Data Evaluation Record on the hydrolysis of dimethyl disulfide

PMRA Submission Number {.....} EPA MRID Number 46903532

Data Requirement: PMRA Data Code:
EPA DP Barcode: D332939
OECD Data Point:
EPA Guideline: 161-1/835.2120

Test material:

Common name:	Dimethyl disulfide.
Chemical name:	
IUPAC name:	Dimethyl disulfide.
CAS name:	Not reported.
CAS No.:	624-92-0.
Synonyms:	Dimethyldisulfide; DMDS; 2,3-dithiabutane; methyl disulfide; (methyldithio)methane; (methyldisulfanyl)methane; methyldithion ethane.
Smiles string:	S(SC)C (EPI Suite, v3.12 SMILES String).

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Secondary Reviewer: Kathleen Ferguson
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Date: 5/14/10

Company Code:
Active Code:
Use Site Category:
EPA PC Code: 029088

CITATION: Fenn, L. 2006. Hydrolysis of dimethyl disulfide in aqueous media. Unpublished study performed, sponsored and submitted by Cerexagri, Inc., King of Prussia, Pennsylvania. Study No.: KP-2006-02. Experiment started February 13, 2006 and completed April 11, 2006 (p. 6). Final report issued July 14, 2006.

EXECUTIVE SUMMARY

The hydrolysis of [^{14}C]dimethyl disulfide (radiochemical purity 96.6%) was studied in aqueous buffered pH 4 (0.01M phthalate), pH 7 (0.01M phosphate) and pH 9 (0.01M borate) solutions at 50°C in the dark for 5 days. Concentrations at time 0 averaged at 14.97 mg/L (range 13.52-17.05 mg/L). The experiment was conducted in accordance with OPPTS 835.2110 and 835.2130 guidelines and in compliance with USEPA GLP standards (40 CFR 160). The test system consisted of amber HPLC vials (2 mL) that were completely filled with buffer solution, capped with septum-closed caps, treated through the cap, and then maintained in a water bath with agitation (80 shakes/minute). Volatiles were not trapped. Three vials of each buffer were collected for analysis after 0, 1, 2, 3, 4 and 5 days of incubation. Samples were analyzed without manipulation or modification for total [^{14}C] residues using LSC and for dimethyl disulfide using HPLC. [^{14}C]Dimethyl disulfide was identified by comparison to an unlabeled reference standard and quantified using a calibration curve. Transformation products were not addressed.

During the study, the temperature of the buffer solutions was 50 ± 0.1°C; supporting data were not provided. The pH ranges throughout the study were 4.039-4.069, 7.056-7.090 and 9.044-9.088. The sterility of test solutions was not reported.

Overall recoveries of of the [^{14}C] residues averaged 98.2 ± 4.3% of the applied (range 91.9-101.2%) from the pH 4 buffer solution, 102.1 ± 6.1% (range 96.8-111.6%) from the pH 7 buffer solution and 95.3 ± 6.2% (range 90.0-100.0%) from the pH 9 buffer solution. Recoveries were variable with standard deviations up to 11.5%, which the study author attributed to the treatment procedures.

[^{14}C]Dimethyl disulfide was stable in the pH 4 and pH 7 solutions, with final concentrations of 107.5% and 96.3% of the time 0 concentration, respectively, and a steadily increasing measured concentration between 3 and 5 days posttreatment. In pH 9 buffer solution, the concentrations of [^{14}C]dimethyl disulfide were extremely variable, averaging 91.2% of the time 0 concentration at 1 day posttreatment, 96.0% at 2 days, 89.4-90.1% at 3-4 days, and 92.7% at 5 days. Transformation products were not addressed; no peaks that might correspond to transformation products appear on the HPLC chromatograms provided by the study author (pH 4, 1 day posttreatment; pH 7, 4 days; pH 9, 3 days only).

A transformation pathway was not developed.

