DIMETHYL SULFOXIDE

(CAS #67-68-5)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 10, 2017

Expiration Date: April 10, 2020

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GreenScreen® Executive Summary for Dimethyl Sulfoxide (CAS #67-68-5)

Dimethyl sulfoxide is a polar solvent that is commonly used as a solvent for polar compounds, acids, alkalis and mineral salts. It is used as a solvent for chemical synthesis, pharmaceuticals, and paint and varnish removers. Dimethyl sulfoxide is also used as an analytical reagent, in the manufacture of synthetic fibers, industrial cleaners, pesticides, and electronics, as a preservative for organ transplantation, and in the treatment of interstitial cystitis.

Dimethyl sulfoxide was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard score combinations:

- Benchmark 3c ("Moderate T (Group II or II* Human)")
  - Moderate Group II Human Health Hazard (skin irritation (IrS) and eye irritation (IrE))
- Benchmark 3d ("Moderate Flammability or Moderate Reactivity")
  - Moderate Flammability (F)

A data gap (DG) exists for endocrine activity (E). As outlined in GreenScreen® Guidance Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), dimethyl sulfoxide meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if dimethyl sulfoxide were assigned a High score for the data gap endocrine activity (E), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:

As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal, and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 3 ("Use but Still Opportunity for Improvement") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Dimethyl Sulfoxide

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	*L*	**L**	DG	**L**	**L**	**L**	**L**	**L**	**L**	*L*	*M*	*M*	**L**	*L*	*L*	**vL**	*L*	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Dimethyl Sulfoxide (CAS #67-68-5)

Method Version: GreenScreen® Version 1.3[1]
Assessment Type[2]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment Prepared By:
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Organization: ToxServices LLC
Date: January 26, 2015
Expiration Date[3]: January 26, 2018

Quality Control Performed By:
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Title: Toxicologist
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Date: February 10, 2015

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Date: April 5, 2017
Expiration Date[4]: April 10, 2020

Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: April 10, 2017

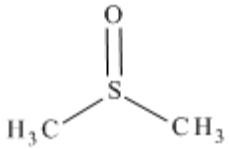
Confirm application of the *Disclosure and Assessment Rules and Best Practice*[5]: (List disclosure threshold and any deviations) Commercially available DMSO has the purity of >99% w/w (OECD 2008). Identities of impurities were not reported.

Notes related to production specific attributes[6]:
No relevant information is available. The screen is performed on the theoretical pure substance.

Chemical Name: Dimethyl Sulfoxide

CAS Number: 67-68-5

Chemical Structure(s):



[1] Use GreenScreen® Hazard Assessment Guidance (Guidance) v1.3
[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)
[3] Assessments expire three years from the date of completion.
[4] Assessments expire three years from the date of completion.
[5] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

[6] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen assessment of the generic chemical by CAS #.

Also called: Dimethyl sulphoxide; Methane, sulfinylbis-; Sulfinylbis-methane; Methane, 1,1'-sulfinylbis-; Methyl sulfoxide; DMSO (ChemIDplus 2017)

Suitable analogs or moieties of chemicals used in this assessment (CAS #'s):
No surrogates were used in the assessment. ToxServices used the U.S. EPA's Analog Identification Methodology (AIM) software and the structural similarity search function of ChemIDplus in an attempt to identify surrogates for the endocrine activity endpoint, but no suitable surrogate was identified. A sufficiently complete database was identified to assign a Benchmark Score for dimethyl sulfoxide.

Identify Applications/Functional Uses (OECD 2008)**:**
1. Solvent for polar compounds, acids, alkalis and mineral salts
2. Analytical reagent
3. Manufacture of synthetic fibers, industrial cleaners, pesticides, and electronics
4. Preservative for organ transplantation
5. Treatment of interstitial cystitis

GreenScreen® Summary Rating for Dimethyl Sulfoxide[7,8 9,10]**:** Dimethyl sulfoxide was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement") (CPA 2017a). This score is based on the following hazard score combinations:

- Benchmark 3c ("Moderate T (Group II or II* Human)")
  - Moderate Group II Human Health Hazard (skin irritation (IrS) and eye irritation (IrE))
- Benchmark 3d ("Moderate Flammability or Moderate Reactivity")
  - Moderate Flammability (F)

A data gap (DG) exists for endocrine activity (E). As outlined in GreenScreen® Guidance (CPA 2017b) Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), dimethyl sulfoxide meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if dimethyl sulfoxide were assigned a High score for the data gap endocrine activity (E), it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Dimethyl Sulfoxide

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	*L*	**L**	DG	**L**	**L**	**L**	**L**	**L**	**L**	*L*	*M*	*M*	**L**	*L*	*L*	**vL**	*L*	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ

[7] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[8] See Appendix A for a glossary of hazard endpoint acronyms
[9] For inorganic chemicals only, see GreenScreen® Guidance v1.3 Section 13 (Exceptions for Persistence).
[10] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen Guidance v1.3 Section 8.2.1.

from Group II* Human Health endpoints in that they have four hazard scores (i.e. vH, H, M, and L) instead of three (i.e. H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings[11]**:**

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[12]

Dimethyl sulfoxide is expected to undergo biodegradation (ECHA 2017a); however, no measured biodegradation products were identified. Dimethyl sulfide has been identified as a product of anaerobic biodegradation (HSDB 2015). Dimethyl sulfoxide may undergo photodegradation, and the primary degradation product is dimethyl sulfone (ECB 2000). It also disproportionates in water over time to produce dimethyl sulfone (CAS #67-71-0) and dimethyl sulfide (CAS #75-18-3). At high temperatures (>190°C) dimethyl sulfoxide may undergo thermal degradation, producing methane thiol, formaldehyde, dimethyl sulfur, and dimethyl sulfone (ECB 2000). Because these temperatures are not expected to apply to most of dimethyl sulfoxide's use as a solvent, ToxServices did not consider these compounds to be relevant. However, for specific applications at high temperatures, evaluation of these products may be warranted.

Table 1: Transformation Product Summary Table

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Feasible and Relevant?	GreenScreen® List Translator Score or Benchmark Score[13,14]
Unknown	Unknown	Photodegradation; Disproportionation	Dimethyl sulfone	67-71-0	Y	LT-U
Unknown	Unknown	Anaerobic biodegradation; Disproportionation	Dimethyl sulfide	75-18-3	Y	LT-U

Introduction

Dimethyl sulfoxide is a polar solvent that is commonly used as a solvent for polar compounds, acids, alkalis and mineral salts. It is used as a solvent for chemical synthesis, pharmaceuticals, and paint and varnish removers. Dimethyl sulfoxide is also used as an analytical reagent, in the manufacture of synthetic fibers, industrial cleaners, pesticides, and electronics, as a preservative for organ transplantation, and in the treatment of interstitial cystitis (OECD 2008). Dimethyl sulfoxide is manufactured by the catalytic oxidation of dimethyl sulfide with oxygen or by oxidation with nitrogen dioxide. It is also generated as a by-product in paper manufacture (HSDB 2015).

ToxServices assessed dimethyl sulfoxide against GreenScreen® Version 1.3 (CPA 2017b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2016).

[11] See GreenScreen® Guidance v1.3 Section 12.

[12] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[13] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2017b,c). Pharos (Pharos 2017) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

[14] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2017a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Dimethyl sulfoxide is not listed on the SCP SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2017b,c). Pharos (Pharos 2017) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b)[15] and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for dimethyl sulfoxide can be found in Appendix C.

- Dimethyl sulfoxide is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.

Hazard Statement and Occupational Control

No EU harmonized classification is available for dimethyl sulfoxide. A majority (323/555, 58%) of EU notifiers did not self-classify dimethyl sulfoxide with any hazard statements. Available occupational exposure limits and recommended personal protective equipment are presented in Table 3 below.

