MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Dimethyl Disulfide (CAS# 624-92-0)

FROM: Keisha Williams, Air Quality Division

DATE: November 20, 2015

SUBJECT: Screening Level Update for Dimethyl Disulfide (DMDS)

The initial threshold screening level (ITSL) for chronic exposure to dimethyl disulfide (DMDS) is 16 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1232 (1) (a). The ITSL for acute exposure is 1200 µg/m^3 (24 hour averaging time) based on Rules 336.1229 (2) (b).

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online, National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Aggregated Computational Toxicology Resource (ACToR) Database, EPA TSCATS database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Chemical Safety Program Protective Action Criteria, Texas Commission on Environmental Quality Effects Screening Levels, and European Chemicals Agency Registered Substances Dossiers.

Background Information

DMDS (Figure 1) has been used as a pesticide/fumigant, as a food additive, in chemical manufacturing and as a solvent (USEPA, 2010; USFDA, 21 CFR §172.515). DMDS is also commonly found in food and as a byproduct of industrial processing of paper and sewage treatment (AGCIH, 2007).

DMDS, an organic sulfide, is a volatile organic compound and is also often grouped under total reduced sulfur compounds emitted from a source. Chemical properties are listed in Table 1 and health benchmark values are listed in Table 2.

Figure 1. Chemical structure for DMDS

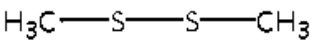

Table 1. Chemical and physical properties of DMDS

Molecular weight: 94.19904 grams/mole
Melting point: -85 °C
Boiling point: 110 °C
Vapor pressure: 28.7 mmHg at 25°C
Physical state: liquid
Color: Colorless to yellow
Odor: Garlic-like, disagreeable (ACGIH, 2007)
Odor threshold: 0.026-5.6 ppb (ACGIH, 2007)

Reference: National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/compound/12232

Very little information is available on DMDS toxicity in humans, and no information was found that describes toxicity induced by DMDS alone. Some epidemiological studies have explored toxicity associated with sulfide mixtures that include DMDS. Occupational exposure to these mixtures has been associated with cardiovascular, respiratory and neurotoxic effects (Partti-Pellinen et al, 1996; ACGIH, 2007). Since reports of DMDS-specific effects in humans are not available at this time, *in vivo* data is the next best resource for derivation of a screening level.

Table 2. Health benchmark values for DMDS

Agency	Benchmark Value
American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold Limit Value (TLV): 2.0 mg/m^3 (ACGIH, 2007) NOTE: DMDS was also identified as a dermal toxicant
American Industrial Hygiene Association (AIHA)	Emergency Response Planning Guideline (ERPG)-1: 0.01 ppm (≈0.039 mg/m^3) ERPG-2: 50 ppm (≈190 mg/m^3) ERPG-3: 250 ppm (≈960 mg/m^3) (AIHA, 2014)
US Department of Energy (DOE) Chemical Safety Program (Values are based on ERPGs)	Protective Action Criteria (PAC)-1: 0.039 mg/m^3 PAC-2: 190 mg/m^3 PAC-3: 960 mg/m^3 (DOE)
Texas Commission on Environmental Quality (TCEQ)	Effect screening level (ESL) for long-term exposure: 2 µg/m^3 ESL for short-term exposure: 20 µg/m^3 (TCEQ, 2015)

Evaluation of Cancer Risk

There are no *in vivo* studies, and very little available data to evaluate the carcinogenicity of DMDS. The National Toxicology Program has performed genetic toxicity testing *in vitro*, and these results show DMDS to be negative for causing genetic toxicity (NTP). Because of the lack of information on DMDS-induced carcinogenicity, DMDS will not be regulated as a carcinogen at this time.