RESULTS SYNOPSIS:

pH	Half life (days)	Transformation products
pH 4	Stable, concentrations are increasing between 3 and 5 days.	None.
pH 7	Stable, concentrations are increasing between 3 and 5 days.	None.
pH 9	Stable, the concentration at 5 days is greater than that at 3 days.	None.

Study Acceptability: This study is classified as Supplemental. The study should be conducted for at least 30 days or one half-life per OPPTS Guidelines 835-2120. The measured concentrations of dimethyl disulfide and the total [^{14}C] recoveries were variable over time (standard deviations up to 11.5%), so that there was some uncertainty whether the observed changes in concentration at pH 9 were the result of sample variability or the dissipation of dimethyl disulfide. The study was conducted for 5 days at 50°C, and sterility was not confirmed.

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: This study was conducted in accordance with EPA guidelines OPPTS 835.2110 and 835.2130, OECD test guideline 111 (1981) and Annex V to Directive 67/548/EEC, testing method C.7 (pp. 1, 9, 20). Several deviations from the objectives of Subdivision N guidelines were noted:

> The measured concentrations of dimethyl disulfide and the total [^{14}C] recoveries were variable over time (sd up to 11.5%).
>
> The study was conducted for 5 days at 50°C.
>
> The sterility of the test solutions was not confirmed.

COMPLIANCE: This study was conducted in compliance with USEPA GLP standards (40 CFR 160; p. 3). Signed and dated Data Confidentiality, GLP, Quality Assurance and Certificate of Authenticity statements were provided (pp. 2-5).

A. MATERIALS

1. Test Material [^{14}C]Dimethyl disulfide (p. 9).

Chemical Structure: See DER Attachment 1.

Description: The test substance was dissolved in ethanol.

Purity: Radiochemical purity: 96.6% (Appendix VI, pp. 78-79).
Batch No.: 49520-1-4C.
Log No.: RL 12-1-1.
Analytical purity: 2.4% in ethanol (pp. 9, 11).
Specific activity: 2.667 mCi/mL (Appendix VI, pp. 78-79).
Location of the radiolabel: Labeled on both carbons of the molecule.

Storage conditions of test chemicals: Stored frozen at <0°C (p. 9; Appendix VI, pp. 78-79).

Physico-chemical properties of dimethyl disulfide:

Parameter	Value	Comment
Molecular weight (g/mol)	94.2 g/mol	
Chemical formula	$C_2H_6S_2$	
Water Solubility (mg/L)	2702	At 20°C.
Vapor Pressure	28.5 mm Hg	At 20°C.
UV Absorption	Not reported.	
pKa	Not reported.	
log K_{ow}	1.77	
Stability of compound at room temperature, if provided	Not reported.	

Log Kow obtained from p. 16 of MRID 46917014. Molecular weight, chemical formula, and solubility obtained from MRID 46903510. Vapor pressure obtained from MRID 46903506.

2. Buffer Solution: The following buffer solutions were prepared:

Table 1: Description of buffer solutions.

pH	Type and molarity of buffer	Composition
4	0.01M Phthalate	0.4 mL of 0.1N NaOH was mixed with 50 mL of 0.1M potassium biphthalate and diluted to 100 mL with water.
7	0.01M Phosphate	29.6 mL of 0.1N NaOH was mixed with 50 mL of 0.1M monopotassium phosphate and diluted to 100 mL with water.
9	0.01M Borate	21.3 mL of 0.1N NaOH was mixed with 50 mL of 0.1M boric acid in 0.1M potassium chloride and diluted to 100 mL with water.

Data obtained from pp. 9-10 of the study report.