Table 2: H Statements for Dimethyl Sulfoxide (CAS #67-68-5) (ECHA 2017b)

H Statement	H Statement Details
No hazard statements identified	

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Dimethyl Sulfoxide (CAS #67-68-5)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, safety glasses, goggles, other protective eyewear, impervious clothing, full-face respirator when aerosol or vapor exposure possible	HSDB 2015; Sigma-Aldrich 2016	WEEL: 250 ppm (TWA)	Sigma-Aldrich 2016

TWA: Time weighted average
WEEL: Workplace Environmental Exposure Level

Physicochemical Properties of Dimethyl Sulfoxide

Dimethyl sulfoxide is an organosulfur, colorless liquid that dissolves both polar and nonpolar compounds. It is miscible in a wide range of organic solvents as well as water. Its vapor pressure of 0.61 mmHg indicates that it is highly volatile and is likely to exist as a mixture of liquid and vapor. It is

[15] DOT lists are not required lists for GreenScreen List Translator v1.3. They are reference lists only.

soluble in water (1 x 10^6 mg/L) and is more soluble in water than in octanol (log K_{ow} = -1.35). Its log K_{ow} value indicates that it is unlikely to bioaccumulate.

Table 4: Physical and Chemical Properties of Dimethyl Sulfoxide (CAS #67-68-5)		
Property	**Value**	**Reference**
Molecular formula	C_2H_6O	ChemIDplus 2017
SMILES Notation	CS(=O)C	ChemIDplus 2017
Molecular weight	78.1344 g/mol	ChemIDplus 2017
Physical state	Liquid	U.S. EPA 2009
Appearance	Clear	ECHA 2017a
Melting point	18.5°C	ChemIDplus 2017
Vapor pressure	0.61 mmHg at 25°C 0.417 mm Hg at 20°C (EU Method A.4)	U.S. EPA 2009 ECHA 2017a
Water solubility	1 x 10^6 mg/L at 25°C	U.S. EPA 2009
Dissociation constant	pKa = 35.1	ECHA 2017a
Density/specific gravity	1.1 g/cm^3 at 20°C 1.1 g/cm^3 at 20°C (EU Method A.3)	U.S. EPA 2009 ECHA 2017a
Partition coefficient	log K_{ow} = -1.35	U.S. EPA 2009

Toxicokinetics

- ECHA 2017a
    - *Oral*: Rhesus monkeys (*Macaca mulatta*) (3 total) were administered oral doses of 3g/kg/day dimethyl sulfoxide in water via gavage for 14 days. Serum, urine, and feces were collected and analyzed via gas-liquid chromatography. A peak serum concentration of dimethyl sulfoxide of 2.3 mg/mL was reached 4 hours after dosing. A rapid decline in serum dimethyl sulfoxide to 0.95 mg/mL was observed until 24 hours after dosing, its half-life was 16 hours and elimination rate constant was 4%/hour. A steady-state concentration of 0.9 mg/mL serum was obtained after 4 days. After the last day of dosing, serum dimethyl sulfoxide levels decreased rapidly and was less than the limit of detection after 72 hours. Dimethyl sulfone was detectable in the serum 2 hours after dosing and reached 0.18 mg/mL 24 hours after dosing. A steady state concentration for dimethyl sulfone of 0.34 mg/mL was reached in the serum after 4 days. Cessation of dosing caused a slow decline in dimethyl sulfone levels over 96 hours, and trace concentrations were detected after 120 hours. The elimination half-life for dimethyl sulfone was calculated as 38 hours and the elimination rate constant was 2%/hour. Excretion of dimethyl sulfoxide in the urine occurred rapidly and reached a steady state level of 9 g/day after 2 days. After the last dose was administered, urinary levels of dimethyl sulfoxide decreased rapidly and only trace amounts were measured after 72 hours. Approximately 60% of the ingested dimethyl sulfoxide was excreted un-metabolized. Excretion of dimethyl sulfone in the urine increased slowly and reached a maximum level of 3 g/day after 5 days of dosing. After the last dosing, urinary levels of dimethyl sulfone decreased slowly over 5 days. Approximately 16% of the ingested dose was excreted in the urine as dimethyl sulfone. No dimethyl sulfoxide or dimethyl sulfone was detected in the fecal samples owing to the activity of gut bacteria during sample storage.
    - *Oral*: Male Sprague-Dawley rats (number not specified) were administered oral doses of ^{35}S-radiolabeled dimethyl sulfoxide (purity not specified) at 550 mg/kg. Blood, urine, and feces were collected. Radioactivity was detected in the plasma 30 minutes after dosing and

the maximum level was reached 0.5-1 hour after dosing. By 24 hours after dosing, the plasma levels declined to 5-10% of the peak concentration. The plasma half-life was 6 hours. The animals were killed at various times to evaluate the radioactivity in different tissues. All tissues had appreciable concentrations of radioactivity 30 minutes after dosing. The level of radioactivity present in plasma, lung, heart, kidney, spleen, and testes were slightly greater than the levels in liver, adipose, brain, small intestine, skeletal muscle, and red blood cells. After 30 minutes, increases in the level of radioactivity were observed in the brain, skeletal muscle, heart, and testes but the levels in other tissues remained constant. After 4 hours, the ratio of dimethyl sulfone to dimethyl sulfoxide was approximately 6.5% in the liver, kidney, testes, spleen, small intestine, plasma, and heart, indicating that the majority of radioactivity present in these tissues was as dimethyl sulfoxide. Approximately 67% of the dose was excreted in the urine within 24 hours of dosing compared to 10% in the feces.

- *Oral*: Male human volunteers (6 total) were administered oral doses of 1 g/kg dimethyl sulfoxide (purity not specified) in water. Serum levels of dimethyl sulfoxide and dimethyl sulfone were monitored after dosing. Peak serum dimethyl sulfoxide was observed within 4 hours of dosing and the levels decreased fairly rapidly thereafter, with an estimated half-life of 20 hours. After 120 hours, dimethyl sulfoxide was no longer detected in the serum. Dimethyl sulfone levels in the serum reached a maximum 72-96 hours after dosing and decreased slowly with a half-life of 71 hours. After 400 hours, only trace levels of dimethyl sulfone were detected. Urinary excretion of dimethyl sulfoxide began immediately after dosing and continued for 120 hours at an even rate. On average, 50.8% of the dose was excreted as dimethyl sulfoxide. Urinary excretion of dimethyl sulfone was not detected until 20 hours after dosing and proceeded until 120 hours after dosing for most subjects. In 2 individuals, the excretion of dimethyl sulfone was detected until 480 hours after dosing. In these two individuals, 22% of the dose was excreted as dimethyl sulfone while the remaining individuals excreted 9.6% of the dose as dimethyl sulfone. An average of 60.4% of the dose was accounted for after 120 hours.
- *Oral*: As part of the previous study, one male volunteer was administered dimethyl sulfoxide (purity not specified) at 500 mg/kg/day orally for 14 days. Serum and urine samples were collected and evaluated for dimethyl sulfoxide and dimethyl sulfone starting 1 hour after dosing and then at intervals of 24 hours. A maximum serum concentration of dimethyl sulfoxide of 1,850 µg/mL was observed after 196 hours after nine dosing events. No detectable levels of dimethyl sulfoxide were measured in the serum 72 hours after the final dose was administered. Maximum serum dimethyl sulfone levels were measured 196 hours into the dosing period. Forty-eight hours after the final dosing, serum levels of dimethyl sulfone declined rapidly, with a level of 170 µg/mL achieved after 556 hours. Approximately 49% and 11.1% of the total dose administered up to the day of the last dose was excreted as dimethyl sulfoxide and dimethyl sulfone, respectively, for this individual. After 368 hours and 560 hours, 53.7% and 17.2% of the dose was excreted as dimethyl sulfoxide and dimethyl sulfone, respectively. A total of 70.9% of the dose was accounted for via urinary excretion.
- *Dermal*: Two male volunteers were administered topical applications of 1 g/kg of a 70% ^{35}S-radiolabeled dimethyl sulfoxide (purity not specified) in water over the entire body surface via gauze pad. The solution was gently rubbed into the skin until absorbed. Once all of the solution was applied, the gauze was washed with a small amount of water and the washings were applied to the skin. Peak serum levels of dimethyl sulfoxide were achieved 4-8 hours after dosing and the half-life was determined to be 11-14 hours. Dimethyl sulfoxide could