Review of Relevant Studies for Non-carcinogenic Effects

Study formerly used to derive the ITSL

The former ITSL (MDNR, 1993; see attached) was based on a 20 day inhalation study in rats (N=4) (Gage, 1970). A no observable adverse effect level (NOAEL) was observed at 100 ppm (approximately 385 mg/m^3), while critical effects of "lethargy, respiratory difficulty, low wt. gain and …congestion of organs" were seen at the 250 ppm dose. Using Rule 336.1232 (1) (d), as shown in Equation 1, the former ITSL was calculated as follows:

Equation 1.

$$Former\ ITSL = \frac{NOAEL}{35\ x\ 100} x \frac{hours\ exposed\ per\ day}{24\ hours\ per\ day}$$

$$Former\ ITSL = \frac{385 \frac{mg}{m^3}}{35\ x\ 100} x \frac{6\ hours}{24\ hours} = 0.0275\ \frac{mg}{m^3}$$

$$Former\ ITSL = 0.0275\ \frac{mg}{m^3} x\ 1000 \frac{\mu g}{mg} = 27.5 \frac{\mu g}{m^3} \approx 28\ \frac{\mu g}{m^3}, annual\ averaging\ time$$

Since the original derivation of the former ITSL, a number of studies have been performed to evaluate the health effects of DMDS. As summarized by the California Environmental Protection Agency (CalEPA) and the United States Environmental Protection Agency (USEPA), and the European Chemical Agency (ECHA), a range of effects have been studied including reproductive toxicity, teratology, DNA damage and neurotoxicity (CalEPA, 2013; ECHA, 2015; USEPA, 2010)[1]. A NOAEL from various studies was repeatedly identified at 5 ppm (approximately 19.3 mg/m^3) as shown in Table 3. Since this NOAEL and the LOAEL are lower than the NOAEL (385 mg/m^3) used to derive the former ITSL, the chronic ITSL is being updated at this time.

[1] AQD did not obtain the original studies from ATOCHEM or WIL research that were summarized by CalEPA (2013), ECHA (2015) and USEPA (2010). The summaries are presented by reputable agencies, and were determined to be of sufficient detail for evaluation by AQD.

Table 3. Studies where NOAEL was identified at 19 mg/m^3

Animal & Exposure Description	Critical Effect(s)
Female rats (N=25-30) 0, 19, 57, 190 mg/m^3 for 6hrs/day for 7 days/wk for 9 days of gestation	"Lower mean body weights" in female rats NOTE: Developmental toxicity was also evaluated and decreased fetal body weights were observed, but this effect was not found to be the critical effect *ATOCHEM, 1991*
Female and male rats (N=12) 0, 19, 190, 570 mg/m^3 for 6hrs/day for 7 days/wk for up to 72 days in dams Female and male rat pups (N=12, where 1 of each sex was taken from each litter) 0, 19, 190, 570 mg/m^3 for 6hrs/day for 7 days/wk from postnatal days 28 through 34	Decreased body weight and body weight gains in both sexes of rat pups in the F1 generation Decreased "body weight gain and food consumption" in the adult male rats
Female and male rats(N=30/sex/group) 0, 19, 76, and 304 mg/m^3 for 6hrs/day, 7 days/wk for 2 generations	In parental generations, lower "body weights and food consumption noted for both sexes" NOTE: No dose-response related adverse developmental effects, including effects on pup body weight, were observed
(Concurrently run w/ 2 gen. study) Female rats (N=12) 0, 19, 76, and 304 mg/m^3 for 6 hrs/day for 7 or 14 days during different lactation stages	"Lower body weight gain" NOTE: No adverse developmental effects, specifically pup body weight effects, were observed
Female rats (N=27) 0, 19, 76, and 304 mg/m^3 for 6hrs/day for 7 days/wk for 14 days	"Lower mean body weight gain and food consumption" especially during the beginning and middle of the exposure period. NOTE: Developmental toxicity was also evaluated and decreased fetal body weights were observed, but was not found to be the critical effect
Female and male rats (N=12/sex/grp) 0, 19, 76, and 304 mg/m^3 for 6hrs/day for 7 days/wk for 13 weeks	"Degeneration of the olfactory epithelium in the nasal turbinates of both sexes" *Nemec, 2006a; Nemec, 2006b; Nemec, 2006c; Nemec, 2007; ECHA 2015*[2]
Female and male rats (N=10/sex/grp) 0, 19, 95, 475 mg/m^3 for 6hrs/day for 5 days/wk for 13 weeks	Decreased body weights in males, and decreased AST and BUN in both sexes *Kim et al., 2006*

Key study for chronic ITSL derivation

A subchronic inhalation study was performed using Crl: CD (SD) rats to investigate DMDS-induced neurotoxicity along with other measures of toxicity (Nemec, 2006a). This is an unpublished study and only summaries of it were obtained by AQD (as noted in Footnote 1). However, the study was evaluated, and deemed acceptable and reliable by both the USEPA and ECHA (ECHA, 2015; USEPA, 2010).