B. EXPERIMENTAL CONDITIONS

1. Preliminary Study: No preliminary experiments were described.

2. Experimental conditions:

Table 2: Experimental parameters

Parameters		Details
Duration of study		5 days.
Test concentrations Nominal: Measured		 14.91 mg/L. 13.52-17.05 mg/L. [1]
No. of replications		Triplicate.
Preparation of test medium	Volume used/treatment	Samples were treated individually. 8 µL of the test solution was added by syringe through the septum cap to 2.04 mL of buffer solution. (p. 11)
	Method of sterilization	Glassware was sterilized by rinsing with acetone and drying for ≥2 hours in an oven (170°C).
	Co-solvent	Methanol, *ca.* 0.4% by volume.
Test apparatus (type/material/volume)		Sterilized amber HPLC vials (2 mL) were completely filled (no headspace remained) with buffer solution (2.04 mL) and sealed with a septum-closed cap. The buffer solutions were treated through the cap, then the vials were shaken by hand. The samples were placed in a beaker and the beaker was placed in a reciprocating water bath (80 shakes/minute) maintained at 50 ± 0.1°C. The water bath was covered with aluminium foil.
Details of traps for volatile, if any		Volatile traps were not used.
If no traps were used, is the test system closed/open?		Closed.
Is there any indication of the test material adsorbing to the walls of the test apparatus?		None.
Experimental conditions Temperature (°C): Lighting: pH ranges:		 50 ± 0.1°C. Dark. 4.039-4.069, 7.056-7.090 and 9.044-9.088.
Other details, if any		None.

Data were obtained from pp. 10-13, 19 and Tables 5- 8, pp. 21-24 of the study report.
1 Range of concentrations in time 0 samples (n = 9).

3. Supplementary Experiments: A supplementary experiment was performed to determine whether co-eluents or interference to the dimethyl sulfide peaks existed in the samples (p. 14). Aliquots of extra samples of each treated buffer were transferred by syringe to test tubes containing 1 mL hexane. The test tubes were capped, shaken and centrifuged. The sample was partitioned twice more with hexane (1 mL). The aqueous phase was analyzed by LSC. Hexane fractions were combined and analyzed by LSC and HPLC (p. 15).

4. Sampling:

Table 3: Sampling details.

Criteria	Details
Sampling intervals	0, 1, 2, 3, 4 and 5 days.
Sampling method	Three vials of each buffer solution were collected at each interval.
Method of collection of CO_2 and organic volatile compounds	Volatiles were not collected.
Sampling intervals/times for: pH measurement: Sterility check:	 At each sampling interval. Not reported.
Sample storage before analysis	Samples were analyzed at the time of collection.
Other observation, if any:	None.

Data were obtained from pp. 11-12 of the study report.

C. ANALYTICAL METHODS

Extraction/clean up/concentration methods: Samples were analyzed as collected, without manipulation or modification (p. 12).

Volatile residue determination: Volatiles were not trapped.

Total ^{14}C measurement: One (pH 7 and 9) or two (pH 4) aliquots (10 µL) from each sample were analyzed for total [^{14}C]residues using LSC (p. 12).

Derivatization method, if used: A derivatization method was not employed.

Identification and quantification of parent compound: The solutions (10 µL) were analyzed directly by HPLC under the following conditions: Mac-Mod HydroBond AQ (100 x 4.6 mm, 5 µm) column, an isocratic mobile phase of 0.1% formic acid in methanol:water (55:45, v:v), a run time of 10 minutes, a flow rate 0.75 mL/minute, run time 10 minutes, with radioactive flow detection (pp. 12-13). Dimethyl sulfide was quantified by comparing peak heights to a calibration curves generated using a nonlabeled dimethyl sulfide reference standard (purity 99.5%; p. 9; Table 2, p. 13; Appendix VI, p. 80).

Column recoveries ranged from 95-109% for the pH 4 buffer, 85-119% for the pH 7 buffer, and 82-123% for the pH 9 buffer solution (Tables 5-7, pp. 21-23).

Identification and quantification of transformation products: Transformation products were not addressed. No reference standards for transformation products were identified.

Detection limits (LOD, LOQ) for the parent compound: LOD and LOQ were not reported.

Detection limits (LOD, LOQ) for the transformation products: Transformation products were not addressed.

II. RESULTS AND DISCUSSION

A. TEST CONDITIONS: During the study, the temperature of the waterbath was maintained at 50 ± 0.1°C; the temperature reached 51.0°C on two occasions (Appendix I, p. 37). The pH ranges throughout the study were 4.039-4.069, 7.056-7.090 and 9.044-9.088 (Table 8, p. 24). The sterility of test solutions was not reported.