no longer be detected in the serum after 36-48 hours. The metabolite dimethyl sulfone ($DMSO_2$) reached peak levels in the serum 36-72 hours after dosing and was still detectable in the serum after 312 hours. The half-life for dimethyl sulfone was 60-70 hours. Dimethyl sulfoxide was detected in the urine shortly after dosing and continued to be detected in the urine for 48 hours after dosing. The dimethyl sulfoxide excreted in the urine accounted for 13% of the administered dose. Urinary excretion of dimethyl sulfone became significant 8 hours after dosing and continued for 456 hours (19 days). The amount of dimethyl sulfone excreted in the urine accounted for 17.8% of the administered dose. A total of 30.8% of the administered dose was accounted for in the urine as either dimethyl sulfoxide or dimethyl sulfone.

- *Dermal*: Male New Zealand White rabbits (6 total) were administered dermal applications of 550 mg/kg ^{35}S-radiolabeled dimethyl sulfoxide (purity not specified). Blood, urine, and fecal samples were collected following dosing. Pairs of animals were sacrificed after 30 minutes, 4 hours, and 24 hours and the tissues were assayed for total radioactivity. After 30 minutes, 85% of the dose remained at the site of application, while 11% of the radioactivity remained at the application site after 4 hours. At 24 hours, the level of radioactivity at the site of application was equal to that of the surrounding skin. Thirty minutes after dosing, all tissues except the lens had appreciable levels of radioactivity. After 4 hours, the levels were 3-60 times that measured after 30 minutes and the highest levels were measured in the plasma, lungs, heart, bile, cornea, vitreous humor, and aqueous humor. Concentrations measured in the fat were lower than the levels observed in other tissues. The levels of radioactivity declined after 24 hours. The rabbits excreted 30% of the dose in urine as dimethyl sulfoxide and dimethyl sulfone.
- *Dermal*: Male Sprague-Dawley rats (number not specified) were administered dermal doses of ^{35}S-radiolabeled dimethyl sulfoxide (purity not specified) at 550 mg/kg. The animals were placed in a metabolism cage to collect expired air. Blood, urine, and feces were also collected. Radioactivity was detected in the plasma 30 minutes after dosing and the maximum level was reached 2 hours after dosing. By 24 hours after dosing, the plasma levels declined to 5-10% of the peak concentration. The plasma half-life was 6 hours. After 0.5, 1, and 2 hours, the amount of radioactivity remaining at the application site were 63%, 19%, and 14%, respectively. After 24 hours, the amount of radioactivity at the site of the application was the same as that of the surrounding skin. Appreciable levels of radioactivity were measured in tissues 30 minutes after dosing, and levels measured in the liver, plasma, spleen, and lungs were greater than in other tissues. After 4 hours, increased concentrations were observed in the liver, kidney, spleen, brain, testes, lungs, skeletal muscle, plasma, red blood cells, and heart. Minimal values in all tissues were detected 24 hours after dosing. Total radioactivity excreted in the urine, expired air, and feces over 24 hours was 66%, 6%, and 4%, respectively.
- *Dermal*: Female Sprague-Dawley rats (3-10/group) were administered dermal doses of 50 mC ^{35}S-radiolabeled dimethyl sulfoxide (purity not specified) in physiological saline without occlusion. The animals were killed 2 hours after dosing and the soft tissues, bone, and cartilage were isolated for assessment of radioactive content. The radioactivity detected in the organs were highest in (descending order) the spleen stomach, long, vitreous humor, thymus, brain, kidney, scleral coats, and colon, with slightly lower levels in the skeletal muscle, heart, skin, liver, and aorta. Bone and cartilage had less radioactivity than the soft tissues. In the blood, the radiolabeled dimethyl sulfoxide was associated with the albumin fraction. The biologic half-lives for dimethyl sulfoxide were inversely proportional to the level of radioactivity, that is, the shortest half-lives were measured for the tissues with the

greatest levels of radioactivity. The cartilage and other hard tissues retained radioactivity longer than the soft tissues.

- OECD 2008
    - Dimethyl sulfoxide may be metabolized to dimethyl sulfide via sulfoxide reductases in the liver and kidney, but can be re-oxidized to dimethyl sulfoxide to dimethyl sulfoxide by mixed-function oxidases. Dimethyl sulfoxide may be irreversiblely oxidized to dimethyl sulfone.
    - No absorption data are available for the inhalation route of exposure but the physiochemical properties of dimethyl sulfoxide (high polarity and water solubility and low molecular size) suggests that it may be significantly absorbed via the inhalation route.
- NICNAS Undated
    - Dimethyl sulfoxide enhances skin penetration of other chemicals. The mechanism of action remains to be elucidated. It has been proposed that dimethyl sulfoxide acts by removing the lipid matrix of the stratum corneum, making holes in the penetration barrier; by producing reversible configurational changes in protein structures; or by functioning as a swelling agent.
- In summary, dimethyl sulfoxide is rapidly and significantly absorbed into the systemic circulation following oral, dermal and inhalation dosing. It also enhances the skin permeability of other substances. It distributes widely in the body to most soft tissues as well as bone and cartilage. It is metabolized to dimethyl sulfone and dimethyl sulfide, with dimethyl sulfone being the metabolite monitored in the toxicokinetic studies due to its irreversible formation. Peak formation of dimethyl sulfone was achieved 72-96 hours after dosing in human studies. Levels of dimethyl sulfoxide and dimethyl sulfone decreased rapidly after dosing such that only trace amounts were present in tissues up to 72 hours after dosing. Urinary excretion of un-metabolized dimethyl sulfoxide and dimethyl sulfone represented 30-70% of the administered dose depending on route of administration and species. Much smaller fractions are excreted via expired air and feces.

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*

Dimethyl sulfoxide was assigned a score of Low for carcinogenicity based on a lack of carcinogenic transformation potential in *in vitro* assays, a lack of tumor formation in tests of dermal tumor promotion potential in rats and mice, a lack of histopathological changes in a chronic oral toxicity study in dogs, and negative modeling results. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and are negative, and the chemical is not present on authoritative or screening lists (CPA 2017c). The confidence in this score is reduced due to the lack of a standard 2-year carcinogenicity study.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2006
    - The carcinogenic potential of dimethyl sulfoxide has been tested in *in vitro* test systems, and no evidence of carcinogenic transformation potential was seen in hamster cheek epithelium, Syrian hamster embryos, or hamster sternal hyaline cartilage. A lack of effects on the number of mitosis cells in the adrenal cortex of male Wistar rats administered 2.5 and 5.0

mL dimethyl sulfoxide indicates that it is not a tumor promotor or active carcinogen. No additional details were provided.