[2] For the female and male rat, and female and male pup study, a citation of the original study was not included with the summary in ECHA

Groups of rats (N=12 per sex per group) were exposed to 0, 5, 20 or 80 ppm DMDS for 6 hours/day, 7 days/week for 13 weeks. Several endpoints were measured including mortality, mean body weight, body weight gain, food consumption, change in ambulatory activity, motor activity, brain length, brain weight and histologic analysis of nervous tissue and the upper respiratory tract. While neurotoxicity effects were not observed, portal of entry (POE) effects were observed at the 20 ppm exposure concentration, where "microscopic examination of the nasal turbinates revealed degeneration of olfactory epithelium in both sexes" (CalEPA, 2013). In the USEPA summary, these effects were more specifically identified to occur at levels II thru IV (USEPA, 2010). In the CalEPA review, it was noted that these histopathological changes were observed "in an exposure-related manner". The NOAEL was taken as 5 ppm, and using USEPA guidance (2002, 2012) a reference concentration (RfC) value can be calculated as follows:

$$Chronic\ ITSL = RfC = \frac{NOAEL_{HEC}}{UFs}$$

-HEC is the human equivalent concentration
-UFs are uncertainty factors

$$NOAEL_{HEC} = NOAEL_{ADJ}\ x\ dosimetric\ adjustment\ factor$$

$$NOAEL_{ADJ} = NOAEL_{rat}\ x\ time\ adustment\ factor$$

-$NOAEL_{rat}$ is 5 ppm, the NOAEL observed in the rat study

$$NOAEL_{rat}\frac{\mu g}{m^3} = ppm\ x\ \frac{molecular\ weight}{24.45}$$

$$NOAEL_{rat}\frac{\mu g}{m^3} = 5\ ppm\ x\ \frac{94.2\frac{grams}{mole}}{24.45} x \frac{\frac{10^3 \mu g}{m^3}}{\frac{1\ mg}{m^3}} = 19,264\frac{\mu g}{m^3} \approx 19,300\ \frac{\mu g}{m^3}$$

$$NOAEL_{ADJ} = \frac{19{,}300\ \mu g}{m^3}\ x \frac{6\ hrs}{24hrs} = \frac{4{,}825\ \mu g}{m^3} \approx 4,800\ \frac{\mu g}{m^3}$$

-DMDS is considered a category 1 gas with portal of entry effects, so the dosimetric adjustment factor is the default value of 1

$$NOAEL_{HEC} = NOAEL_{ADJ}\ x\ dosimetric\ adjustment\ factor$$

$$NOAEL_{HEC} = \frac{4{,}800\ \mu g}{m^3}\ x\ 1 = 4,800\ \frac{\mu g}{m^3}$$

-A UF of 10 is used to extrapolate from the subchronic exposure to a chronic exposure
-A UF of 10 is used for intraspecies extrapolation
-A UF of 3 is used for interspecies extrapolation

$$RfC = \frac{NOAEL_{HEC}}{UFs}$$

$$RfC = \frac{\frac{4{,}800\ \mu g}{m^3}}{10x10x3} = 16\frac{\mu g}{m^3}, annual\ averaging\ time$$

Comparable results have been observed in a couple of other studies. Another unpublished study that was also summarized by both the USEPA and CalEPA showed the occurrence of POE effects (CalEPA, 2010; USEPA, 2013). The research group observed "squamous cell metaplasia…in the nasal cavity of both sexes" of rats at the 10 ppm exposure concentration, the lowest concentration given in that study (CalEPA, 2013). Furthermore, "atrophy and microcavitation of the olfactory epithelium" was observed at the 50 and 250 ppm exposure concentrations. Since a NOAEL was not identified in this study, it was deemed less appropriate for ITSL derivation.