B. MASS BALANCE: Overall recoveries of [^{14}C]residues averaged 98.2 ± 4.3% of the average time 0 concentration (range 91.9-101.2%) from the pH 4 buffer solution, 102.1 ± 6.1% (range 96.8-111.6%) from the pH 7 buffer solution and 95.3 ± 6.2% (range 90.0-100.0%) from the pH 9 buffer solution (Tables 5-7, pp. 21-23). Recoveries were variable with standard deviations up to 11.5%, which the study author attributed to the treatment procedures (individual samples were treated, p. 19).

Table 4a: Hydrolysis of dimethyl disulfide, expressed as percentage of the recovered or applied radioactivity (mean ± s.d., n = 3), at pH 4.

Compound	Sampling times (days)					
	0	1	2	3	4	5
% of dimethyl disulfide at time 0						
Dimethyl disulfide	100.0 ± 9.3	102.6 ± 9.6	105.6 ± 10.7	102.5 ± 2.9	106.5 ± 4.1	107.5 ± 4.2
Transformation product	Transformation products were not addressed.					
% of [^{14}C]residues at time 0						
CO_2	Volatiles were not collected.					
Volatile organics	Volatiles were not collected.					
Total Recovery	100.0 ± 3.0	97.7 ± 3.3	100.1 ± 3.9	98.4 ± 4.9	101.2 ± 4.0	91.9 ± 1.1

Means and standard deviations calculated by the reviewer using data obtained from Table 5, p. 21 the study report. Concentrations of dimethyl disulfide and total [^{14}C]residues were not converted to percent of applied because there appears to have been some problem with the application procedures. Also, the concentrations of dimethyl disulfide was determined independent of the concentration of total [^{14}C]residues.

Table 4b: Hydrolysis of dimethyl disulfide, expressed as percentage of the recovered or applied radioactivity (mean ± s.d., n = 3), at pH 7.

Compound	Sampling times (days)					
	0	1	2	3	4	5
% of dimethyl disulfide at time 0						
Dimethyl disulfide	100.0 ± 7.7	97.8 ± 5.0	96.5 ± 6.6	88.3 ± 2.2	93.9 ± 9.0	96.3 ± 2.8
Transformation product	Transformation products were not addressed.					
% of [^{14}C]residues at time 0						
CO_2	Volatiles were not collected.					
Volatile organics	Volatiles were not collected.					
Total Recovery	100.0 ± 6.1	104.1 ± 1.5	97.3 ± 1.4	96.8 ± 0.5	102.9 ± 6.0	111.6 ± 4.0

Means and standard deviations calculated by the reviewer using data obtained from Table 6, p. 22 the study report. Concentrations of dimethyl disulfide and total [^{14}C]residues were not converted to percent of applied because there appears to have been some problem with the application procedures. Also, the concentrations of dimethyl disulfide was determined independent of the concentration of total [^{14}C]residues.

Table 4c: Hydrolysis of dimethyl disulfide, expressed as percentage of the recovered or applied radioactivity (mean ± s.d., n = 3), at pH 9.

Compound	Sampling times (days)					
	0	1	2	3	4	5
% of dimethyl disulfide at time 0						
Dimethyl disulfide	100.0 ± 7.4	91.2 ± 7.4	96.0 ± 4.3	90.1 ± 3.0	89.4 ± 9.5	92.7 ± 9.5
Transformation product	Transformation products were not addressed.					
% of [^{14}C]residues at time 0						
CO_2	Volatiles were not collected.					
Volatile organics	Volatiles were not collected.					
Total Recovery	100.0 ± 4.0	95.9 ± 1.6	99.3 ± 11.5	94.4 ± 3.3	90.0 ± 1.7	92.3 ± 7.1

Means and standard deviations calculated by the reviewer using data obtained from Table 7, p. 23 the study report. Concentrations of dimethyl disulfide and total [^{14}C]residues were not converted to percent of applied because there appears to have been some problem with the application procedures. Also, the concentrations of dimethyl disulfide was determined independent of the concentration of total [^{14}C]residues.