- ECHA 2017a
    - In a study designed to evaluate tumor promoting activity, no skin tumors were observed in 20 female ICR/Ha Swiss mice that were dermally administered 0.1 mL dimethyl sulfoxide 3 times/week for 400 days following a single primary treatment with 20 µg DMBA. No additional details were provided.
    - In a study designed to evaluate tumor promoting activity of a dimethyl sulfoxide, a vehicle control group of 40 Sprague-Dawley rats (sex not specified) were dermally administered 0.02 mL dimethyl sulfoxide 3 times/week for at least 26 weeks. No skin tumors were observed. No additional details were provided.
    - In the chronic oral toxicity study in male and female Pembrokeshire Corgis described below for systemic toxicity, animals (5/sex/dose) were administered 1,100, 3,300, or 9,900 mg/kg/day dimethyl sulfoxide (pharmaceutical grade purity) via gavage 5 days/week for 2 years (equivalent to 786, 2,357, or 7,071 mg/kg/day when adjusted for 5 days/week exposure). No effects on histopathology were seen.
- Toxtree 2016
    - Toxtree predicts that dimethyl sulfoxide is negative for both genotoxic and non-genotoxic carcinogenicity (Appendix D).
- Based on the weight of evidence, a low confidence score of Low was assigned. Several studies have evaluated the potential for dimethyl sulfoxide to enhance tumor incidence when used as a solvent for known carcinogens. ToxServices did not consider these studies relevant to the assessment, as it is not possible to attribute the carcinogenic effects to dimethyl sulfoxide. Therefore, these studies were not summarized. Two studies evaluating the tumor promoting activity of dimethyl sulfoxide found that this compound did not produce dermal lesions. While these are not guideline studies and did not test if dimethyl sulfoxide is a complete carcinogen, ToxServices considered these studies in the weight of evidence as they demonstrated a lack of tumor formation following repeated dermal exposures in rats and mice. Although the chronic oral toxicity study in dogs is limited by small sample sizes, this study also did not show any evidence of carcinogenicity. Negative results in the *in vitro* carcinogenic transformation assays described by U.S. EPA also lend support to a low hazard for carcinogenicity, as does a lack of mutagenic activity (described in Mutagenicity/Genotoxicity, below). Toxtree did not identify structural alerts for genotoxic or non-genotoxic carcinogenicity. ToxServices attempted to perform modeling with VEGA (2017), but the compound was out of the model's applicability domain. Modeling could not be performed with OncoLogic (U.S. EPA 2013) because the chemical does not fall into the chemical classes evaluated by the program. Overall, the weight of evidence suggests that dimethyl sulfoxide is a low hazard for carcinogenicity, but confidence in this score is reduced due to the lack of a standard 2-year carcinogenicity study.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Dimethyl sulfoxide was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity obtained in a battery of *in vitro* and *in vivo* tests. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data for mutagenicity and clastogenicity are available,there are no structural alerts, and they are not classified under GHS (CPA 2017c). The confidence in the score is high as it is based on data from high quality studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.

- ECHA 2017a
    - Note: Numerous genotoxicity studies were reported in the REACH dossier. Only those reported with a Klimisch score of 1 (reliable) or 2 (reliable with restrictions) and conducted according OECD or similar guidelines were included in the evaluation.
    - *In vitro*: In a bacterial mutagenicity assay similar to OECD Guideline 471 conducted by NTP, *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537 were treated with concentrations of 0, 100, 333, 1,000, 3,333 and 10,000 µg/plate dimethyl sulfoxide (purity and vehicle not specified) with and without metabolic activation. There was no evidence of mutagenicity in any strain at any dose. Positive controls exhibited the expected responses. Authors concluded that dimethyl sulfoxide is not mutagenic.
    - *In vitro*: In an *in vitro* sister chromatid exchange (SCE) assay that was conducted according to methods similar to OECD Guideline 479 in Chinese hamster ovary (CHO) cells, cells were treated with dimethyl sulfoxide (purity not specified) in water at concentrations of 0, 500, 1,500, and 5,000 µg/ml in the presence and absence of metabolic activation. There were no effects on cell cycle or cytotoxicity, and there was no increase in the incidence in SCE at any dose. The positive controls showed the expected responses. Authors concluded that dimethyl sulfoxide was negative under the conditions of the assay.
    - *In vitro*: In an *in vitro* chromosome aberration assay that was conducted according to methods similar to OECD Guideline 473 in Chinese hamster ovary (CHO) cells, cells were treated with dimethyl sulfoxide (purity not specified) in cell culture medium at concentrations of 0, 499, 1,500, and 4,990 µg/ml in the presence and absence of metabolic activation. There were no effects on cell cycle or cytotoxicity, and there was no increase in the incidence in chromosome aberrations at any dose. The positive controls showed the expected responses. Authors concluded that dimethyl sulfoxide was negative under the conditions of the assay.
    - *In vitro*: In an *in vitro* mammalian cell mutagenicity assay that was conducted according to methods similar to OECD Guideline 476, Chinese hamster ovary (CHO) cells were treated with dimethyl sulfoxide (purity not reported) without vehicle at concentrations of 2, 4, 5, 8, 10, and 16% without metabolic activation. Cells were not treated in the presence of metabolic activation. Cell survival ranged from 41-86% in treated cultures. There was no treatment-related increase in mutagenicity, and authors concluded that dimethyl sulfoxide was not mutagenic under the conditions of the assay. There were no data on positive controls.
    - *In vitro*: In an *in vitro* mammalian cell mutagenicity assay that was conducted according to methods similar to OECD Guideline 476, mouse lymphoma L5178Y cells were treated with dimethyl sulfoxide (purity not reported) without vehicle at concentrations of 0.704, 0.986, 1.268, 1.408, 1.549, 1.689, 1.831, and 2.131 M without metabolic activation. Cells were not treated in the presence of metabolic activation. Cytotoxicity was seen at concentrations $\geq$ 1.83 M. Authors reported that dimethyl sulfoxide may produce mutagenicity at cytotoxic doses.
    - *In vitro*: In an *in vitro* mammalian cell mutagenicity assay that was conducted according to methods similar to OECD Guideline 476, mouse lymphoma L5178Y cells were treated with dimethyl sulfoxide (purity not reported) without vehicle at concentrations of 0, 0.746, 1.0, 1.25, 1.39, and 1.55 mol/L without metabolic activation. Cells were not treated in the presence of metabolic activation. Cytotoxicity was seen at concentrations $\geq$ 1 mol/L. An increase in mutagenicity was seen only at cytotoxic concentrations. Authors concluded that results were ambiguous.

- *In vivo*: Dimethyl sulfoxide was negative in a GLP-compliant *in vivo* micronucleus assay conducted according to OECD Guideline 474 in Han Wistar rats. Animals (6/sex/dose) were administered 0, 200, 1,000 or 5,000 mg/kg/day dimethyl sulfoxide (purity not specified) in purified water via intraperitoneal injection on 5 consecutive days, and were evaluated 24 hours after the final dose. Animals showed no clinical signs of toxicity. There was no significant increase in the mean ratios of PCE:NCE or in micronucleus frequency. Authors concluded that dimethyl sulfoxide is not clastogenic *in vivo*.
- *In vivo*: Dimethyl sulfoxide was negative in an *in vivo* dominant lethal assay in male Swiss mice (15/dose) that received two doses of 5.0, 7.5, or 10.0 g/kg dimethyl sulfoxide (purity and vehicle not reported) at 20 hour intervals prior to being paired with 2-3 females at weekly intervals for 5 weeks. Mortality rates were 7, 20, and 73% for the low, medium, and high doses, respectively. There were no effects on dead implantations.
- *In vivo*: Dimethyl sulfoxide was negative in an *in vivo Drosophila* SLRL test in male flies (*D. melanogaster*) that were injected intra-abdominally with a single dose of dimethyl sulfoxide (purity not reported) at concentrations of 0.1, 1.0, or 5.0%. Mating procedures were not described. There was no treatment-related increase in mortality, and there were no treatment-related effects on sex-linked recessive lethals or chromosome loss. Authors concluded that the test substance was negative.