A 2006 study investigated the toxic effects of DMDS in male and female Fischer 344 rats (N=10 per sex) after 6 hrs/day, 5 days/wk for 13 weeks at 0, 5, 25, or 125 ppm DMDS (19300, 96500, or 482500 µg/m^3, respectively) (Kim et al, 2006). Several endpoints were measured including mortality, clinical signs of toxicity, changes in body weight, changes in organ weights, histologic changes, changes in food consumption, hematologic changes, and changes in blood chemistry. Statistical analyses included comparisons of the DMDS groups to the control group, where statistical significance was considered $p < 0.05$. The lowest observable adverse effect level (LOAEL) was shown to be 25 ppm where mean body weights in males were significantly decreased, ALT was significantly decreased in male rats, and AST and BUN were significantly decreased in both male and female rats as compared to controls. Except for the ALT decrease, all of these changes exhibited a dose-dependent response. Statistically significant increases in both RBC concentrations and HCT% in male rats was observed at the 5 ppm exposure concentration. However, the authors noted that these values "were within historical control range for the rat strain" and were not considered "treatment-related effects." Significant histologic differences in the nasal cavity were not observed. While POE effects were not seen in this study, the NOAEL of 5ppm is the same as described above.

<u>Key study for acute ITSL derivation</u>

POE effects were observed acutely in 2 independent studies as seen in Table 4. The most notable is a 24 hour inhalation study performed in male Sprague-Dawley rats (N=10). This is an unpublished study, but it has been summarized by a number of regulatory agencies (USEPA, 2010; CalEPA, 2013; ECHA, 2015). Unlike the summaries for the 13-week, rat study (Nemec, 2006a) used to derive the chronic ITSL where all the agencies identified the same critical effect and corresponding response level, the 3 different agencies surmised 3 different NOAEL values for the 24 hour, rat study (USEPA, 2010; CalEPA, 2013; ECHA, 2015). As a result, a two-tailed, Student's t-test was utilized to evaluate exposure differences compared to controls since the European Chemical Agency (ECHA) summary provided tables of the results data on the degeneration of the olfactory epithelium, and inflammation of the olfactory and respiratory epithelium (Table 5). While both ECHA staff and the study authors indicate that the NOAEL is 12.5 ppm based on "degeneration of the olfactory epithelium", statistical analysis (via the Student's t-test) of the olfactory epithelium degeneration in nasal level V shows that there is a significant DMDS-induced effect at the 12.5 ppm exposure concentration ($p=0.001735$). Although these effects were observed to be minimal and reversible, they are still statistically different than the control group, and increase in incidence and severity with increasing exposure. As a result, the NOAEL will be taken to be 9 ppm, similar to what is suggested by USEPA (2010).

Table 4. Studies that show POE effects after acute exposure to DMDS

Animal & Exposure	Portal of Entry Results
Study#1: Male rats (N=10) 0, 5, 9, 12.5 and 18 ppm for 24hrs	"Epithelial cell degeneration in the nasal turbinates" *Kirkpatrick, 2009*
Study#2a: Female and male rats (N=10) 0, 50, 150, 300 and 600 ppm for 6hrs	"Acute inflammation, degeneration, and hyperplasia in nasal tissues in both sexes" *Kirkpatrick, 2008*
Study#2b: Female and male rats (N=10) 0, 50, 150, 300 and 600 ppm for 6hrs/day for 5 days	Increased lung weights, histological changes in nasal epithelium *Kirkpatrick, 2008*

Table 5. Histolopathological Results from Nasal Cavity (Modified from table in ECHA, 2015)

