of mutagenic potential if (1) a statistically significant dose-related increase in the number of revertant colonies is obtained in

two separate experiments, and (2) the increase in the number of revertant colonies is at least twice the concurrent solvent control value.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : CONTROL MATERIALS
- Negative: culture medium
- Solvent: Dimethylsulphoxide
- Positive:
* With S-9 mix
2-Aminoanthracene at 5 µg/plate for strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.
* Without S-9 mix
2-Nitrofluorene at 5 µg/plate for strains TA 1538 and Ta98
9-Aminoacridine at 150 µg/plate for strain TA 1537.
Sodium azide at 10 µg/plate for strains TA 1535 and TA 100.

ACTIVATION
- S9 derived from Sprague-Dawley rats induced with a single intraperitoneal injection of Aroclor 1254, 500 mg/kg, five days prior to sacrifice.
- S9 mix composition:

Component	volume
S9	100 µl
Sodium phosphate buffer 0.2M (pH 7.4)	500 µl
glucose 6 -phosphate	5 µl
NADP 0.1 M	40 µl
KCl 1.65 M	20 µl
MgCl2 0.4	20 µl

TEST ORGANISMS
- Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537 and a 1538
- test organisms were properly maintained and were checked for appropriate genetic markers (rfa mutation, R factor)

TEST CONCENTRATIONS
(a) Preliminary cytotoxicity assay:
Plate incorporation assay: 0, 50, 144, 500, 1444 and 5000 µg per plate were evaluated without S9 activation with strains TA100 and TA 1538. Two plate was used, per dose, per condition.

(b)Mutation assays:
Plate incorporation assay: 0, 50, 166, 500, 1666 and 5000 µg per plate were evaluated in triplicate in the presence and absence of S9 activation; all test strains were used.

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Purity: no data

Conclusion : Dimethyldisulfide was negative in the Ames/Salmonella tester strains TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation preparation over the dose range 50-5000 µg/plate.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
31.12.2005 (27)

Type : Chromosomal aberration test
System of testing : Human Lymphocytes
Test concentration : 3.7; 11.1; 33.3; 100; 300 µg/ml
Cycotoxic concentr. : >= 300 µg/ml

Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	OECD Guide-line 473
Year	:	1983
GLP	:	yes
Test substance	:	

Method :

- Preliminary Cytotoxicity Assay:
The dose levels used in the chromosome aberration assay were established on the basis of the results of a preliminary toxicity test carried out with 6 concentrations of the test substance (ranging from 0.5 to 1000.0 µg/ml), both in the absence and in the presence of the metabolic activation system (S-9 mix). The highest concentration for the toxicity test was determined by the limit of the solubility of the test substance in the tissue culture medium.

- Cytogenetic Assay:
* Cell Treatment
After 48 h of incubation, the cultures were centrifuged. The cell pellets were resuspended in tissue culture medium supplemented with 20 mM HEPES (and 10% S-9 mix, for the test with metabolic activation) and appropriate test solutions. An untreated culture and a culture receiving DMSO served as negative controls. For each concentration of the test substance and for the controls one culture was used. Without S9, the cultures were incubated in closed tubes for another 24 hours including a 2 hour colcemid treatment.
With S-9 mix, the exposure of the cells to the test substance was reduced to only 2 hours, because of the toxicity of the S-9 mix for the cells. After the 2 hour incubation period, the cells washed and supplied with freshly prepared culture medium. The cells were incubated for a further 22 hours (including a 2 hour colcimid treatment.
* Cell harvesting:
Two hours before the end of the total incubation period the cells were arrested in the metaphase stage of the mitosis by the addition of colcemid. The cells were harvested, treated with a hypotonic solution, fixed three hours, and transferred to clean microscope slides. Two slides were prepared from each culture. The slides were stained 1000 stimulated lymphocytes were examined (500 from each slide) to determine the mitotic index (percentage of cells in mitosis).
* Metaphase analysis:
From each culture, 100 well-spread metaphases (each containing 46 chromosomes) were analysed by microscopic examination for a wide range of structural chromosome aberrations (gaps, breaks, fragments, dicentrics, exchanges etc.) and other anomalies (endoreduplication, polyploidy), according to the criteria recommended by Savage (1975).

- Evaluation criteria:
The major crite rion to designate the results of a chromosome aberration test as positive is a dose-related, statistically significant increase in the number of cells with structural chromosome aberrations. However, a clear dose-response relationship can be absent because the yield of chromosome aberrations can vary markedly with post-treatment sampling time of an asynchronous population and because increasing doses of clastogens can induce increasing degrees of mitotic delay. A test substance producing neither a dose-related,

statistically significant increase in the number of cells with structural chromosome aberrations, nor a statistically significant and reproducible positive response at any of the doses is considered non-clastogenic in this system.

Result : The test substance did not induce a statistically significant increase in the number of cells with structural chromosome aberrations at non toxic concentrations, both in the absence and in the presence of the S-9 mix. At the very toxic concentration of 300.0 µg/ml, both in the absence and in the presence of the S-9 mix, the test substance induced a statistically significant increase in the number of cells with structural chromosome aberrations.

The positive control substances, mitomycin C and cyclophosphamide, induced the expected increase in the incidence of structural chromosome aberrations.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : Control Materials:
Negative: DMSO
Solvent: The test article (dissolved in DMSO) was soluble in culture medium at a maximum concentration of 1 mg/mL
Positive: -S9: mitomycin C (MMC) 0.05 µg/mL
+S9: cyclophosphamide (CP) 25 µg/mL

Activation:
S9 derived from adult male Wistar rats (Aroclor 1254 induced rat liver). The composition of the rat liver S9 reaction mix was: 8 mM magnesium chloride, 33 mM potassium chloride, 5 mM glucose-6-phosphate, 4 mM nicotinamide adenine dinucleotide phosphate (NADP), 100 mM sodium phospahte and 40% S9.

Culture Medium:
RPMI 1640 medium supplemented with heat-inactivated foetal calf serum, 100 units penicillin/mL, 100 µg streptomycin/mL, 2 mM L-glutamine and 25 µl phytohaemagglutinin/ml

Test compound concentrations used:

Treatment condition	Treatment time	Recovery time	Dose levels (µg/mL)
-S9	24hr	24 hr	3.7, 11.1, 33.3 100, 300
+S9	2 hr	24 hr	3.7, 11.1, 33.3 100, 300

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.98%

Reliability : (1) valid without restriction
Flag : Material Safety Dataset, Critical study for SIDS endpoint
31.12.2005 (14)

Type : Mammalian cell gene mutation assay
System of testing : HGPRT assay on CHO cells
Test concentration : 0.46; 1.37; 4.12; 12.3; 37.0; 74.0; 111; 333; 667 and 1000 µg/ml
Cycotoxic concentr. : 74.0-1000 µg/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476
Year : 1984
GLP : yes
Test substance :

Method : The dose levels used in the HGPRT assay were established on the basis of the results of a preliminary solubility test. A final concentration of 1,000 µg/ml was chosen as highest concentration for the HGPRT assays.

The two independent HGPRT-assays were carried out with single cultures for each concentration of the test substance and for the negative and positive controls.

Result : In the absence of the S -9 mix, the test substance induced neither a concentration-related increase in the mutant frequency nor a reproducible positive response at one of the test concentrations. In the presence of a metabolic activation system, DMDS induced a slight increase in mutant frequency at several concentrations, in both HGPRT assays. These increases were neither concentration-related nor clearly reproducible. In both HGPRT assays, the test substance appeared to be highly toxic to CHO cells at a concentration range from 74.0-1,000 µg/ml.

The positive control substances, ethylmethanesulfonate and dimethylnitrosamine, induced the expected increase in the mutant frequency.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : - Control Materials:
* Negative: DMSO
* Solvent: The test article (dissolved in DMSO) was soluble in culture medium at a maximum concentration of 1 mg/mL
* Positive: -S9: Ethylmethanesulfonate 0.2 ml/L
+S9: Dimethylnitrosamine 2 or 4 ml/L

- Activation:
S9 derived from adult male Wistar rats
- Culture Medium:
Ham's F-12 medium supplemented with 10% heat-inactivated foetal calf serum, 50 µg gentamicin/mL and 2 mM L-glutamine.

- Evaluation of the results:
The following criteria were used to evaluate the data obtained in the HGPRT assay (Li et al. 1987)
a) the survival (absolute cloning efficiency) of the negative controls should not be less than 50%,
b) the mean mutant frequency of the negative controls should fall within the range of 0-20 6 -TG resistant mutants per 10e6 clonable cells,
c) the positive controls must induce a response of a magnitude appropriate for the mutagen under the experimental conditions applied,
d) the highest test substance concentration should, if possible, result in a clear cytotoxic response (e.g. 10-30% of the relative initial survival).
Any apparent increase in mutant frequency at concentrations of the test substance causing more than 90% toxicity is considered to be an artifact and not indicative of genotoxicity.

Genotoxicity of the test substance was evaluated using the following criteria (Li et al. 1987):
a) a concentration-related increase in mutant frequency,
b) a reproducible positive response for at least one of the test substance concentrations (e.g. the mean mutant

frequency should be more than 20 mutants per 10e6 clonable cells).

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : No evidence for a genotoxic effect of DMDS was found in cultured CHO cells, under the conditions used in the HGPRT assay.

Reliability : (1) valid without restriction

Flag : Material Safety Dataset, Critical study for SIDS endpoint

31.12.2005 (13)

Type : DNA damage and repair assay
System of testing : Rat hepatocytes in primary culture
Test concentration : 1; 5; 10; 50; 100; 200 and 300 µg/ml
Cycotoxic concentr. : >= 100 µg/ml
Metabolic activation : without
Result : negative
Method : OECD Guide-line 482
Year : 1986
GLP : yes
Test substance : other TS

Method : - Cytotoxicity evaluation:
The test compound cytotoxicity was assessed for both DNA repair studies at the end of the treatment:

Each concentration of Dimethyldisulfide was tested in triplicate.