- Based on the weight of evidence, a high confidence score of Low was assigned. Although two *in vitro* mammalian cell mutagenicity assays in mouse lymphoma L5178Y cells showed some evidence of mutagenicity, effects were only seen at cytotoxic doses. In addition, mutagenicity assays in bacteria and CHO cells were negative. Negative results for clastogenicity were also seen *in vitro* assays in CHO cells. A GLP-compliant *in vivo* micronucleus assay and less well documented dominant lethal and Drosophila SLRL assays were also negative. Therefore, experimental data indicate that dimethyl sulfoxide is not mutagenic or clastogenic.

Reproductive Toxicity (R) Score (H, M, or L): *L*
Dimethyl sulfoxide was assigned a score of Low for reproductive toxicity based on a lack of effects on reproductive performance in a one-generation oral reproductive toxicity study in rats, and a lack of effects on estrus cycle and sperm parameters in a subchronic inhalation toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative data, no structural alerts, and no GHS classification are available (CPA 2017c). The confidence in the score is low as it is based on data from a screening study and a subchronic inhalation toxicity test.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
  - *Oral*: In a GLP-compliant reproductive and developmental toxicity screening study conducted according to OECD Guideline 421 in Sprague-Dawley rats, animals (12/sex/dose) were administered 100, 300, or 1,000 mg/kg dimethyl sulfoxide (purity not specified) in water via gavage for 15 days prior to mating and though a 2-week mating period for a total of at least 4 weeks (males) or through pregnancy and lactation day 21 (females). No treatment-related toxicologically significant effects on parental mortality, clinical signs, body weight, mating index, fertility index, gestation, or delivery, or effects on offspring mortality, clinical signs, sex ratio, body weight, gross pathology, or histopathology were seen. Authors identified a NOAEL of 1,000 mg/kg/day for reproductive and developmental toxicity based on the lack of effects.

- *Inhalation*: In the GLP-compliant subchronic toxicity study conducted according to OECD Guideline 413 that is described below for systemic toxicity-repeated dose, male and female Sprague-Dawley rats, animals (10/sex/dose) were administered 0, 0.310, 0.964, or 2.783 mg/L/day dimethyl sulfoxide (>99% purity) via nose-only inhalation for 6 hours/day, 7 days/week for 13 weeks. Estrus cycle and semiology were evaluated after 90 days. No treatment related effects were seen.

- Based on the weight of evidence, a high confidence score of Low was assigned. No effects on reproductive performance were seen in rats in an oral toxicity study conducted according to OECD Guideline 421. In addition, there were no effects on estrus cycle or sperm parameters in a subchronic inhalation study in rats. Therefore a score of Low was assigned.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L

Dimethyl sulfoxide was assigned a score of Low for developmental toxicity based on negative results in GLP-compliant developmental toxicity studies in rabbits and rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and negative results, no structural alerts, and no GHS classification are available (CPA 2017c). The confidence in the score is high as it is based on data from high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK - Pregnancy Risk Group B ("According to currently available information damage to the embryo or fetus must be expected even when MAK and BAT values are observed").
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
  - Note: Numerous developmental toxicity studies were reported in the REACH dossier. Only those reported with a Klimisch score of 1 (reliable) or 2 (reliable with restrictions) and conducted according OECD or similar guidelines were included in the evaluation.
  - *Oral*: In a GLP-compliant prenatal developmental toxicity study according to OECD Guideline 414 in New Zealand White rabbits, does (24/dose) were administered oral doses of dimethyl sulfoxide (purity not specified) in water at 0, 100, 300, or 1,000 mg/kg/day via gavage on gestation days (GD) 7-28 and were sacrificed on gestation day 28. Slight maternal toxicity (slight decrease in weight gain during the first 2 days of treatment) was seen at the mid and high dose. No effects on embryo-fetal development or teratogenic effects were seen at any dose. Authors identified a NOAEL of 1,000 mg/kg/day based on the lack of effects.
  - *Oral*: In a GLP-compliant prenatal developmental toxicity study according to OECD Guideline 414/EPA OTS 798.4900 in Sprague-Dawley rats, dams (25/dose) were administered oral doses of dimethyl sulfoxide (purity not specified) in water at 0, 200, 1,000, or 5,000 mg/kg via gavage on GD 6-15 and were sacrificed on gestation day 20. Food consumption and body weight gain were slightly reduced, and terminal body weight was reduced by 4%, in females of the high dose group. No effects on pre- or post-implantation losses, number of fetuses, or sex ratio were seen. Fetal body weights were slightly reduced at the high dose. No treatment-related, toxicologically significant external, soft tissue, or skeletal variations or malformations were seen. An increase in reduced or delayed ossification of ribs was seen in offspring at the high dose and was considered to be due to reduced maternal body weights. Authors identified a NOAEL of 1,000 mg/kg/day.
- HPVIS 2015

- Note: Only studies conducted according to or similar to recognized guidelines and reported as valid or valid with restrictions were included in the assessment.
- *Oral*: In a GLP-compliant prenatal developmental toxicity study (no guideline specified) in Sprague-Dawley rats, dams (7/dose) were administered 1,000, 5,000, or 10,000 mg/kg dimethyl sulfoxide (99.89% purity) via gavage on gestation days 6-15 and animals were sacrificed on gestation day 20. Evaluations of corpora lutea, implantation sites, resorptions, and live and dead fetuses were made. External examinations were performed on fetuses. There were no clinical signs of toxicity or mortality in treated animals. Decreased food consumption and body weight gain were seen in females at the mid and high doses. There were no treatment-related effects on number of corpora lutea, implantation sites, resorptions, or dead fetuses. Higher rates of early resorptions per animal and higher total post implantation loss were seen in the mid and high dose groups. There was a slight treatment-related decrease in live fetuses at the mid and high doses (magnitude of effect not specified). Fetal weights were also slightly reduced at these doses. Authors noted that effects on weight corresponded to reduced maternal food consumption and body weight. Authors identified a NOAEL of 1,000 mg/kg/day.

- Based on the weight of evidence, a high confidence score of Low was assigned. Although dimethyl sulfide was classified to Pregnancy Risk Group B on the German MAK list, which corresponds to a score of Moderate to High, two GLP-compliant OECD guideline oral toxicity studies have been conducted in rabbits and rats, and one GLP-compliant non-guideline study was conducted in rats. In the study in rabbits, there was no evidence of embryotoxicity or teratogenicity at any dose up to 1,000 mg/kg/day. In the first study in rats, fetal body weight was slightly but not significantly decreased at the high dose of 5,000 mg/kg/day. Also at this dose, there was an increase in delayed ossification of ribs which the authors attributed to the slightly reduced maternal body weight. Delayed ossification is frequently seen with reduced body weight, and is usually reversible and is considered to be a "less serious" skeletal effect (Pohl et al. 1998). Therefore, ToxServices did not consider delayed ossification in conjunction with a non-significant decrease in body weight at the high dose of 5,000 mg/kg/day to be a toxicologically significant effect. In the second study in rats, effects on early resorptions, post-implantation loss, and live fetuses were seen at doses of 5,000 and 10,000 mg/kg/day. The magnitude of effects was not stated, but was described as "slight". Considering that effects in rats were slight, were not consistent between studies, and were seen only at very high doses ($\geq$ 5,000 mg/kg/day) that also affected maternal food consumption and body weight, ToxServices did not consider these effects to be evidence of selective developmental toxicity. The basis of the German MAK classification was not identified, and this classification appears to be a preliminary and the compound may be later classified to Pregnancy Risk Group C, which is equivalent to a score of Low to Moderate. Of all the regulatory agencies that evaluated this endpoint (OECD, NICNAS, U.S. EPA, WHMIS, Germany), only Germany classified dimethyl sulfoxide as a potential developmental toxicant. Dimethyl sulfoxide was reported to be teratogenic/embryotoxic in hamsters, rats, mice and chicken by the parenteral route (Reprotox 2016). However, this route of exposure is typically not considered in a GreenScreen® assessment, and high quality oral studies did not identify these effects in animals. Therefore, a score of Low was assigned.