Incidences of Degeneration of Olfactory Epithelium					
Target Exposure Level (ppm):	0	5	9	12.5	18
Olfactory epithelium, degeneration					
Nasal Level II_a	10	10	10	10	10
Total incidence	0	0	0	2	5
Minimal	-	-	-	2	2
Mild	-	-	-	0	2
Moderate	-	-	-	0	1
Nasal Level III_a	10	10	10	10	10
Total incidence	1	0	2	2	10
Minimal	1	-	2	2	5
Mild	0	-	0	0	2
Moderate	0	-	0	0	3
Nasal Level IV_a	10	10	10	10	10
Total incidence	1	0	2	5	10
Minimal	1	-	2	5	3
Mild	0	-	0	0	7
Nasal Level V_a	**10**	**10**	**10**	**10**	**10**
Total incidence	**0**	**0**	**2**	**6**	**10**
Minimal	**-**	**-**	**2**	**6**	**9**
Mild	**-**	**-**	**0**	**0**	**1**

Table 5. continued

Incidences of Degeneration of Olfactory Epithelium					
Target Exposure Level (ppm):	0	5	9	12.5	18
Nasal Level VI_a	10	10	10	10	10
Total incidence	0	0	0	3	4
Minimal	-	-	-	3	3
Mild	-	-	-	0	1
Number of Nasal Levels with Degeneration of Olfactory Epithelium					
Target Exposure Level (ppm):	0	5	9	12.5	18
Olfactory epithelium, degeneration$_b$	2	0	4	6	10
One level	2	0	3	1	0
Two levels	0	0	0	1	0
Three levels	0	0	1	2	2
Four levels	0	0	0	1	7
Five levels	0	0	0	1	1
Incidences of Inflammation of Olfactory and Respiratory Epithelia in Selected Nasal Levels					
Target Exposure Level (ppm):	0	5	9	12.5	18
Nasal Level II_a	10	10	10	10	10
Olfactory epithelium, inflammation, minimal	0	0	0	0	1
Respiratory epithelium, inflammation, minimal	1	0	0	0	0
Nasal level III_a	10	10	10	10	10
Olfactory epithelium, inflammation, minimal	0	0	0	2	4
Respiratory epithelium, inflammation, minimal	1	1	1	1	4
Nasal level IV_a	10	10	10	10	10
Olfactory epithelium, inflammation, minimal	2	0	3	3	5
Respiratory epithelium, inflammation, minimal	0	1	1	2	3
Nasal level V_a	10	10	10	10	10
Olfactory epithelium, inflammation, minimal	1	0	0	0	3
Respiratory epithelium, inflammation, minimal	1	1	0	0	6
Nasal level VI_a	10	10	10	10	10
Olfactory epithelium, inflammation, minimal	0	0	1	0	1
Respiratory epithelium, inflammation, minimal	0	0	1	0	0

a, Number of tissues examined from each group; b, Number with olfactory epithelial degeneration in at least 1 nasal level

Based off of the NOAEL identified in this study, an acute ITSL could be derived as follows:

$$acute\ ITSL = \frac{NOAEL_{HEC}}{UFs}$$

$$NOAEL_{HEC} = NOAEL_{ADJ}\ x\ dosimetric\ adjustment\ factor$$

-DMDS is considered a category 1 gas with portal of entry effects, so the dosimetric adjustment factor is the default value of 1

$$NOAEL_{ADJ} = NOAEL_{rat}\ x\ time\ adustment\ factor$$

-Since this is a 24 hour exposure study, a time adjustment factor is not needed

-$NOAEL_{rat}$ is 9 ppm, the NOAEL observed in the rat study

$$NOAEL_{rat}\frac{\mu g}{m^3} = ppm\ x\ \frac{molecular\ weight}{24.45}$$

$$NOAEL_{rat}\frac{\mu g}{m^3} = 9\ ppm\ x\ \frac{94.2\frac{grams}{mole}}{24.45} x \frac{\frac{10^3 \mu g}{m^3}}{\frac{1\ mg}{m^3}} = 34{,}675\frac{\mu g}{m^3} \approx 34{,}700\ \frac{\mu g}{m^3}$$

$$NOAEL_{HEC} = \frac{34,700\ \mu g}{m^3}\ x\ 1 = 34,700\ \frac{\mu g}{m^3}$$

$$Acute\ ITSL = \frac{NOAEL_{HEC}}{UFs}$$

$$RfC = \frac{\frac{34,700\ \mu g}{m^3}}{10x3} = 1,157\frac{\mu g}{m^3} \approx 1{,}200\ \frac{\mu g}{m^3}, 24\ hour\ averaging\ time$$