- Autoradiography:
Autoradiographs were prepared by dipping slides in a photographic emulsion then developed. Slides were stained in hematoxylin-phloxin.

- Slide assessment:
For each cell, following
nuclear grain court, cytoplasmic count was performed on 3 areas of the same size as the nucleus and adjacent to it.

- Data interpretation
The test compound is considered positive when the mean nuclear grain court is statisticaly greater than that of the control, the mean net nuclear grain court is above 3 grains per nucleus, and the percentage of treated cells in repair is significantly different from that of the controls. In addition, the effect must be shown to be reproducible between experiments.

Result : Results
- Cytotoxic at 100, 200 and 300 µg/ml
IC50 evaluated by LDH release: 98 µg/ml (2nd study)
- not genotoxic at concentrations of 10, 50, 100 and 200 µg/ml

The positive controls responded as expected.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : - Control Materials:
* Negative: pyrene 1 µM
* Solvent: DMSO
The test article was soluble in culture medium at a maximum

concentration of 100 µg/mL
* Positive:
. 7,12-DMBA (10 µM)
. 2-aminofluorene (0.1 and 0.5 µM)

- Number of cultures/concentration/study: 3

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : Not genotoxic in vitro in the DNA repair test.
Reliability : (1) valid without restriction
Flag : Material Safety Dataset, Critical study for SIDS endpoint
31.12.2005 (16)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : Swiss
Route of admin. : inhalation
Exposure period : 6 h/day for 4 days
Doses : 0 , 250 and 500 ppm
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1983
GLP : yes
Test substance : other TS

Method : Three groups of mice were exposed during 6 hours a day for 4 consecutive days (days 0 through 3) to atmospheres containing 0 ppn (5/sex), 250 ppm (5/sex) and 500 ppm DMDS (10/sex).
The positive control group (5/sex) was treated once intraperitoneally, 24 hours before sacrifice, with 1.5 mg Mitomycin C per kg body weight.

Bone marrow cells were collected from the femur and processed into smears for microscopic examination. One smear from each animal was examined for the presence of micronucleated poly- and normochromatic erythrocytes, (abbreviated MPE and MNE, respectively), and the total numbers of poly- and normochromatic erythrocytes (PE and NE) in a total of at least 2000 erythrocytes (E) in such a way that a minimum of 1000 PE was observed.

Result : Exposure to DMDS resulted in clear signs of intoxication both at the 250 ppm and the 500 ppm level. Mortality was observed in some animals at 500 pmm group.
Exposure to 250 ppm and 500 ppm DMDS resulted in body weight loss both in males and females.

There were no indications for increases in the incidences of MPE, MNE or ME attributable to treatment with the test material.

Mean numbers of PE per 1000 E were slightly lower in mice exposed to 500 ppm DMDS, both in males and females ($0.001<P<0.01$) pointing to slight cytotoxic effects on bone marrow cells.

Animals treated with the mutagen Mitomycin C showed an increased incidence of MPE.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : * CONTROL MATERIALS
- Positive :
Mitomycin C, single ip administration, 1.5 mg/kg

Test substance : Test substance: D imethyl disulfide
C AS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : It was concluded that the results of the micronucleus test did not provide any indication of chromosomal damage and/or damage to the mitotic apparatus in bone marrow cells of mice exposed to DMDS.

Reliability : (1) valid without restriction

Flag : Material Safety Dataset, Critical study for SIDS endpoint

31.12.2005 (5)

Type : Unscheduled DNA synthesis
Species : rat
Sex : male
Strain : Wistar
Route of admin. : inhalation
Exposure period : 4 hours
Doses : 0 and 500 ppm
Result : negative
Method : other: OECD Guide-line 482
Year : 1986
GLP : yes
Test substance : other TS

Method : Dimethyldisulfide (DMDS) was examined for its potential to induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes after short-term exposure of male wistar rats to the test substance by inhalation.

For the genotoxicity assay male rats were exposed by inhalation for a period of 4 h to one high concentration of 500 ppm DMDS (maximally tolerated concentration). Immediately after exposure and after subsequent non-exposure periods of 16 and 24 h, animals were sacrificed for isolation of hepatocytes. The DNA-repair activities were examined by autoradiography in monolayer cultures of hepatocytes, incubated in the presence of [methyl-3H]thymidine.

The hepatocarcinogen 2-acetylaminofluorene (2 AAF), was used as a positive control in the in vivo/in vitro DNA-repair assay and in the in vitro DNA-repair assay (2 AAF). Hepatocytes isolated from animals exposed to air only served as negative controls.

Result : DMDS did not induce DNA-repair activities in hepatocytes, either during the 4 h exposure period or during the subsequent 16 h or 24 h after the exposure period.

The positive control substance, 2-AAF, induced the expected increase in DNA-repair activities.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : * CONTROL MATERIALS
- Positive :
. in vivo: 2-AAF, 50 mg/kg single oral administration
. in vitro: 2-AAF, 10e-4M

Test substance	:	Test substance: Dimethyl disulfide CAS no.: 624-92-0 Source: Atochem Purity: 99.88%
Conclusion	:	It was concluded that DMDS did not induce DNA-repair in rat hepatocytes.
Reliability	:	(1) valid without restriction
Flag	:	Material Safety Dataset, Critical study for SIDS endpoint

31.12.2005 (2)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	other: Crl: CD(SD)BR
Route of admin.	:	inhalation
Exposure period	:	day 6 to day 15 of gestation
Frequency of treatm.	:	6 h/day
Duration of test	:	up to gestation day 20
Doses	:	5; 15; 50 ppm
Control group	:	yes, concurrent no treatment
NOAEL maternal tox.	:	= 5 ppm
NOAEL teratogen.	:	= 50 ppm
NOAEL Fetotoxicity	:	= 15 ppm
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1981
GLP	:	yes
Test substance	:	

Method : Three groups of 30 mated female rats were exposed to DMDS by whole body exposure at 5, 15 or 50 ppm for 6 hours daily from day 6 to day 15 of gestation. A similar group of 30 rats, exposed to filtered air only over the same period, served as controls. All animals were maintained until day 20 of gestation, killed and their uterine content assessed.

Result :

The chamber concentrations of the test article were close to target values throughout the exposure period. There were no deaths. A higher incidence of rough haircoat was observed at 50 ppm. Clinical condition at 5 and 15 ppm did not differ from controls. Dosage-related reductions in weight gain were observed at 15 and 50 ppm. Food intake was lower than controls at 50 ppm but comparable at 5 or 15 ppm.

No unusual lesions were observed at necropsy. There was no effect of treatment on pre or post-implantation loss, litter size or sex ratio. Litter and foetal weights were reduced at 50 ppm. At 5 and 15 ppm these parameters were comparable to controls. No malformations were observed in foetuses from the treated groups. A slightly higher incidence of retarded ossification was observed at 50 ppm but was considered to indicate delayed maturation, as a result of the lower foetal weight, rather than a teratogenic

effect.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test condition : TEST ORGANISMS:
- Number of animals: 100 rats : 25 females / dose group (3 dose groups + 1 control group)
- Aclimatation period: no data

ADMINISTRATION:
- Type of inhalation study: whole body
- Vehicle: filtered air
- Exposure chamber test article concentration
* Measured concentration
Samples for analysis were withdrawn from the exposure chambers twice hourly.

EXPERIMENTAL OBSERVATION
- Morbidity and mortality
All females were examined twice daily to detect any which were dead or moribund.
- Clinical observations
All females were examined daily from day 3 to day 20 of gestation. Any abnormalities of appearance or behaviour or other signs of reaction to treatment or ill health were recorded.
- Body weight
The body weight of each female was recorded
- Food intake
The amount of food consumed by each cage of females was recorded daily from day 3 to day 20 of gestation and reported on the body weight intervals.
- Terminal studies
* Necropsy
All females were killed on day 20 of gestation, in random group order and examined macroscopically.
* Uterine/implantation data
pregnancy status
number of corpora lutea
number and intrauterine position of implantations
subdivided into:
live foetuses
early intrauterine deaths
late intrauterine deaths
dead foetuses
- Foetal data
Foetuses were weighed individually, examined externally and sexed. The viscera of approximately one half of the foetuses in each litter were examined. The skeleton was examined and preserved and stored in absolute glycerol (containing thymol crystals).

The remaining foetuses were placed in Bouin's fluid for at least two weeks then transferred to 70% industrial methylated spirit.

Foetal abnormalities were recorded as malformations (rare and/or potentially lethal defects) and variations (cormnonly occurring non-lethal abnormalities).

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Conclusion : Exposure to DMDS at 50 ppm elicited maternal toxicity, with

associated fetal growth retardation (demonstrated by low weight and retarded ossification). There was no indication of a teratogenic effect. At 15 ppm, less marked maternal toxicity was observed and there were no fetal effects. There was no adverse effect of treatment, maternal or fetal, at 5 ppm.

Reliability : (1) valid without restriction
Flag : Material Safety Dataset, Critical study for SIDS endpoint
31.12.2005 (3)

Species : rat
Sex : female
Strain : other: Crl: CD(SD)BR
Route of admin. : inhalation
Exposure period : day 6 to day 15 of gestation
Frequency of treatm. : 6 h/day
Duration of test : up to gestation day 20
Doses : 10, 50 and 250 ppm
Control group : yes, concurrent no treatment
NOAEL maternal tox. : < 10 ppm
Method : other: range-finding study
Year :
GLP : yes
Test substance : other TS

Method : Three groups of 7 time-mated female rats were exposed by inhalation (whole body) to concentrations of 10, 50 or 250 ppm of DMDS daily from day 6 to day 15 of gestation. A similar group of animals exposed to filtered air by the same route and over the same period acted as controls. All animals were maintained to day 20 of gestation when they were killed and their uterine contents assessed.

Result : All animals survived to day 20 of gestation. Comnon clinical signs were observed at
an incidence which increased with dose, in the treated groups only. Dosage-related reductions in body weight gain were apparent in all treated groups over the exposure period. Dosage-related reductions in food intake were apparent in all treated groups over the exposure period. In the intermediate and high dose groups the lower intake persisted until termination.