Endocrine Activity (E) Score (H, M, or L): DG

Dimethyl sulfoxide was assigned a score of Data Gap for endocrine activity based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.

    - *Screening:* Not listed on any screening lists for this endpoint.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- No data were identified for this endpoint.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): L

Dimethyl sulfoxide was assigned a score of Low for acute toxicity based on oral LD_{50} values of 14,500-28,300 mg/kg in rats and mice and dermal LD_{50} values of 40,000 mg/kg in rats and 50,000 mg/kg in mice. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
    - *Oral*: LD_{50} (rat, male and female Carworth CFN) = 28,300 mg/kg (non-GLP-compliant, similar to OECD Guideline 401)
    - *Oral*: LD_{50} (mouse, male and female albino) = 21,400 mg/kg (non-GLP-compliant, similar to OECD Guideline 401)
    - *Oral*: LD_{50} (rat, male Carworth-Wistar) = 20,500 mg/kg (non-GLP-compliant, similar to OECD Guideline 401)
    - *Dermal*: LD_{50} (rat, male and female, Sprague-Dawley) = 40,000 mg/kg (non-GLP-compliant)
    - *Dermal*: LD_{50} (mouse, male and female, strain not specified) = 50,000 mg/kg (non-GLP-compliant)
    - *Inhalation*: 4-hour nose-only vapor LC_{50} (rat, male and female Sprague-Dawley) > 5.33 mg/L (saturation) (GLP-compliant, OECD Guideline 403)
    - *Inhalation*: 4-hour whole body aerosol LC_{50} (rat, male Sprague-Dawley) > 1.6 mg/L
    - Additional acute toxicity studies were identified in the REACH dossier for dimethyl sulfoxide. However, they were assigned Klimisch scores of 3 (not reliable). Therefore, ToxServices did not include them in this assessment.
- Based on the weight of evidence, a score of Low was assigned. The experimental oral and dermal LD_{50} values were > 2,000 mg/kg in rats and mice, and inhalation LC_{50} values exceeded a saturated atmosphere. As numerous acute toxicity studies reported with sufficient detail were available, a high confidence score of Low was assigned.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L): L**

Dimethyl sulfoxide was assigned a score of Low for systemic toxicity (single dose) based on a lack of evidence of systemic toxicity in acute dermal studies of rats administered greater than 2 g/kg and mice administered greater than 22 g/kg, and in acute inhalation studies of rats administered a saturated atmosphere. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when no evidence of systemic toxicity is seen below the guidance values of 2,000 mg/kg for a dermal study and 20 mg/L for an inhalation study (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- HSDB 2015
    - There is one case report of fatigue, cyanosis, and dyspnea in a 43-year old woman that treated interstitial cystitis with two treatments (1.5 hours apart) of 4 ounces of a 50% solution of dimethyl sulfoxide for a total dose of 1.8 g/kg. The patient was treated for sulfhemoglobinemia 10 days after dimethyl sulfoxide treatment. Interpretation of this study is confounded by concurrent treatment with lansoprazole, phenazopyridine, and alprazolam.
- ECHA 2017a
    - *Inhalation*: In the GLP-compliant acute inhalation study conducted according to OECD Guideline 403 in male and female Sprague-Dawley rats that identified an LC_{50} of > 5.33 mg/L, animals (5/sex/dose) were administered dimethyl sulfoxide (99.88% purity) via nose only inhalation at concentrations of 0, 0.9, and 5.33 mg/L for 4 hours and were observed for 14 days. Evaluations of body weight, food and water consumption, clinical signs, histopathology, and gross pathology were conducted. No treatment-related effects were seen. ToxServices identified a NOAEL of 5.33 mg/L/4h (saturation).
    - *Inhalation*: In the acute inhalation study in male Sprague-Dawley rats that identified an LC_{50} of > 1.6 mg/L, 8 animals were administered 1.6 mg/L dimethyl sulfoxide (spectrograde purity) via whole body inhalation for 4 hours and were observed for 14 days. Evaluations of clinical signs, unusual behavior, body weight, organ weights, histopathology, clinical chemistry, and hematology were performed at the conclusion of the study. No treatment related effects were seen. ToxServices identified a NOAEL of 1.6 mg/L/4h.
    - *Dermal*: In the acute dermal study in male and female Sprague-Dawley rats that identified an LD_{50} of 40,000 mg/kg, animals (14/sex/dose for 100% solution and 3/sex/dose for other solutions) were dipped in solutions of 40, 60, 80, or 100% dimethyl sulfoxide (2, 13, 33, or 44 g/kg, purity not reported) and were observed for 24 hours. There were no treatment-related effects on clinical signs, body weight, or microscopic pathology. At the high dose, 13/14 animals died, but no animals died at other doses. ToxServices identified a NAOEL of 33,000 mg/kg.
    - *Dermal*: In the acute dermal study in male and female albino mice that identified an LD_{50} of 40,000 mg/kg, animals (4-6/sex/dose) were dipped in solutions of 40, 60, 80, or 100% dimethyl sulfoxide (22, 37, 49, or 91 g/kg, purity not reported) and were observed for 24 hours. There were no treatment-related effects on clinical signs, body weight, or microscopic pathology. At the high dose, 3/4 animals died, but no animals died at other doses. ToxServices identified a NAOEL of 49,000 mg/kg.
- Based on the weight of evidence, a high confidence score of Low was assigned. One case report of sulfhemoglobinema in a woman that was treated for cystitis with dermal administration of dimethyl sulfoxide was identified, but interpretation of the study was complicated by co-exposure to other medications. No effects on clinical signs, body weight, or microscopic pathology were seen in dermal studies in rats and mice, and there were no effects on clinical signs, body weight, organ

weights, histopathology, clinical chemistry, and hematology in acute inhalation studies in rats. Therefore the weight of evidence indicates that dimethyl sulfoxide is a low hazard for systemic toxicity. Confidence in this score is high, as it is based on numerous high quality studies in animals.