C. TRANSFORMATION OF PARENT COMPOUND: Concentrations of [^{14}C]dimethyl disulfide were variable over time at all pHs, with standard deviations up to 10.7%[^{14}C]Dimethyl disulfide appeared to be stable in the pH 4 and pH 7 solutions, with final concentrations of 107.5% and 96.3% of the time 0 concentration, respectively, and a steadily increasing measured concentration between 3 and 5 days posttreatment. In pH 9 buffer solution, [^{14}C]dimethyl disulfide

averaged 91.2% of the time 0 concentration at 1 day posttreatment, 96.0% at 2 days, 89.4-90.1% at 3-4 days, and 92.7% at 5 days.

HALF-LIVES/DT50/DT90: Dimethyl disulfide was stable in the pH 4 and pH 7 buffer solutions (Tables 5-6, pp. 21-22).

Dimethyl disulfide is probably stable in the pH 9 solution, since the average concentration at 5 days posttreatment is greater than at 1, 3, and 4 days posttreatment (Table 7, p. 23).

The study author concluded that dimethyl disulfide was stable to hydrolysis in all buffer solutions and did not attempt to calculate half-lives (pp. 19-20; Figure 1, p. 25).

Half-lives/DT50/DT90

pH	First order linear			DT50	DT90
	Half-life (days)[1]	Regression equation	r^2		
4	Stable, concentrations are increasing between 3 and 5 days.			--	--
7	Stable, concentrations are increasing between 3 and 5 days.			--	--
9	Stable, the concentration at 5 days is greater than that at 3 days.[1]			--	--

1 Refer to Reviewer's Comment.

TRANSFORMATION PRODUCTS: Transformation products were not addressed. HPLC chromatograms (pH 4, 1 day posttreatment; pH 7, 4 days; pH 9, 3 days) give no evidence of any compound other than dimethyl disulfide and a contaminant of the test substance in the test solutions (Appendix II, pp. 44-45; Appendix III, pp. 52-53; Appendix IV, pp. 61-62). Chromatograms for 5 days posttreatment (study termination) were not provided.

Table 5: Chemical names and CAS numbers for the transformation products of dimethyl disulfide.

Applicants Code Name	CAS Number	Chemical Name	Chemical Formula	MW (g/mol)	Smiles String
Transformation products were not addressed.					

VOLATILIZATION: Volatiles were not collected.

TRANSFORMATION PATHWAY: Since dimethyl disulfide was relatively stable to hydrolysis over the duration of the study, a transformation pathway could not be developed.

D. SUPPLEMENTARY EXPERIMENT-RESULTS: No co-elutant or interference peaks were observed at or near the dimethyl disulfide retention time (p. 19; Appendix V, pp. 69-73).

III. STUDY DEFICIENCIES

1. The measured concentrations of dimethyl disulfide and the total [^{14}C]recoveries were variable over time (standard deviations up to 11.5%), so that there was some uncertainty whether the observed decreases in concentration were the result of sample variability or the dissipation of dimethyl disulfide (Tables 5- 8, pp. 21-24 of the study report). For example, in the pH 9 buffer solution, total [^{14}C]residues were 36,019-38,930 dpm in triplicate samples at time 0, 34,817-42,475 dpm at 2 days posttreatment, and 31,898-37,178 dpm at 4-5 days (Table 7, p. 23). The study author attributed the variability to the fortification of each test vial rather than bulk solutions (p. 19).

   The study author provided considerable amounts of raw data, but did not provide HPLC chromatograms for the 5 day posttreatment samples to conclusively demonstrate that dimethyl disulfide was the only [^{14}C]compound in solution. HPLC chromatograms are provided for pH 4, 1 day posttreatment (Appendix II, pp. 44-45); pH 7, 4 days (Appendix III, pp. 52-53), and pH 9, 3 days (Appendix IV, pp. 61-62). Only two peaks are present on these chromatograms. Dimethyl disulfide is >95%, a second peak (Rt *ca.* 3.6 minutes) is also present on chromatograms of the reference standard and is considered to be a contaminant of the test substance.