Pregnancy incidence was within the expected range in all groups. Pre-implantation loss was within the expected range in all treated groups. There was no adverse effect of treatment on the incidence of intrauterine deaths. Litter size was within the expected range in all treated groups. Sex ratio was within the expected range in all groups. Mean litter weight was higher than controls in all treated groups. Mean foetal weight showed a dosage-related reduction in the treated groups, but was considered an equivocal result as values for the control and low dose groups exceeded normal limits. No malformations were observed at
external examination of foetuses and the incidence of variations did not indicate an adverse effect of treatment.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Test substance : Test substance: Dimethyl disulfide
CAS no.: 624-92-0
Source: Atochem
Purity: 99.88%

Reliability : (1) valid without restriction

31.12.2005 (4)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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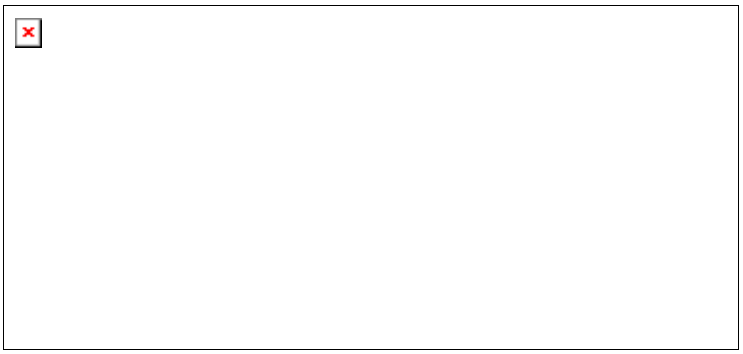
10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

Appendix IV

IUCLID 5 Report for Disulfide Oil



Printing Date 2008-11-10 14:42:46 CET

Restriction of specific regulatory purposes

Confidentiality

Name	Disulfides, dialkyl and di-Ph, naphtha sweetening
Legal entity owner	Lyondell Chemie Nederland B.V. / Rotterdam / Netherlands

Substance: Disulfides, dialkyl and di-Ph, naphtha sweetening

UUID IUC5-30cf773d-ab97-43e9-b5de-19496d0ddae4
Dossier UUID 0
Author jrfowles / Lyondell Chemie Nederland B.V. / Rotterdam / Netherlands
Date 2008-11-10 11:55:21 CET
Remarks

0 Related Information
0.1 Templates
0.2 Categories
0.3 Mixtures
1 General Information
1.1 Identification
Substance identification

Chemical name Disulfides, dialkyl and di-Ph, naphtha sweetening
Legal entity Lyondell Chemie Nederland B.V. / Rotterdam / Netherlands

Reference substance

Reference substance Disulfides, dialkyl and di-Ph, naphtha sweetening / Disulfides, dialkyl and di-Ph, naphtha sweetening / 68955-96-4

EC number	EC name

CAS number	CAS name
68955-96-4	Disulfides, dialkyl and di-Ph, naphtha sweetening

IUPAC name

Type of substance

Composition UVCB
Origin petroleum product

Trade names

Name DSO
Name Disulfide oil

1.2 Composition
Substance composition

Name Disulfides, dialkyl and di-Ph, naphtha sweetening
Brief description Reclaimed substancesextracted from light hydrocarbon streams during petroleum refining

Degree of purity

87.1 % (w/w)

Constituents

Reference substance	dimethyl disulphide / dimethyl disulfide / 624-92-0 **EC number** **EC name** 210-871-0 dimethyl disulphide **CAS number** **CAS name** 624-92-0 **IUPAC name** dimethyl disulfide
Typical concentration	12 % (w/w)

Reference substance	methyl ethyl disulphide / methyldisulfanylethane / 20333-39-5 **EC number** **EC name** **CAS number** **CAS name** 20333-39-5 **IUPAC name** methyldisulfanylethane
Typical concentration	18.2 % (w/w)

Reference substance	isopropyl methyl disulphide / 2-(methyldisulfanyl)propane / 40136-65-0 **EC number** **EC name** 254-808-5 isopropyl methyl disulphide **CAS number** **CAS name** 40136-65-0 **IUPAC name** 2-(methyldisulfanyl)propane
Typical concentration	14.4 % (w/w)

Reference substance	diethyl disulphide / 1,1'-disulfanediyldiethane / 110-81-6 **EC number** **EC name** 203-805-7 diethyl disulphide **CAS number** **CAS name** 110-81-6 **IUPAC name** 1,1'-disulfanediyldiethane
Typical concentration	11.2

Reference substance	methyl propyl disulphide / 1-(methyldisulfanyl) propane / 2179-60-4 **EC number** **EC name** 218-551-2 methyl propyl disulphide **CAS number** **CAS name** 2179-60-4 **IUPAC name** 1-(methyldisulfanyl)propane
Typical concentration	7.7 % (w/w)

Reference substance	ethyl isopropyl disulphide / 2-(ethyldisulfanyl)-propane / 53966-36-2 **EC number** **EC name** **CAS number** **CAS name** 53966-36-2 **IUPAC name** 2-(ethyldisulfanyl)-propane
Typical concentration	11.6 % (w/w)

Reference substance	ethyl n-propyl disulphide / 1-(ethylsulfanyl)-propane / 30453-31-7 **EC number** **EC name** **CAS number** **CAS name** 30453-31-7 **IUPAC name** 1-(ethylsulfanyl)-propane
Typical concentration	7 % (w/w)

Reference substance	diisopropyl disulphide / 2-propan-2-yldisulfanylpropane / 4253-89-8 **EC number** **EC name** 224-225-0 diisopropyl sulphide **CAS number** **CAS name** 4253-89-8 **IUPAC name** 2-propan-2-yldisulfanylpropane
Typical concentration	2 % (w/w)

Reference substance	ethyl n-butyl sulphide / 1-(ethylsulfanyl) butane / 63986-03-8
	EC number **EC name**
	CAS number **CAS name**
	63986-03-8
	IUPAC name
	1-(ethylsulfanyl)butane
Typical concentration	0.5 % (w/w)

Reference substance	dipropyl disulphide / 1,1'-disulfanediyldipropane / 629-19-6
	EC number **EC name**
	211-079-8 dipropyl disulphide
	CAS number **CAS name**
	629-19-6
	IUPAC name
	1,1'-disulfanediyldipropane
Typical concentration	2.5 % (w/w)

Impurities

Reference substance	benzene / benzene / 71-43-2
	EC number **EC name**
	200-753-7 benzene
	CAS number **CAS name**
	71-43-2
	IUPAC name
	benzene
Typical concentration	< 0.1 % (w/w)
Remarks	The benzene levels in DSO have been reduced in recent years and are currently present at concentrations less than 0.1%. Past samples used in the acute toxicity testing performed over fifteen years ago contained benzene levels up to 1.0%.

1.3 Identifiers
1.4 Analytical information
1.5 Joint submission
1.6 Sponsors

1.7 Suppliers
1.8 Recipients
1.9 Product and process oriented research and development
2 Classification and Labelling
2.1 GHS
2.2 DSD - DPD
3 Manufacture, use and exposure
3.1 Technological process
3.2 Estimated quantities
3.3 Sites
3.4 Form in the supply chain
3.5 Identified uses and exposure scenarios
3.6 Uses advised against
3.7 Waste from production and use
3.8 Exposure estimates
3.9 Biocidal information
3.10 Application for authorisation of uses
4 Physical and chemical properties
4.5 Particle size distribution (Granulometry)

Particle size distribution (Granulometry).001

UUID	IUC5-869e6464-28f9-405a-9661-6c34be94e8e3
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-09-25 16:10:13 CEST
Remarks	

Administrative Data

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Data waiving	study scientifically unjustified
Justification for data waiving	Test material is a liquid

5 Environmental fate and pathways

Environmental fate and pathways

UUID	IUC5-05cdc3e8-d73e-4892-a303-d8fe2b5199c9
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 14:02:31 CEST
Remarks	

Administrative Data

Discussion

The environmental fate of DSO has not been examined; however, structure- activity information and suggestive anecdotal test data is available for DMDS and the remaining disulfides in the mix. Many of the disulfides in DSO are naturally found in the environment either as ingredients in vegetables, especially garlic and onions, or as products of the microbial oxidation of assimilated mercaptans (TGSC, 2008).

Preliminary studies with DMDS and DPDS have shown that these two disulfides are relatively stable in soil and water (Arnault *et al*., 2004). DMDS, in particular, has been found in many environmental compartments and is considered to have an integral role in the global sulfur cycle (Caron and Kramer, 1994). Natural background concentrations of DMDS have been measured in a wide variety of media including air, surface waters, sediment, wastewater effluent, vegetation, and expired human air (HSDB, 2005). Interestingly, DMDS has been shown to be absorbed from air into moist and dry soils at a rate that was influenced by the presence of soil microbes, which facilitated the uptake into moist soil only (Bremner and Banwart, 1976). This may be an important environmental process for the disulfides in DSO because of their tendency to partition into the soil compartment.