Group II* Score (repeated dose) **(H, M, or L): L**

Dimethyl sulfoxide was assigned a score of Low for systemic toxicity (repeated dose) based on the lowest NOAEL/NOAECs of 1,100 mg/kg/day from a 2-year oral toxicity study in dogs, 8,910 mg/kg/day from an 18 month dermal toxicity study in monkeys, and of 2.783 mg/L/6h from a 13-week inhalation toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when no effects are seen below the guidance values of 100 mg/kg/day for an oral study, 200 mg/kg/day for a dermal study, and 1.0 mg/L/6h (vapor) for an inhalation study (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
    - Note: Due to the large number of studies reported in the REACH dossier, only those reported as key studies, which were well reported and conducted according to or similar to recognized guidelines and received Klimisch scores of 1 (reliable) or 2 (reliable with restriction), were included in the assessment.
    - *Oral*: In a chronic oral toxicity test similar to OECD Guideline 452 in male and female Pembrokeshire Corgis, animals (5/sex/dose) were administered oral doses of dimethyl sulfoxide (purity not specified) in water at 0, 1,100, 3,300, or 9,900 mg/kg/day via gavage 5 days/week for 2 years (equivalent to 786, 2,357, or 7,071 mg/kg/day when adjusted to a 7-day/week exposure frequency[16]). No effects on body weight, organ weights, gross pathology, or histopathology were seen. Changes in the lens of the eye (alteration of the refractive index transitory equatorial opacities, central (nuclear) opalescence, and changes in the vitreous humor) were seen in both sexes at all doses. Effects were apparent at 5-10 weeks at the high dose and occurred more slowly at the low and mid doses. Diuresis was observed at the mid and high dose. Overnight urine volume and water intake were increased but no renal damage or functional changes were observed. Persistently increased CV and hemoglobin levels were seen at the high dose. Authors identified a LOAEL of 1,100 mg/kg/day (786 mg/kg/day for 7 days/week) for ocular effects and NOAEL of 1,100 mg/kg/day and LOAEL of 3,300 mg/kg/day (2,357 mg/kg/day for 7 days/week) for other systemic effects.
    - *Oral*: In a GLP-compliant chronic oral toxicity study conducted according to OECD Guideline 452 in male and female Sprague-Dawley rats, animals (50/sex/dose) were administered oral doses of dimethyl sulfoxide (purity not specified) in water at 0, 1,100, 3,300, or 9,900 mg/kg/day via gavage 5 days/week for 18 months (equivalent to 786, 2,357, or 7,071 mg/kg/day when adjusted to a 7-day/week exposure frequency). Body weight and weight gain were slightly decreased (<10%) at the low dose and above. Some degree of refractive change in the lens was seen in 3 rats in the high dose group. Hemoglobin and PCV were slightly reduced in males at the high dose. Authors identified a NOAEL and LOAEL of 3,300 and 9,900 mg/kg/day (equivalent to 2,357 and 7,071 mg/kg/day for 7 days/week).

[16] 1,100 mg/kg/day * 5days/7days = 786 mg/kg/day

- *Oral*: In a chronic oral toxicity study similar to OECD Guideline 452 in male and female rhesus monkeys (*Macaca mulatta*), animals (1-3/sex/dose) were administered oral doses of dimethyl sulfoxide (purity not specified) in water at 0, 990, 2,790, or 8,910 mg/kg/day gavage daily for 18 weeks. The highest dose was not well tolerated and resulted in death of 5 animals. No effects on physical examination (blood pressure, respiratory rate, body temperature, 48- hour water consumption, neurological reflexes, and electrocardiograms were seen. Body weight was markedly reduced in the high dose group. No evidence of ophthalmoscopic changes to the lens typical in other species was seen in any animal. No effects on hematology, clinical chemistry, urinalysis, or gross pathology were seen. Authors identified a NOAEL of 2,970 mg/kg/day and LOAEL of 8,910 mg/kg/day.
- *Dermal*: In a chronic dermal toxicity study similar to OECD Guideline 452 in male and female rhesus monkeys (*Macaca mulatta*), animals (1-3/sex/dose) were openly administered 990, 2,790, or 8,910 mg/kg/day dimethyl sulfoxide (purity not specified) in water to the abdomen daily for 18 months. No mortality or clinical signs of toxicity were seen. Body weight gain was slightly reduced in all doses but was not considered by authors to be biologically significant due to the limited number of animals and wide range of initial weights. Dermal irritation was seen at all doses. No effects on ophthalmoscopic examination, urinalysis, neurobehavior, organ weights, or gross pathology were seen. Authors identified a NOAEL of 8,910 mg/kg/day for systemic toxicity.
- *Inhalation*: In a GLP-compliant subchronic inhalation toxicity study according to OECD Guideline 413/EPA OPPTS 870.3465 in male and female Sprague-Dawley rats, animals (10/sex/dose) were administered 0, 0.310, 0.964, or 2.783 mg/kg/day dimethyl sulfoxide (pure, 100% purity) vapor or vapor/aerosol atmosphere via nose-only inhalation for 6 hours/day, 7 days/week for 13 weeks. Local respiratory tract irritation was seen at the high dose. Reduced weight gain in treated animals was considered by authors to be a result of the irritating effects. No effects on ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology. Authors identified a NOAEC of 2.783 mg/L/6h.

- U.S. EPA 2009
  - U.S. EPA reports an inhalation NOAEC of 2.8 mg/L in rats and oral and dermal NOAELs of 1,000 mg/kg/day in monkeys. No additional details were provided.
- OECD 2008
  - OECD reports that dimethyl sulfoxide is of low toxicity. The NOAEC for systemic toxicity is 2.8 mg/L from a 13-week inhalation toxicity study in rats. Other non-guideline studies showed only slight systemic toxicity, including decreased weight gain and hematological effects, at very high doses. The most common effects were changes to the refractive power of the lens, which was apparent after repeated oral doses of 3,000 mg/kg/day in rats for 18 months and 1,000 mg/kg/day in dogs for 2. Similar ocular effects were seen at a dose of 1,000 mg/kg/day in dermal studies in rabbits for 30 days, dogs for 118 days, and pigs for 18 weeks. Ocular effects were not apparent at high dermal doses in dermal studies in monkeys that resulted in systemic toxicity, and have not been seen in humans including after dermal exposure to 1,000 mg/kg/day for 3 months. OECD reported a NOAEL of 1,000 mg/kg/day for oral and dermal routes.
- HSDB 2015
  - When 9 mL of 90% dimethyl sulfoxide was dermally administered twice daily for 3 weeks to the trunk of 20 human volunteers, there were no treatment-related effects on complete blood count, urinalysis, blood sedimentation rate, and SGOT, BUN, and fasting blood sugar. Dermal irritation was seen with repeated exposure. Systemic effects (rash, abdominal

cramps, nausea, chills, and chest pain) were seen in two individuals but resolved despite continued treatment. In a similar study involving the same treatment for 26 weeks, no adverse effects were seen.

- Based on the weight of evidence, a high confidence score of Low was assigned. Several well conducted and reported studies were identified for several species, and the lowest NOAEL/NOAECs identified were 1,100 mg/kg/day from a 2-year oral toxicity study in dogs, 8,910 mg/kg/day from an 18 month dermal toxicity study in monkeys, and of 2.783 mg/L/6h from a 13-week inhalation toxicity study in rats. These values all correspond to a Low score, and the confidence level is high due to the large number of well reported studies consistently demonstrating a low order of toxicity.

Neurotoxicity (N)

***Group II Score (single dose)* (vH, H, M, or L): L**

Dimethyl sulfoxide was assigned a score of Low for neurotoxicity (single dose) based on a lack of neurological effects in oral studies of rats and mice at doses of greater than 10 g/kg and in an inhalation study of rats administered a saturated atmosphere. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when no evidence of neurotoxicity is seen below the guidance values of 2,000 mg/kg for an oral study and 20 mg/L for an inhalation study (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- U.S. EPA 2006
  - Massive single doses of dimethyl sulfoxide produce rapid breathing, restlessness, and coma leading to hypothermia and death in experimental animals. Lethal oral doses cause ataxia, myasthenia, decreased motor activity, while non-lethal oral doses produced only decreased motor activity.
- HSDB 2015
  - Mixed sensorimotor peripheral neuropathy and segmental demyelination were seen in a 63 year old arthritic patient following topical administration of a 90% solution of dimethyl sulfoxide. The duration of exposure is not clear from the study description.
- ECHA 2017a
  - *Oral*: In the acute oral toxicity study in male and female Carworth CFN rats that identified an LD_{50} of 28,500 mg/kg, animals (5/sex/dose) received a single oral dose of 10, 20, or 40 g/kg dimethyl sulfoxide (purity not specified) via gavage and were observed for 14 days. Ataxia, myasthenia, decreased motor activity, and bradypnea were seen at lethal doses. Decreased motor activity was seen at non-lethal doses.
  - *Oral*: In the acute oral toxicity study in male and female albino mice that identified an LD_{50} of 21,400 mg/kg, animals (5/sex/dose) received a single oral dose of 10, 20, or 40 g/kg dimethyl sulfoxide (purity not specified) via gavage and were observed for 14 days. Ataxia, myasthenia, decreased motor activity, and bradypnea were seen at lethal doses. Decreased motor activity was seen at non-lethal doses.
  - *Inhalation*: In the GLP-compliant acute inhalation study conducted according to OECD Guideline 403 in male and female Sprague-Dawley rats that identified an LC_{50} of > 5.33 mg/L, animals (5/sex/dose) were administered dimethyl sulfoxide (99.88% purity) via nose only inhalation at concentrations of 0, 0.9, and 5.33 mg/L for 4 hours and were observed for 14 days. No effects on behavior were seen. No additional details were provided.