2. The study was conducted for 5 days at 50°C. OPPTS and OECD guidelines would not require that a study be conducted at 25°C since <10% of the applied dissipated during the 5 days of incubation.

3. It was not specified that the buffer solutions were sterile, and the sterility of the test solutions during the study was apparently not determined. It was assumed that the solutions were intended to be sterile since the glassware used in the study was sterilized before use (p. 10). Growth of most common microorganisms would be deterred at 50°C.

IV. REVIEWER'S COMMENTS

1. The study author reported that the samples were treated at 14.91 ppm (p. 19). In fact, the time 0 concentrations ranged from 13.52-17.05 ppm (14.97 ± 1.10 ppm; Tables 5-7, pp. 21-23).

2. The chemical purity of the test substance was reported to be 2.4% in ethyl alcohol (p. 9). The study author did not report what other compound(s) was mixed with the radiolabeled dimethyl disulfide. The radiochemical purity of the test substance was 96.6%, and no significant peaks other than dimethyl disulfide were seen on the radiochromatograms.

3. In Tables 5-7 (pp. 21-23), the study author presents the total residue recoveries in terms of dpm and total average recovery of total residues at time 0 and the dimethyl disulfide concentrations in terms of ppm and total average recovery of dimethyl disulfide at time 0. Because the concentrations of total radioactivity were highly variable, the reviewer did not attempt to

convert the concentrations of dimethyl disulfide to percent of applied. Also, it appeared that the concentrations of dimethyl disulfide were determined independent of total recoveries.

4. Raw data were provided with the study. The chromatograms and other printout are often provided without explanation, so it is not clear what the data represent. The study author apparently did not provide chromatograms for the final sampling interval, which would have supported the conclusion that the test substance was stable to relatively stable during the study.

5. On the chromatograms for the test substance, reference standard, and samples, a small peak appears at about 3 minutes. It appears likely that this is contaminant in the test substance. The study author does not mention this peak.

V. REFERENCES

1. U.S. Environmental Protection Agency. 1982. Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 161-1. Hydrolysis studies. Office of Pesticide and Toxic Substances, Washington, DC. EPA 540/9-82-021.

2. U.S. Environmental Protection Agency. 1989. FIFRA Accelerated Reregistration, Phase 3 Technical Guidance. Office of the Prevention, Pesticides, and Toxic Substances, Washington, DC. EPA 540/09-90-078.

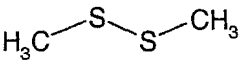
3. U.S. Environmental Protection Agency. 1993. Pesticide Registration Rejection Rate Analysis - Environmental Fate. Office of the Prevention, Pesticides, and Toxic Substances, Washington, DC. EPA 738-R-93-010.

Attachment 1: Structures of Parent Compound and Transformation Products

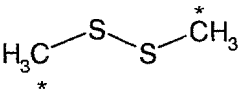
Dimethyl disulfide [dimethyldisulfide; DMDS; 2,3-dithiabutane; methyl disulfide; (methyldithio)methane; (methyldisulfanyl)methane; methyldithion ethane]

IUPAC Name: Dimethyl disulfide.
CAS Name: Not reported.
CAS Number: 624-92-0
SMILES String: S(SC)C (EPI Suite, v3.12 SMILES String).

Unlabeled



[^{14}C]dimethyl disulfide



* = Location of the radiolabel.

Identified Compounds

Dimethyl disulfide [dimethyldisulfide; DMDS; 2,3-dithiabutane; methyl disulfide; (methyldithio)methane; (methyldisulfanyl)methane; methyldithion ethane]

IUPAC Name: Dimethyl disulfide.
CAS Name: Not reported.
CAS Number: 624-92-0
SMILES String: S(SC)C (EPI Suite, v3.12 SMILES String).