5.2 Biodegradation

5.2.1 Biodegradation in water: screening tests

Biodegradation in water: screening tests.001

UUID	IUC5-a1ec8565-ab04-451c-8f39-7883ead6ddee
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 13:59:44 CEST
Remarks	

Administrative Data

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliablility	2 (reliable with restrictions)
Rationale for reliability	study conducted to OECD methods but with no GLP

Data source

Reference

Reference type	other: HPV submission		
Author	HPV testing group, API (submitter)	**Year**	2008
Title	US EPA HPV Challenge Program Data Review and Assessment for Reclaimed Substances: Disulfides, Diethyl and Diphenyl, Naphtha Sweetening (aka Disulfide Oil) CAS # 68955-96-4		
Bibliographic source			
Testing laboratory		**Report no.**	
Owner company	American Petroleum Institute		
Company study no.		**Report date**	2008-09-10

Reference type	study report		
Author	ELF ATOCHEM	**Year**	1995
Title	Dimethyl disulfide. Détermination de la biodégradabilité facile.Essai en fioles fermées.		
Bibliographic source			
Testing laboratory		**Report no.**	Ref 95/SAEk/0415/NM (as cited in DMDS robust summary, 2005)
Owner company			
Company study no.		**Report date**	

Data access

data submitter is data owner

Materials and methods

Test type

ready biodegradability

Test guideline

Qualifier	according to
Guideline	OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test)
Deviations	

GLP compliance

no

Test materials

Test material identity

Identifier	CAS number
Identity	624-92-0

Details on test material

Dimethyl disulfide

Study design

Duration of test (contact time)

28 d

Parameter followed for biodegradation estimation

O2 consumption

Reference substance

benzoic acid, sodium salt

Results and discussions

% Degradation of test substance

% Degr.	< 10
St. dev.	
Parameter	O2 consumption
Sampling time	28 d
Remarks	

Applicant's summary and conclusion

Interpretation of results

under test conditions no biodegradation observed

Conclusions

Not readily biodegradable

Executive summary

The biodegradability of the ten DSO disulfides was examined using the BIOWIN (v 4.00) subroutine in the EPI Suite program. The BIOWIN routine uses eight different

methods to evaluate the biological degradation of a target chemical under either aerobic or anaerobic conditions. Although several of the methods suggest that the probability of disulfide biodegradation is relatively high, it is believed that the most reliable information comes from the results for DMDS itself and from those models indicating a lack of ready biodegradability (see table below). A closed bottle ready biodegradability test performed with DMDS indicated that less than 10% of the material was degraded over a 28-day period (ELF ATOCHEM, 1995). Ready biodegradability, as defined in accordance with OECD guidelines, only occurs when at least 70% of a chemical is biologically removed from the environment within the 28-day period. Accordingly, DSO is expected to fail the biodegradability test and these conclusions are in agreement with actual test data for DMDS.

Disulfide	Ready Biodegradation Probability linear	Ready Biodegradation Probability non-linear	Readily Biodegradable
dimethyl disulfide	0.43	0.46	no (no†)
methyl ethyl disulfide	0.44	0.47	no
methyl isopropyl disulfide	0.30	0.26	no
diethyl disulfide	0.45	0.47	no
methyl n-propyl disulfide	0.45	0.47	no
ethyl isopropyl disulfide	0.31	0.26	no
ethyl n-propyl disulfide	0.46	0.48	no
diisopropyl disulfide	0.31	0.27	no
ethyl n-butyl disulfide	0.46	0.49	no
dipropyl disulfide	0.46	0.49	no
DSO	0.43#	0.46#	no#

†Actual measured degradation of 10% over 28-days (DMDS test plan, 2005).
#Estimated value.

6 Ecotoxicological Information
6.1 Aquatic toxicity
Aquatic toxicity

UUID	IUC5-2a436f97-8317-4414-8f3b-f45a41c1a9b2
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 11:07:53 CEST
Remarks	

Administrative Data

Discussion

Evidence suggests that the aquatic and terrestrial toxicity of DSO mimics the effects observed with DMDS. Initial modeling of DMDS and the remaining disulfide constituents of DSO using EPA's ECOSAR software package (Meylan and Howard, 1998) reveled that the ecotoxicity of the disulfides increased as a function of alkyl chain length. Although this finding is consistent with the observed increase in octanol/water partition coefficients for these disulfides, the results are inconsistent with available test data and knowledge of disulfide metabolism. The modeling results, therefore, have not been utilized since the assumed mode of action, non-polar narcosis, is most likely incorrect, a condition that often occurs when this endpoint is invoked indiscriminately (de Roode *et al*., 2006).

The underpinnings for the SAR routines used in the ECOSAR program assume that non-polar narcosis is the operant mode of action for the disulfides; but this class of chemicals is not explicitly represented in the training sets used to develop the mathematical relationships. In fact, disulfides are more likely to operate in terrestrial and aquatic organisms by the same mode of action observed in mammals, which involves disulfide bond cleavage and redox cycling of the free radical intermediates (Münchberg *et al*., 2007; Lesser, 2006). The reactive oxygen species produced in this reaction can lead to oxidative stress and protein interactions that are typically more severe and less consistent across species than those elicited by narcotic chemicals (Jager *et al*., 2007). This lack of applicability is evident when test data for DMDS are compared to the estimates obtained using ECOSAR (see Table 6). The toxicity of DMDS is generally under predicted by a factor 10-200 fold, which signals that a mode of action other than narcosis is in effect.

Table 6. A Comparison of Actual and Estimated Ecotoxicity Values for DMDS

Ecotoxicity Endpoint	Estimated Toxicity (mg/L)	Actual Toxicity (mg/L)
Acute Fish		

96-hr LC_{50}	92.51	0.97*
Chronic Fish 30-day	11.67	--
Acute Invertebrate 48-hr EC_{50}	98.24	7†
Acute Plant 96-hr EC_{50}	60.96	35#
Earthworm 14-day LC_{50}	635.4	32*

* Actual measured value taken from Arkema, Inc. (2007).

† Actual measured value taken from ELF ATOCHEM (1996).

Additional test results for algae (ErC_{50}, EbC_{50}, NOECr, and NOECb) are available (ELF ATOCHEM, 2000).

Additional support for the use of DMDS as a surrogate for the disulfides in DSO comes from available test data for higher homologs in the series. When the acute toxicity of DMDS to fish (0.97 mg/L) is compared to the LC_{50} results obtained with DEDS (7.43 mg/L), DPDS (2.62 mg/L), and diisopropyl disulfide (8.31 mg/L), there is no apparent increase in toxicity as a function of chain length (NITE, 2003; Chevron Phillips Chemical Company, 2005; Russom *et al*., 1997). In addition, the 24-hr EC_{50}value for DEDS (14.5 mg/L) in *Daphnia magna* is nearly 2-fold greater than the 48-hr value for DMDS (7 mg/L) (Gälli *et al*., 1994). Taken together, these data are consistent with the expected change in potency for the oxidative stress caused by disulfide bond cleavage (see section 5), and confirms that DMDS is the most toxic member of the disulfide series in DSO. Additional testing with DSO is not expected to result in effect concentrations less than those observed DMDS, and therefore no further testing can be justified for the endpoints listed. Despite the lack of DMDS test data for chronic fish toxicity, testing will not be performed within the context of this submission because it will be completed in conjunction with the previously submitted test plan for DMDS. When this voluntary testing is completed, a full complement of ecotoxicity data will be available for DMDS and by analogy DSO.

7 Toxicological information
7.1 Toxicokinetics, metabolism and distribution
Toxicokinetics, metabolism and distribution

UUID	IUC5-061810ab-28f3-480c-b273-04a0f2b19afd
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 17:40:41 CEST
Remarks	

Administrative Data

Discussion

Sufficient information is available to make reliable and sensible determinations of the health effects of DSO. Whereas some test data is available on the oil itself, the majority of information can be extracted from the robust summary and test plan for DMDS (DMDS Robust Summary, 2005). The rationale and justification for using the health effects data of DMDS as a substitute for the disulfides in DSO are based on sound scientific principles and a plethora of mechanistic information showing that all of the dialkyl disulfides in DSO operate through a common toxic mechanism. This mechanism, which has been well studied and clearly elucidated in the published literature, focuses on the unique characteristics of the disulfide bridge and the ease with which free radical intermediates can be formed once the bridge is cleaved.

The metabolism of many, if not all, disulfides is initiated by a thiol-disulfide exchange reaction that substitutes the sulfhydral group of glutathione for a mercaptide fragment within the disulfide molecule. The reaction for DPDS, whose *in vivo* metabolism has been examined in the greatest detail of the ten DSO disulfides (Germain *et al*., 2008; Teyssier and Siess, 2000). Evidence shows that this same initial glutathione exchange reaction also takes place for a host of alkyl, alkenyl, phenyl, and branched chain disulfides (Bach *et al*., 2008; Munday and Manns, 1994; Munday, 1989; Nishikawa *et al*., 1987). Using an expert knowledge based system for predicting the metabolic reactions that take place *in vivo* (Meteor, v 9.0.0), the disulfides in DSO were all predicted to undergo reductive cleavage of the disulfide bond with a high degree of probability (Greene *et al*., 1999).

The exchange reaction with glutathione is catalyzed by a thioltransferase, also known as glutaredoxin, which is widely distributed in nature and shows high levels of activity in the tissues and organs affected by alkyl disulfide toxicity (Lillig and Holmgren, 2007). This reaction is the key step in the toxic mechanism for dialkyl disulfides. The activation mechanism has been associated with the initiation of a redox cycle that

generates excessive quantities of highly reactive free radical intermediates that are capable of interacting with tissue macromolecules at or near the site where they are formed. In some cases this site has been the red blood cell and in other cases the liver depending on the species examined (Munday, 1989). The sequence of reactions in the redox cycling of alkyl disulfide is depicted generically in Figure 3. The first product of the initial thioltansferase exchange reaction is an alkyl mercaptan that undergoes a one-electron oxidation to a free radical intermediate following ionization. This intermediate is the proximal toxicant, responsible for producing a continuous supply of hydroxyl radicals and other reactive oxygen species that can sustain the redox cycling, cause oxidative stress, and precipitate tissue injury at sites where it is formed.

Importantly, the reactivity of the mercaptans formed in the exchange reaction is directly affected by the length and branching pattern of the attached alkyl substitutents, with longer chain lengths leading to reduced radical stabilization and lower oxidation rates (Munday, 1989). In addition, the reactivity and toxicity of alkyl disulfides has been shown to decrease in the following order *n* > *sec* > *tert* due to the influence of steric factors on thioltransferase activity. These data indicate that DMDS will be the most reactive member of the series with the longer chain lengths and higher branching patterns of the remaining homologs ameliorating the toxicity by affecting the rate of formation and ultimate stabilization of the free radical intermediates. This fact provides strong justification for the use of DMDS as a surrogate for the higher chain length disulfides in DSO and validates its use in a “read across” transfer to other disulfides in the category. The test data for DMDS is therefore offered as a reasonable and mechanistically supportable substitute for DSO, since it represents the most toxic member of the disulfide series. As such, the existing information on DSO and the disulfide category is deemed sufficient, and no further testing is needed nor required to assess the health hazards associated with this category of reclaimed substances.