-An uncertainty factor of 10 is used for intraspecies extrapolation
-An uncertainty factor of 3 is used for interspecies extrapolation

<u>Other considerations for acute ITSL derivation</u>
The TLV for dimethyl disulfide is based on two, 90-day rodent studies (ACGIH, 2007). Furthermore, the TCEQ As a result, the 24 hour rodent study described above was deemed more appropriate for the acute ITSL derivation.

One of the five developmental studies described in Table 3 showed decreased pup weights for both female and male rats after 190 mg/m^3 exposure for 6hrs/day for 7 days. This study was preliminary in the larger project undertaken by the WIL research group, and used a large exposure range with a relatively small number of exposure groups. As a result, the LOAEL was observed at 190 mg/m^3 whereas the NOAEL was tenfold smaller at 19 mg/m^3. This effect was not seen in this research group's subsequent, larger 2 generation study where no observable adverse effects were seen in age-matched female and male pups exposed to 19, 76 or 304

mg/m^3. Because the decreased body weights seen with the 7-day exposure in 28 day to 35 day pups could not be reproduced in the other 4 developmental studies which covered more developmental life stages, decreased pup weight was not used as a critical effect for acute ITSL derivation.

The chronic ITSL for DMDS is 16 µg/m^3, annual averaging time, and the acute ITSL is 1200 µg/m^3, 24 hour averaging time.

References

ACGIH. 2007. Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

AIHA. 2014. ERPG/WEEL Handbook: Current ERPG Values (2014). Accessed August 25, 2015. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2014%20ERPG%20Values.pdf

ATOCHEM. 1991. Dimethyl Disulfide (DMDS): Inhalation Teratology Study in the Rat, Hazleton UK, Report 6205-514/9. (as cited in ECHA, 2015).

CalEPA. 2013. Summary of Toxicology Data: Dimethyl Disulfide. California Environmental Protection Agency, Department of Pesticide Regulation, Medical Toxicology Branch. Accessed August 25, 2015. http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/5899.pdf

ECHA. 2015. Registered Substances: Full, joint submission for dimethyl disulphide. Accessed October 29, 2015. http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d679bc-1d9a-560e-e044-00144f67d031/DISS-97d679bc-1d9a-560e-e044-00144f67d031_DISS-97d679bc-1d9a-560e-e044-00144f67d031.html

Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. British Journal of Industrial Medicine. 27:1-18.

Kim, H. Y., S. B. Lee, Y. H. Chung, C. H. Lim, I. J. Yu, S. C. Park, J. Y. Shin, S. H. Kim, D. H. Shin, and J. C. Kim. 2006. Evaluation of subchronic inhalation toxicity of dimethyl disulfide in rats. Inhalation Toxicology. 18, no. 5: 395-403.

Kirkpatrick, D.T. 2008. A 5-Day Inhalation Toxicity Study of Dimethyl Disulfide (DMDS) in Albino Rats with Microscopic Examination of the Upper Respiratory Tract: Final Report. Project Number: WIL/160131 (as cited in ECHA, 2015).

Kirkpatrick, D.T. 2009. A Single Exposure Inhalation Toxicity Study of Dimethyl Disulfide (DMDS) in Albino Rats with Microscopic Examination of the Upper Respiratory Tract. WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160135. (as cited in CalEPA, 2013; ECHA, 2015; USEPA, 2010).

MDNR. 1993. Memo from Mary Lee Hultin to File. Subject: ITSL for Dimethyl Disulfide. February 3, 1993.

National Center for Biotechnology Information. PubChem Compound Database. Accessed August 25, 2015. CID=12232, https://pubchem.ncbi.nlm.nih.gov/compound/12232

Nemec, M. 2006a. A Subchronic Inhalation Neurotoxicity Study of Dimethyl Disulfide in Rats. WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160123 (as cited in CalEPA, 2013; ECHA, 2015; USEPA, 2010).