Figure 3. Mechanism of Redox Cycling and Free Radical Formation from Alkyl Disulfide Metabolism (Munday and Manna, 1994)

2 GSH + RSSR ¿ GSSG + 2 RSH

RSH ¿ RS¿ + H^+

(Hb)$Fe^3O_2^{\bullet}$¿ + RS¿ + $2H^+$ ¿ (Hb)Fe^3 + $RS^{\bullet}$ + H_2O_2

$RS^{\bullet}$+ RS¿ ¿ $(RSSR)^{\bullet}$¿

$(RSSR)^{\bullet}$¿ + 0_2 ¿ RSSR + $0_2^{\bullet}$¿

RSH + $0_2^{\bullet}$¿+- H^+ ¿ $RS^{\bullet}$ + H_2O_2

7.1.1 Basic toxicokinetics

Basic toxicokinetics

UUID	IUC5-0b007d33-7e62-4d14-8deb-058c31d9f6f0
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 17:35:09 CEST
Remarks	Created

Administrative Data

7.2 Acute Toxicity
7.2.1 Acute toxicity: oral
Acute toxicity: oral - supporting study on DMDS.003

UUID	IUC5-301e61a2-a179-4390-8bc6-0dde2d34f070
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-07 16:47:11 CET
Remarks	

Administrative Data

Purpose flag	supporting study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	study conducted to EPA method and GLP

Data source

Reference

Reference type	study report		
Author	Penwalt Corp.	**Year**	1985
Title	Dimethyl Disulphide EPA Acute LD50		
Bibliographic source			
Testing laboratory	Products Safety Labs	**Report no.**	T-5150
Owner company	Penwalt Corp.		
Company study no.		**Report date**	1985-06-24

Data access

data submitter is data owner

Materials and methods

Test guideline

Qualifier	
Guideline	other guideline: EPA 40 CFR 163.81-1
Deviations	

GLP compliance

yes

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	624-92-0

Details on test material

Dimethyl siulfide

Test animals

Species

rat

Strain

Wistar

Sex

male/female

Administration / exposure

Route of administration

oral: gavage

Doses

0, 125, 188, 250, 375 and 500 mg/kg

No. of animals per sex per dose

5

Results and discussions

Effect levels

Sex	male/female
Endpoint	LD50
Effect level	190 mg/kg bw
95% CL	150 — 240
Remarks	

7.5 Repeated dose toxicity
7.5.2 Repeated dose toxicity: dermal
Repeated dose toxicity: dermal - supporting study.002

UUID	IUC5-02163804-7758-4960-b365-31029fa602b8
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-07 17:22:37 CET
Remarks	

Administrative Data

Purpose flag	supporting study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	range-finding study to full OECD study with GLP

Data source

Reference

Reference type	study report		
Author	ELF Atochem	**Year**	1989
Title	Repeated-dose (14-day) dermal toxicity range-finding stuyd with Dimethyl Disulfide (DMDS) in rabbits.		
Bibliographic source			
Testing laboratory	TNO-CIVO Institutes	**Report no.**	V 89.058/280553
Owner company	ELF Atochem		
Company study no.		**Report date**	1989-07-31

Data access

data submitter is data owner

Materials and methods

Test guideline

Qualifier	
Guideline	other guideline: range-finding study
Deviations	

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier CAS number

Identity 624-92-0

Details on test material

Dimethyl disulfide

Test animals

Species

rabbit

Strain

New Zealand White

Sex

male/female

Administration / exposure

Type of coverage

occlusive

Details on study design

0, 106, 503 and 1063 mL/kg/day

Results and discussions

Effect levels

Endpoint	NOAEL
Effect level	< 103 mg/kg bw/day (nominal)
Sex	male/female
Basis for effect level / Remarks	
Endpoint	LOAEL
Effect level	103 mg/kg bw/day (nominal)
Sex	
Basis for effect level / Remarks	

Observations

Remarks on results including tables and figures

Dose-related lethargy or unconsciousness was observed in all treatment groups that dissipated by the end of the day

7.6 Genetic toxicity
Genetic toxicity

UUID	IUC5-e5cc156b-75e5-4e83-8056-a891b8376c9c
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 16:15:21 CEST
Remarks	

Administrative Data

Key parameter (optional)
Genetic toxicity

negative

Discussion

Although there are no results available for DSO, DMDS has been examined in a variety of *in vivo* and *in vitro* genetic toxicology screening assays (DMDS Robust Summary, 2005). The test results revealed that DMDS was negative in bacterial mutagenicity assays (Penwalt, 1985c), negative in mammalian mutagenicity tests (ELF ATOCHEM, 1990a), negative for DNA damage and repair (ELF ATOCHEM, 1990b), and ambiguously positive in a chromosomal aberration study using human lymphocytes (ELF ATOCHEM, 1990c). Except for the DNA damage and repair assay, these tests were all performed in the presence and absence of metabolic activation. Similarly, negative results were obtained when DMDS was evaluated *in vivo* in a mouse micronucleus assay at inhalation concentrations of 250 and 500 ppm (ATOCHEM, 1989b), and did not cause unscheduled DNA synthesis in the hepatocytes of rats exposed to 500 ppm (ATOCHEM, 1990). By comparison, DPDS did not cause any reverse mutations in an *S. typhimurium* assay using strain TA98 (Tsai *et al*., 1996). None of the disulfides in DSO were judged to be genotoxic by an expert knowledge based system used to predict the health effects of untested chemical substances (Derek, v 9.0.0) (Greene *et al*., 1999).

7.6.1 Genetic toxicity in vitro

Genetic toxicity in vitro - Chromosome aberration.001

UUID	IUC5-c0639a16-2dd3-4480-8d55-9deb7d6caefe
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-03 14:34:07 CET
Remarks	

Administrative Data

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliablility	1 (reliable without restriction)
Rationale for reliability	study conducted to OECD guidelines with GLP

Data source

Reference

Reference type	study report		
Author	ELF ATOCHEM	**Year**	1990
Title	Chromosome analysis of cultured human lymphocytes following in vitro treatment with DMDS		
Bibliographic source			
Testing laboratory	TNO-CIVO	**Report no.**	V 89.045
Owner company			
Company study no.		**Report date**	

Materials and methods

Type of genotoxicity

chromosome aberration

Type of study

in vitro mammalian chromosome aberration test

Test guideline

Qualifier	according to
Guideline	OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test)
Deviations	

GLP compliance

yes

Test materials

Test material identity

Identifier	CAS number
Identity	624-92-0

Method

Species/strain

Species/strain	lymphocytes:
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	Aroclor-induced rat (wistar) liver S9 fraction

Test concentrations

3.7; 11.1; 33.3; 100; 300 µg/ml

Vehicle

dimethyl sulphoxide

Controls

Negative controls	
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes
Positive control substance	cyclophosphamide
Remarks	+S9
Negative controls	
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes
Positive control substance	mitomycin C
Remarks	-S9

Details on test system and conditions

- Preliminary Cytotoxicity Assay: The dose levels used in the chromosome aberration assay were established on the basis of the results of a preliminary toxicity test carried out with 6 concentrations of the test substance (ranging from 0.5 to 1000.0 µg/ml), both in the absence and in the presence of the metabolic activation system (S -9 mix). The highest concentration for the toxicity test was determined by the limit of the solubility of the test substance in the tissue culture medium.
- Cytogenetic Assay:
*
Cell Treatment After 48 h of incubation, the cultures were centrifuged. The cell pellets were resuspended in tissue culture medium supplemented with 20 mM HEPES (and 10% S-9 mix, for the test with metabolic activation) and appropriate test solutions. An untreated culture and a culture receiving DMSO served as negative controls. For each concentration of the test substance and for the controls one culture was used. Without S9, the cultures were incubated in closed tubes for another 24 hours including a 2 hour colcemid treatment. With S-9 mix, the exposure of the cells to the test substance was reduced to only 2 hours, because of the toxicity of the S -9 mix for the cells. After the 2 hour incubation period, the cells washed and supplied with freshly prepared culture medium. The cells were incubated for a further 22 hours (including a 2 hour colcimid treatment.
*
Cell harvesting: Two hours before the end of the total incubation period the cells were arrested in the metaphase stage of the mitosis by the addition of colcemid. The cells were harvested, treated with a hypotonic solution, fixed three hours, and transferred to clean microscope slides. Two slides were prepared from each culture. The slides were stained 1000 stimulated lymphocytes were examined (500 from each slide) to determine the mitotic index (percentage of cells in mitosis).
*
Metaphase analysis:
From each culture, 100 well-spread metaphases (each containing 46 chromosomes) were analysed by microscopic examination for a wide range of structural chromosome aberrations (gaps, breaks, fragments, dicentrics, exchanges etc.) and other anomalies (endoreduplication, polyploidy), according to the criteria recommended by Savage (1975).

Evaluation criteria

- Evaluation criteria:
The major crite rion to designate the results of a chromosome aberration test as positive is a dose-related, statistically significant increase in the number of cells with structural chromosome aberrations. However, a clear dose-response relationship can be absent because the yield of chromosome aberrations can vary markedly with post-treatment sampling time of an asynchronous population and because increasing doses of clastogens can induce increasing degrees of mitotic delay. A test substance producing neither a dose-related, statistically significant increase in the number of cells with structural chromosome aberrations, nor a statistically significant and reproducible positive response at any of the doses is considered non-clastogenic in this system.