Nemec, M. 2006b. A Two-Generation Reproductive Toxicity Inhalation Study of Dimethyl Disulfide in Rats. WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160122 (as cited in CalEPA, 2013; ECHA, 2015; USEPA, 2010).

Nemec, M. 2006c. Inhalation Prenatal Developmental Toxicity Study of Dimethyl Disulfide in Rats. WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160128 (as cited in CalEPA, 2013; ECHA, 2015).

Nemec, M. 2007. A Lactational Inhalation Phased-Exposure Study of Dimethyl Disulfide in Rats. WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160126 (as cited in CalEPA, 2013; ECHA, 2015; USEPA, 2010).

NTP. Dimethyldisulfide-M910023. Accessed August 25, 2015. http://ntp.niehs.nih.gov/testing/status/agents/ts-m910023.html

Partti-Pellinen, K., O. Marttila, V. Vilkka, J.J. Jaakkola, P. Jäppinen, T. Haahtela. 1996. The South Karelia Air Pollution Study: effects of low-level exposure to malodorous sulfur compounds on symptoms. Archives of Environmental Health: An International Journal, 51(4), 315-320.

TCEQ. 2015. Effects Screening Levels (ESL) Lists Used in the Review of Air Permitting Data: Current ESL List. Accessed January 7, 2015. https://www.tceq.texas.gov/toxicology/esl/list_main.html

USDOE. Protective Action Criteria (PAC): Chemicals with AEGLs, ERPGs, & TEELs. Accessed September 29, 2015. http://www.atlintl.com/DOE/teels/teel.html

USEPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-02/002F.

USEPA. 2010. Pesticide Fact Sheet. Office of Chemical Safety and Pollution Prevention. Accessed August 25, 2015. http://www.epa.gov/pesticides/chem_search/reg_actions/pending/fs_PC-029088_09-Jul-10.pdf

USEPA. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-12/044.

USFDA. 21 CFR §172.515 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Accessed August 25, 2015. http://www.ecfr.gov/cgi-bin/ECFR?page=browse

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

February 3, 1993

TO: File for Dimethyl Disulfide (CAS# 624-92-0)

FROM: Mary Lee Hultin, Toxics Unit

SUBJECT: ITSL for Dimethyl Disulfide

A search was conducted of the following sources in order to find data sufficient for a risk assessment:

RTECS
EPA IRIS database
DNR Nutshell (library) and EPB databases
ACGIH TLV, NIOSH REL references
NTP Management Status Report
CAS Online database

No chronic studies were found. The only two references available for use in risk assessment were a subacute inhalation toxicity study (Gage, J., 1970) with a NOAEL of 100 ppm and an inhalation LC50 = 805 ppm (Tansy, et al., 1981). The subacute study was chosen for use in deriving a screening level due to the duration (20 days) as opposed to an acute data point. In the Gage study, groups of 4 rats per dose were exposed to 100 or 250 ppm via inhalation for 6 hours per day, 5 days per week for up to 20 exposures. The rats in the 250 ppm group exhibited lethargy, respiratory difficulty, low wt. gain and upon autopsy revealed congestion of "organs". No effects were noted in the 100 ppm group either upon observation or autopsy.

Using the conversion equation from the EPA Interim Methods for Development of Inhalation Reference Concentrations for dose conversion to mg/m^3:

$mg/m^3 = (ppm \times mw)/24.45$

NOAEL = $(100 \text{ ppm} \times 94.2)/24.45 = 385.28 \text{ mg/m}^3$

ITSL = $385.28 \text{ mg/m}^3/(35 \times 100) \times (6/24 \text{ hr.}) = 0.028 \text{ mg/m}^3$

or $28 \mu g/m^3$ based on annual averaging

The threshold odor concentration for this compound is $5 \mu g/m^3$.

References:

1. Gage, J.C., 1970, "The subacute inhalation toxicity of 109 industrial chemicals", Brit. J. Ind. Med., v.27, p. 1-18.
2. Tansy, et al., 1981, J. Toxicol. Environ. Health v.8 (1-2), p. 71-88.