Results and discussions

Test results

Species/strain	lymphocytes:
Metabolic activation	with and without
Test system	
Genotoxicity	
Cytotoxicity	no

Vehicle controls valid

Negative controls valid

Positive controls valid

Additional information on results

cytotoxic concentration 300 µg/ml

Overall remarks, attachments

Overall remarks

The test substance did not induce a statistically significant increase in the number of cells with structural chromosome aberrations at non toxic concentrations, both in the absence and in the presence of the S-9 mix. At the very toxic concentration of 300.0 µg/ml, both in the absence and in the presence of the S-9 mix, the test substance induced a statistically significant increase in the number of cells with structural chromosome aberrations.

Applicant's summary and conclusion

Interpretation of results

negative

Conclusions

dimethyl disulfide was negative for chromosome aberrations in a cultured human lymphocyte test

Executive summary

DSO is prediceted to be similarly negative for chromosome aberrations

Genetic toxicity in vitro Mammalian cell gene mutation assay.002

UUID	IUC5-096ba069-4515-4d76-bae3-7f7f70ceaf17
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-03 13:53:18 CET
Remarks	

Administrative Data

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	study conducted to OECD guidelines with GLP

Data source

Reference

Reference type			
Author	ELF ATOCHEM	**Year**	1990
Title	In Vitro assay for the induction of point mutations in the HGPRT-locus of Chinese hamster ovary cells by dimethyldisulfide (DMDS)		
Bibliographic source			
Testing laboratory	TNO-CIVO	**Report no.**	V 89.257
Owner company			
Company study no.		**Report date**	

Materials and methods

Type of genotoxicity

gene mutation

Type of study

mammalian cell gene mutation assay

Test guideline

Qualifier	according to
Guideline	OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test)
Deviations	

Principles of method if other than guideline

The dose levels used in the HGPRT assay were established on the basis of the results of a preliminary solubility test. A final concentration of 1,000 µg/ml was chosen as highest concentration for the HGPRT assays.
The two independent HGPRT-assays were carried out with single cultures for each concentration of the test substance and for the

negative and positive controls.

GLP compliance

yes

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	624-92-0

Details on test material

Dimethyl disulfide

Method

Species/strain

Species/strain	Chinese hamster Ovary (CHO)
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	S9 derived from adult male Wistar rats

Test concentrations

0.46; 1.37; 4.12; 12.3; 37.0; 74.0; 111; 333; 667 and 1000 µg/ml

Vehicle

Dimethyl sulphoxide

Controls

Negative controls	
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes
Positive control substance	ethylmethanesulphonate
Remarks	-S9
Negative	

controls	
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes
Positive control substance	N-dimethylnitrosamine
Remarks	+S9

Details on test system and conditions

- Activation:
S9 derived from adult male Wistar rats
- Culture Medium:
Ham's F-12 medium supplemented with 10% heat-inactivated foetal calf serum, 50 µg gentamicin/mL and 2 mM L-glutamine.

Evaluation criteria

- Evaluation of the results:
The following criteria were used to evaluate the data obtained in the HGPRT assay (Li et al. 1987)
a) the survival (absolute cloning efficiency) of the negative controls should not be less than 50%,
b) the mean mutant frequency of the negative controls should fall within the range of 0-20 6 -TG resistant mutants per 10e6 clonable cells,
c) the positive controls must induce a response of a magnitude appropriate for the mutagen under the experimental conditions applied,
d) the highest test substance concentration should, if possible, result in a clear cytotoxic response (e.g. 10-30% of the relative initial survival).
Any apparent increase in mutant frequency at concentrations of the test substance causing more than 90% toxicity is considered to be an artifact and not indicative of genotoxicity.
Genotoxicity of the test substance was evaluated using the following criteria (Li et al. 1987):
a) a concentration-related increase in mutant frequency,
b) a reproducible positive response for at least one of the test substance concentrations (e.g. the mean mutant frequency should be more than 20 mutants per 10e6 clonable cells).

Results and discussions

Test results

Species/strain	Chinese hamster Ovary (CHO)
Metabolic activation	with and without
Test system	
Genotoxicity	negative
Cytotoxicity	

Vehicle controls valid	yes
Negative controls valid	
Positive controls valid	yes

Remarks on results including tables and figures

In the absence of the S -9 mix, the test substance induced neither a concentration-related increase in the mutant frequency nor a reproducible positive response at one of the test concentrations. In the presence of a metabolic activation system, DMDS induced a slight increase in mutant frequency at several concentrations, in both HGPRT assays. These increases were neither concentration-related nor clearly reproducible. In both HGPRT assays, the test substance appeared to be highly toxic to CHO cells at a concentration range from 74.0-1,000 ug/ml. The positive control substances, ethylmethanesulfonate and dimethylnitrosamine, induced the expected increase in the mutant frequency.

Applicant's summary and conclusion

Interpretation of results

negative

Conclusions

No evidence for a genotoxic effect of DMDS was found in cultured CHO cells, under the conditions used in the HGPRT assay.

Executive summary

DSO is expected to be similarly negative in an in vitro mammalian cell gene mutation assay

Genetic toxicity in vitro - DNA damage and repair.003

UUID	IUC5-e029b412-545c-4e3f-ae2d-910f2073f3b8
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-03 16:29:27 CET
Remarks	

Administrative Data

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	study conducted to OECD guidelines with GLP

Data source

Reference

Reference type			
Author	ELF ATOCHEM	**Year**	1990
Title	In Vitro DNA Repair Test on Rat Hepatocytes in Primary Culture		
Bibliographic source			
Testing laboratory	Sanofi	**Report no.**	RA860891026/PN1
Owner company			
Company study no.		**Report date**	

Materials and methods

Type of genotoxicity

DNA damage and/or repair

Type of study

DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells in vitro

Test guideline

Qualifier	according to
Guideline	OECD Guideline 482 (Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro)
Deviations	

GLP compliance

yes

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	624-92-0

Details on test material

Dimethyl sulphoxide

Method

Species/strain

Species/strain	hepatocytes: rat
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	without
Metabolic activation system	

Test concentrations

1; 5; 10; 50; 100; 200 and 300 µg/ml

Vehicle

dimethyl sulphoxide

Controls

Negative controls	yes pyrene 1 uM
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes
Positive control substance	7,12-dimethylbenzanthracene
Remarks	10 uM
Negative controls	yes pyrene 1 uM
Solvent / vehicle controls	yes
True negative controls	
Positive controls	yes

Positive control substance	other: 2-aminofluorene
Remarks	0.1 and 0.5 uM

Details on test system and conditions

- Cytotoxicity evaluation: The test compound cytotoxicity was assessed for both DNA repair studies at the end of the treatment:
Each concentration of Dimethyldisulfide was tested in triplicate.
- Autoradiography: Autoradiographs were prepared by dipping slides in a photographic emulsion then developed. Slides were stained in hematoxylin -phloxin.
- Slide assessment:
For each cell, following nuclear grain court, cytoplasmic count was performed on 3 areas of the same size as the nucleus and adjacent to it.

Evaluation criteria

- Data interpretation The test compound is considered positive when the mean nuclear grain court is statisticaly greater than that of the control, the mean net nuclear grain court is above 3 grains per nucleus, and the percentage of treated cells in repair is significantly different from that of the controls. In addition, the effect must be shown to be reproducible between experiments.

Results and discussions

Test results

Species/strain	hepatocytes: rat
Metabolic activation	without
Test system	
Genotoxicity	negative
Cytotoxicity	yes
Vehicle controls valid	
Negative controls valid	
Positive controls valid	yes

Remarks on results including tables and figures

Results

- Cytotoxic at 100, 200 and 300 ug/ml IC50 evaluated by LDH release: 98 ug/ml (2nd study)

- not genotoxic at concentrations of 10, 50, 100 and 200 ug/ml

Applicant's summary and conclusion

Interpretation of results

negative without metabolic activation

Conclusions

DMDS was not genotoxic in vitro in the DNA repair test.

Executive summary

DSO is expected to have similar behaviour to dimethyl disulfide and be negative in a DNA repair test

Genetic toxicity in vitro - Ames test supporting study.004

UUID	IUC5-519a6563-4433-4106-ae8c-811430c0931f
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-07 17:09:15 CET
Remarks	

Administrative Data

Purpose flag	supporting study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	Conducted to OECD method and GLP

Data source

Reference

Reference type	study report		
Author	Penwalt Corp	**Year**	1985
Title	Dimethyl disulfide, Ames Salmonella/Microsome Plate Test (EPA/OECD)		
Bibliographic source			
Testing laboratory	Pharmakon Research International Inc.	**Report no.**	PH 301-P-W-003-85
Owner company	Penwalt Corp.		
Company study no.		**Report date**	1985-05-31

Data access

data submitter is data owner

Materials and methods

Type of genotoxicity

gene mutation

Type of study

bacterial reverse mutation assay (e.g. Ames test)

Test guideline

Qualifier	according to
Guideline	OECD Guideline 471 (Bacterial Reverse Mutation Assay)
Deviations	

GLP compliance

yes

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	624-92-0

Details on test material

Dimethyl disulfide

Method

Species/strain

Species/strain	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	Aroclor derived rat liver S9

Test concentrations

0, 50, 166, 500, 1666, 5000 ug/plate

Results and discussions

Test results

Species/strain	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
Metabolic activation	with and without
Test system	
Genotoxicity	negative
Cytotoxicity	
Vehicle controls valid	
Negative controls valid	
Positive controls valid	

7.6.2 Genetic toxicity in vivo

Genetic toxicity in vivo - UDS.001

UUID	IUC5-0614d85d-1a0f-4eb6-93b6-5d8f70ae3e83
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-03 16:31:17 CET
Remarks	

Administrative Data

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	conducted to OECD guidelines with GLP

Data source

Reference

Reference type	study report		
Author	ELF ATOCHEM	**Year**	1990
Title	An in vivo/in vitro rat hepatocyte DNA-repair assay with dimethyldisulfide (DMDS)		
Bibliographic source			
Testing laboratory	TNO-CIVO	**Report no.**	V 90.082
Owner company			
Company study no.		**Report date**	

Materials and methods

Type of genotoxicity

DNA damage and/or repair

Type of study

unscheduled DNA synthesis

Test guideline

Qualifier	according to
Guideline	other guideline: OECD 482
Deviations	

GLP compliance

yes

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier CAS number

Identity 624-92-0

Details on test material

dimethyl disulfide

Test animals

Species

rat

Strain

Wistar

Sex

male

Administration / exposure

Route of administration

inhalation

Duration of treatment / exposure

4 hours

Doses / concentrations

500 ppm

Basis nominal conc.

Control animals

yes

Positive control(s)

The hepatocarcinogen 2-acetylaminofluorene (2 AAF), was used as a positive control in the in vivo/in vitro DNA-repair assay and in the in vitro DNA-repair assay (2 AAF). Hepatocytes isolated from animals exposed to air only served as negative controls.

Examinations

Tissues and cell types examined

The DNA-repair activities were examined by autoradiography in monolayer cultures o f hepatocytes, incubated in the presence of [methyl-3H]thymidine.

Any other information on materials and methods incl. tables

Dimethyldisulfide (DMDS) was examined for its potential to induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes after short-term exposure of male wistar rats to the test substance by inhalation. For the genotoxicity assay male rats were exposed by inhalation for a period of 4 h to one high concentration of 500 ppm DMDS (maximally tolerated concentration). Immediately after exposure and after subsequent non-exposure periods of 16 and 24 h, animals were sacrificed for isolation of hepatocytes.

Results and discussions

Test results

Sex	male
Genotoxicity	negative
Toxicity	
Vehicle controls valid	
Negative controls valid	
Positive controls valid	

Remarks on results including tables and figures

DMDS did not induce DNA-repair activities in hepatocytes, either during the 4 h exposure period or during the subsequent 16 h or 24 h after the exposure period. The positive control substance, 2-AAF, induced the expected increase in DNA-repair activities.

Applicant's summary and conclusion

Interpretation of results

negative

Conclusions

It was concluded that DMDS did not induce DNA-repair in rat hepatocytes.

Executive summary

DSO is expected to be similarly negative in an in vivo UDS study

7.8 Toxicity to reproduction
Toxicity to reproduction

UUID	IUC5-608b5c61-d410-4905-b9cb-b4a1e4421f0e
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-10-01 17:29:19 CEST
Remarks	

Administrative Data

Effects on fertility
Discussion

Although no studies have been reported on the reproductive or developmental toxicity of disulfide oil, studies performed with DMDS are offered as a reasonable surrogate for the disulfides in DSO. An evaluation of developmental effects was examined in a series of inhalation exposure studies performed in rats with DMDS (DMDS Robust Summary, 2005). In an initial range finding study, pregnant dams were exposed for 6 hr/day on days 6 through 15 of gestation to DMDS concentrations of 10, 50, or 250 ppm (0.04, 0.19, or 0.96 mg/L) (ATOCHEM, 1991a). Treatment-related reductions in body weight gain and food consumption were observed in all treatment groups, but pregnancy incidence, intrauterine death incidence, pre-implantation loss, litter size, sex ratio, and the incidence of malformations were all within the expected range. Mean fetal weights showed an exposure-related reduction in all treatment groups that was considered to be an equivocal finding. The maternal NOAEL was determined to be less than 10 ppm (0.04 mg/L).

In a more detailed study, three groups of 30 mated female rats were exposed to DMDS by whole body exposure at 5, 15 or 50 ppm (0.02, 0.06, or 0.19 mg/L) for 6 hours daily from day 6 to day 15 of gestation (ATOCHEM, 1991b). A similar group of 30 rats, exposed to filtered air only over the same period, served as controls. All animals were maintained until day 20 of gestation, and then sacrificed. No deaths were observed or unusual lesions were observed, but a higher incidence of rough hair coat was seen at 50 ppm (0.19 mg/L). Clinical condition at 5 and 15 ppm (0.02 and 0.06 mg/L) did not differ from controls. Treatment-related reductions in weight gain were observed at 15 and 50 ppm (0.06 and 0.19 mg/L). Food intake was lower than controls at 50 ppm (0.19 mg/L), but comparable at 5 or 15 ppm (0.02 and 0.06 mg/L). There was no effect of treatment on pre or post-implantation loss, litter size or sex ratio.

Maternal toxicity was noted at 15 and 50 ppm (0.06 and 0.19 mg/L), but there was no evidence of developmental effects. Litter and fetal weights were reduced at 50 ppm (0.19 mg/L). At 5 and 15 ppm (0.02 and 0.06 mg/L) these parameters were comparable to controls. No malformations were observed in fetuses from the treated groups. A slightly higher incidence of retarded ossification was observed at 50 ppm (0.19 mg/L), which indicated delayed maturation as a result of the lower fetal weight, rather than teratogenicity. The NOAELs for maternal toxicity, teratogenicity, and fetotoxicity were 5, 50, and 15 ppm (0.02, 0.06, and 0.19 mg/L), respectively.

The effects of DMDS on reproductive organs were assessed in male and female rats exposed to 10, 50, 150, or 250 ppm (0.04, 0.19, 0.58, or 0.96 mg/L) DMDS for 6 hr/day for 90 days (ELF ATOCHEM, 1992). Tissue histopathology did not reveal any lesions or damage to the epididymus, prostrate, or testes of the male rats, nor ovaries or uterus of female rats.

7.8.2 Developmental toxicity / teratogenicity

Developmental toxicity / teratogenicity - supporting study.002

UUID	IUC5-01a7a762-2cca-4878-97dd-f854bd73a746
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-07 17:34:27 CET
Remarks	

Administrative Data

Purpose flag	supporting study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliablility	1 (reliable without restriction)
Rationale for reliability	range-finding study to full OECD method test with GLP

Data source

Reference

Reference type	study report		
Author	Atochem	**Year**	1991
Title	Dimethyl Disulfide (DMDS): Inhalation range-finding study in the pregnant rat		
Bibliographic source			
Testing laboratory	Hazleton UK	**Report no.**	6142-514/8
Owner company	Atochem		
Company study no.		**Report date**	1991-05-31

Data access

data submitter is data owner

Materials and methods

Test guideline

Qualifier	
Guideline	other guideline: range-finding study
Deviations	

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	

624-92-0

Test animals

Species

rat

Strain

Sprague-Dawley

Administration / exposure

Route of administration

inhalation

Type of inhalation exposure (if applicable)

whole body

No. of animals per sex per dose

7 rats per group, 10, 50 and 250 ppm

Results and discussions

Effect levels

Endpoint	NOAEL
Effect type	maternal toxicity
Effect level	< 10 ppm
Basis for effect level / Remarks	

Overall remarks, attachments

Overall remarks

Treatment-related reductions in body weight gain and food consumption were observed in all treatment groups, but pregnancy incidence, intrauterine death incidence, pre-implantation loss, litter size, sex ratio, and the incidence of malformations were all within the expected range. Mean fetal weights showed an exposure-related reduction in all treatment groups that was considered to be an equivocal finding. The maternal NOAEL was determined to be less than 10 ppm (0.04 mg/L).

13 Assessment Reports

Assessment Reports - DSO analysis.002

UUID	IUC5-1b6fc839-f3c9-4ec8-b766-b66697dd2a13
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-05 15:24:47 CET
Remarks	Attachment: Appendix I.doc / 674.5 KB added

Administrative Data

Type of report

other: DSO analysis

Document

Appendix I.doc / 674.5 KB (application/msword)

Assessment Reports - DMDS Test Plan.003

UUID	IUC5-7c43da23-377c-4572-877e-e40158ee07bf
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-05 15:25:22 CET
Remarks	Attachment: Appendix II.pdf / 136.52 KB added

Administrative Data

Type of report

other: DMDS Test Plan

Remarks

Dimethyl disulfide test plan

Document

Appendix II.pdf / 136.52 KB (application/pdf)

Assessment Reports - DMDS Robust Summary.004

UUID	IUC5-2d034750-1f1f-4f43-a413-c6d4f992b4f1
Dossier UUID	0
Author	Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date	2008-11-05 15:25:55 CET
Remarks	Attachment: Appendix III.pdf / 902.07 KB added

Administrative Data

Type of report

other: DMDS Robust Summaries

Remarks

Dimethyl disulfide robust summaries

Document

Appendix III.pdf / 902.07 KB (application/pdf)

Reference substance: Disulfides, dialkyl and di-Ph, naphtha sweetening

UUID IUC5-74e0f525-9301-4ce3-a770-0cd33add3353
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-11-03 15:31:41 CET
Remarks

General information

Reference substance name Disulfides, dialkyl and di-Ph, naphtha sweetening

Reference substance information

CAS information

CAS number 68955-96-4
CAS name Disulfides, dialkyl and di-Ph, naphtha sweetening

Synonyms

Name DSO
Name Disulfide oil

Molecular and structural information

Reference substance: dimethyl disulphide

UUID ECB5-76de1127-bba9-474f-a452-a6c8114a0675
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name dimethyl disulphide

EC inventory

EC number 210-871-0 **CAS number** 624-92-0
EC name dimethyl disulphide
Molecular formula C2H6S2

Reference substance information

CAS information

CAS number 624-92-0

IUPAC name

IUPAC name dimethyl disulfide

Synonyms

Name Disulfide, dimethyl
Name Disulfide, dimethyl

DSL Category: Organics

Molecular and structural information

Molecular formula C2H6S2
Molecular weight range 94.199
SMILES notation CSSC
InChI InChI=1/C2H6S2/c1-3-4-2/h1-2H3
Structural formula

Reference substance: methyl ethyl disulphide

UUID IUC5-2ead9865-02d4-4a38-b146-4c980bc95a1f
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-09-25 12:58:10 CEST
Remarks

General information

Reference substance name methyl ethyl disulphide

Reference substance information

CAS information

CAS number 20333-39-5

IUPAC name

IUPAC name methyldisulfanylethane

Molecular and structural information

Reference substance: isopropyl methyl disulphide

UUID ECB5-df9aa4e7-5225-4652-a16b-b2a2bf927bd1
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name isopropyl methyl disulphide

EC inventory

EC number 254-808-5 **CAS number** 40136-65-0
EC name isopropyl methyl disulphide
Molecular formula C4H10S2

Reference substance information

CAS information

CAS number 40136-65-0

IUPAC name

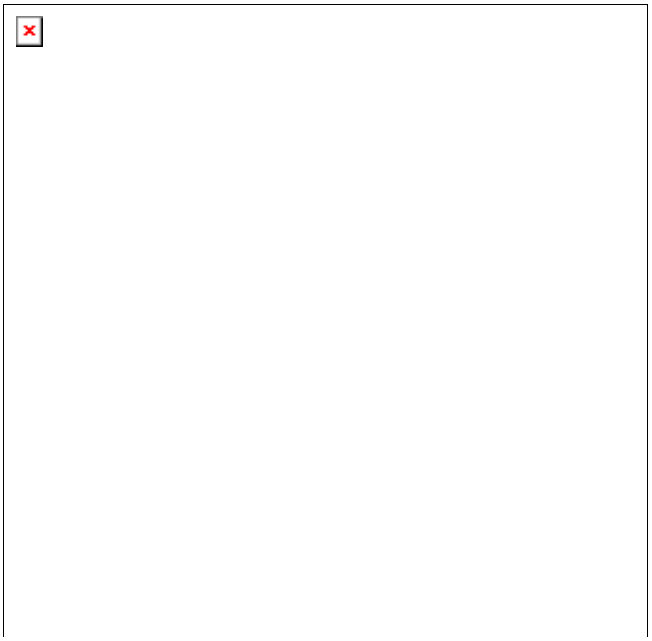
IUPAC name 2-(methyldisulfanyl)propane

Synonyms

Name Disulfide, methyl 1-methylethyl

Molecular and structural information

Molecular formula C4H10S2
Molecular weight range 122.2522
SMILES notation CSSC(C)C
InChI InChI=1/C4H10S2/c1-4(2)6-5-3/h4H,1-3H3
Structural formula



Reference substance: diethyl disulphide

UUID ECB5-6a0faffe-0e34-4d54-9b66-e3d3719f8c5d
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name diethyl disulphide

EC inventory

EC number 203-805-7 **CAS number** 110-81-6
EC name diethyl disulphide
Molecular formula C4H10S2

Reference substance information

CAS information

CAS number 110-81-6

IUPAC name

IUPAC name 1,1'-disulfanediyldiethane

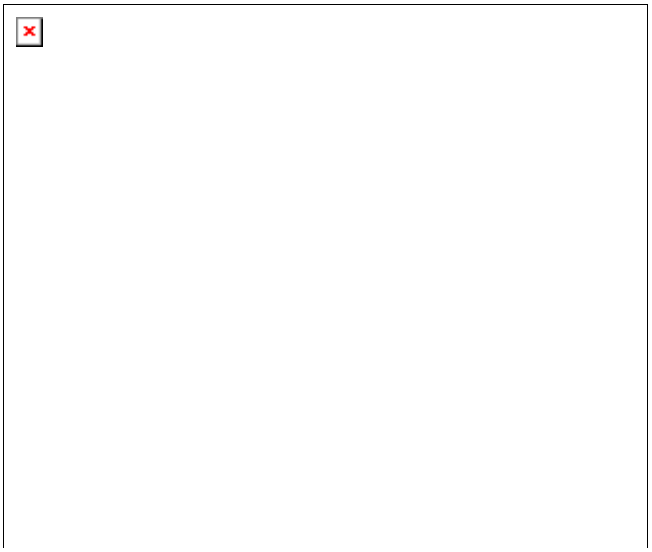
Synonyms

Name Disulfide, diethyl
Name Disulfide, diethyl

DSL Category: Organics

Molecular and structural information

Molecular formula C4H10S2
Molecular weight range 122.2522
SMILES notation CCSSCC
InChI InChI=1/C4H10S2/c1-3-5-6-4-2/h3-4H2,1-2H3
Structural formula



Reference substance: methyl propyl disulphide

UUID ECB5-7a7513ce-2d09-4236-bc86-997d2e91325a
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name methyl propyl disulphide

EC inventory

EC number 218-551-2 **CAS number** 2179-60-4
EC name methyl propyl disulphide
Molecular formula C4H10S2

Reference substance information

CAS information

CAS number 2179-60-4

IUPAC name

IUPAC name 1-(methyldisulfanyl)propane

Synonyms

Name Disulfide, methyl propyl
Name Disulfide, methyl propyl
Name Disulfide, methyl propyl

DSL Category: Organics

Molecular and structural information

Molecular formula C4H10S2
Molecular weight range 122.2522
SMILES notation CCCSSC
InChI InChI=1/C4H10S2/c1-3-4-6-5-2/h3-4H2,1-2H3
Structural formula

Reference substance: ethyl isopropyl disulphide

UUID IUC5-e0b3a767-308b-48ea-90c3-59268fe4df22
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-09-25 13:41:24 CEST
Remarks

General information

Reference substance name ethyl isopropyl disulphide

Reference substance information

CAS information

CAS number 53966-36-2

IUPAC name

IUPAC name 2-(ethyldisulfanyl)-propane

Molecular and structural information

Reference substance: ethyl n-propyl disulphide

UUID IUC5-4a2af2ef-9e2b-4acf-a8ff-72e6cfc98594
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-11-03 15:29:50 CET
Remarks

General information

Reference substance name ethyl n-propyl disulphide

Reference substance information

CAS information

CAS number 30453-31-7

IUPAC name

IUPAC name 1-(ethylsulfanyl)-propane

Molecular and structural information

Reference substance: diisopropyl disulphide

UUID IUC5-6768b0b0-0c19-4e74-8a5e-c8c2727d6811
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-09-25 13:38:39 CEST
Remarks

General information

Reference substance name diisopropyl disulphide

EC inventory

EC number 224-225-0 **CAS number** 4253-89-8
EC name diisopropyl sulphide
Molecular formula C6H14S2

Reference substance information

CAS information

CAS number 4253-89-8

IUPAC name

IUPAC name 2-propan-2-yldisulfanylpropane

Molecular and structural information

Reference substance: ethyl n-butyl sulphide

UUID IUC5-8d4a86ae-93cb-481f-b05d-fb5622842ba0
Dossier UUID 0
Author Chris3 / Bootman Chemical Safety Ltd 3 / Diss / United Kingdom
Date 2008-09-25 13:43:46 CEST
Remarks

General information

Reference substance name ethyl n-butyl sulphide

Reference substance information

CAS information

CAS number 63986-03-8

IUPAC name

IUPAC name 1-(ethylsulfanyl)butane

Molecular and structural information

Reference substance: dipropyl disulphide

UUID ECB5-a8709cff-7bc8-4ccd-9b4a-5f5ef6df0796
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name dipropyl disulphide

EC inventory

EC number 211-079-8 **CAS number** 629-19-6
EC name dipropyl disulphide
Molecular formula C6H14S2

Reference substance information

CAS information

CAS number 629-19-6

IUPAC name

IUPAC name 1,1'-disulfanediyldipropane

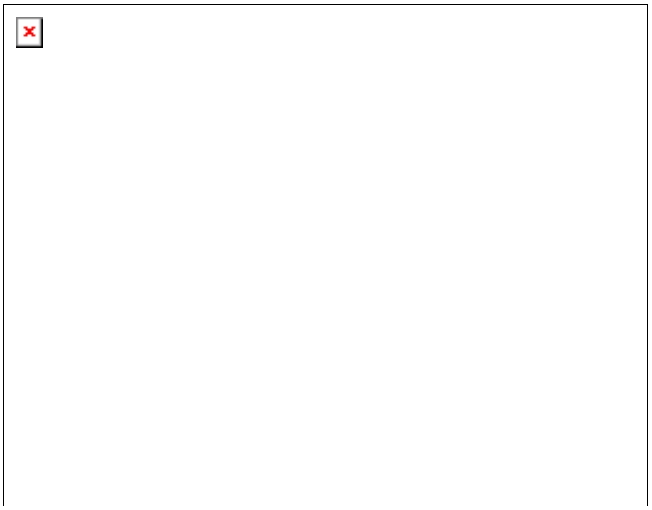
Synonyms

Name Disulfide, dipropyl
Name Disulfide, dipropyl
Name Disulfide, dipropyl

DSL Category: Organics

Molecular and structural information

Molecular formula C6H14S2
Molecular weight range 150.3054
SMILES notation CCCSSCCC
InChI InChI=1/C6H14S2/c1-3-5-7-8-6-4-2/h3-6H2,1-2H3
Structural formula



Reference substance: benzene

UUID ECB5-86bfd927-e2e9-46e6-bde9-ce721eca359b
Dossier UUID 0
Author European Commision/Joint Research Centre/European Chemicals Bureau
Date 2007-05-10 11:00:00 CEST
Remarks Created

General information

Reference substance name benzene

EC inventory

EC number 200-753-7 **CAS number** 71-43-2
EC name benzene
Molecular formula C6H6

Reference substance information

CAS information

CAS number 71-43-2

IUPAC name

IUPAC name benzene

Synonyms

Name Benzene
Name Benzene

DSL Category: Organics

Molecular and structural information

Molecular formula C6H6
Molecular weight range 78.1118
SMILES notation c1ccccc1
InChI InChI=1/C6H6/c1-2-4-6-5-3-1/h1-6H
Structural formula

Legal entity: Lyondell Chemie Nederland B.V.

UUID IUC5-a6de8fc0-4d1d-4406-849b-79d230119bb8
Dossier UUID 0
Author jrfowles / Lyondell Chemie Nederland B.V. / Rotterdam / Netherlands
Date 2008-11-10 14:40:13 CET
Remarks

General information

Legal entity name Lyondell Chemie Nederland B.V.
Legal entity type company

Identifiers

Legal entity identifiers

Identifier type DUNS
ID 405790762

Identifier type VAT
ID NL811582929B01

Other IT system identifiers

IT system LEO
ID 8789

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Country	Netherlands

Sites

Botlek
Maasvlakte