- *Inhalation*: In the acute inhalation study in male Sprague-Dawley rats that identified an LC_{50} of > 1.6 mg/L, 8 animals were administered 1.6 mg/L dimethyl sulfoxide (spectrograde purity) via whole body inhalation for 4 hours and were observed for 14 days. No unusual behavior was reported.

- Based on the weight of evidence, a high confidence score of Low was assigned. Although there is a case report of peripheral neuropathy and segmental demyelination in one individual following topical administration, considering that dimethyl sulfoxide is commonly used in medicine and industry, ToxServices does not consider a single case report sufficient to warrant classification. In addition, ToxServices did not consider decreased motor activity in rats and mice at oral doses of > 10 g/kg to be evidence of narcotic effects due to the extremely high doses and lack of additional narcotic effects in the oral or inhalation studies. No evidence of neurotoxicity was seen in inhalation studies, including a GLP-compliant study in rats that were tested at up to a saturated atmosphere. Therefore, a score of Low was assigned.

Group II* Score (repeated dose) **(H, M, or L): L**

Dimethyl sulfoxide was assigned a score of Low for neurotoxicity (repeated dose) based on a NOAEC of 2.783 mg/L based on the lack of effects in a neurobehavioral battery in a GLP-compliant 13-week inhalation toxicity study in rats, with support from chronic studies in monkeys that demonstrate a lack of effects at oral and dermal doses of 8,910 mg/kg/day. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when no evidence of neurotoxicity is seen below the guidance values of 100 mg/kg/day for an oral study, 200 mg/kg/day for a dermal study, and 1.0 mg/L/6h (vapor) for an inhalation study (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2017a
  - *Oral*: In the chronic oral toxicity study similar to OECD Guideline 452 in male and female rhesus monkeys that was described above for systemic toxicity, animals (1-3/sex/dose) were administered 990, 2,790, or 8,910 mg/kg/day dimethyl sulfoxide (purity not specified) in water via gavage daily for 18 weeks. No effects on physical examination (blood pressure, respiratory rate, body temperature, 48- hour water consumption, neurological reflexes, and electrocardiograms) were seen. No additional details were provided.
  - *Dermal*: In the chronic dermal toxicity study similar to OECD Guideline 452 in male and female rhesus monkeys that was described above for systemic toxicity, animals (1-3/sex/dose) were openly administered 990, 2,790, or 8,910 mg/kg/day dimethyl sulfoxide (pharmaceutical grade purity) to the abdomen daily for 18 months. No effects on neurobehavior were seen. No additional details were provided.
  - *Inhalation*: In the GLP-compliant subchronic inhalation toxicity study according to OECD Guideline 413 in male and female Sprague-Dawley rats described above for repeated dose toxicity, no effects on a neurobehavioral examination conducted prior to exposure, during week 12, and during a 4-week recovery period, or effects on a shortened battery of observations during weeks 1-11 of the study were seen. No additional details were provided. ToxServices identified a NOAEC of 2.783 mg/L based on the lack of neurological effects.
- Based on the weight of evidence, a high confidence score of Low was assigned based on a lack of effects on a neurobehavioral examination in a GLP-compliant 13-week inhalation toxicity study in

rats. Though not well described, a lack of effects on neurobehavior, blood pressure, respiratory rate, and body temperature in chronic oral and dermal studies in monkeys also supports a low potential for neurotoxicity.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L

Dimethyl sulfoxide was assigned a score of Low for skin sensitization based on negative results in guinea pig maximization tests, a mouse LLNA, a mouse ear swelling test, a Buehler test, and several non-standard assays. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative data, no structural alerts, and no GHS classification are available (CPA 2017c). The confidence in the score is high as it is based on measured data from guideline studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
  - A guinea pig maximization test conducted according to OECD Guideline 406 was performed with female Hartley guinea pigs (10/dose group) administered dermal doses of dimethyl sulfoxide (purity not specified). The induction doses were administered as intradermal injections of undiluted dimethyl sulfoxide. The second induction dose was applied an unspecified number of days later as a topical application of undiluted dimethyl sulfoxide without coverage (open). The challenge dose was applied 21 days after the intradermal induction dose as 0.1 mL undiluted dimethyl sulfoxide without coverage for 24 hours. The application sites were evaluated 48 hours after the challenge dose. No positive dermal reactions were observed following challenge with dimethyl sulfoxide. The positive control performed as expected.
  - A mouse local lymph node assay (LLNA) conducted in a manner similar to OECD Guideline 429 was performed with Balb/c mice (3/dose group, sex not specified) administered dermal doses of dimethyl sulfoxide (purity not specified). The animals were administered topical applications of dimethyl sulfoxide in water at 0, 20, 50, or 100% to the dorsal surface of both ears on three consecutive days. The day after the final application, the animals were sacrificed and the draining auricular lymph nodes were isolated for the proliferation assay. The stimulation indices (SI) were 1.01, 1.18, and 2.65 for the 20, 50, and 100% solutions, respectively. As none of the SI values exceeded 3, the study authors concluded that dimethyl sulfoxide was not sensitizing to the skin in this study.
  - A guinea pig maximization test conducted in a manner similar to OECD Guideline 406 was performed with female Hartley guinea pigs (10/dose, three tests total for a total of 30 animals) administered dermal doses of dimethyl sulfoxide (purity not specified). The induction doses were administered as pairs of intra-cutaneous injections of 1:1 dilution of Freund's complete adjuvant (FCA) in sterile distilled water, 5% dimethyl sulfoxide in saline, and 10% dimethyl sulfoxide in 1:1 saline emulsified with FCA. On day 7, the area of the injections was clipped and a 0.5 mL application of dimethyl sulfoxide under occlusive dressing for an unspecified amount of time. The challenge dose was applied on day 21 as 0.5 mL of a 50% or 100% dimethyl sulfoxide solution in ethanol under occlusive dressing for 24 hours. The animals were evaluated 48 and 72 hours after challenge. None of the animals exhibited positive dermal reactions following challenge with 50 or 100% dimethyl sulfoxide. The positive control performed as expected. The study authors concluded that dimethyl sulfoxide was not sensitizing under the conditions of the assay.
  - Dimethyl sulfoxide (purity not reported) tested negative in a human patch test in 23

volunteers. It did not produce skin sensitization responses in any individuals that were induced with five consecutive 48-hour induction exposures of a 75% solution (following 24-hour pre-treatment with 5% sodium laurel sulfate) followed by challenge with a 25% solution of dimethyl sulfoxide.

- Dimethyl sulfoxide was negative in a Draize sensitization assay in female Hartley guinea pigs. Animals (10/treatment) were induced with 0.05 mL of a 0.1% solution of dimethyl sulfoxide (purity not reported) 3 times/week for a total of 10 injections. Animals were challenged 2 weeks after the final induction with in intradermal injection of 0.05 L dimethyl sulfoxide. The test was repeated 3 times. No positive responses were seen in any of the animals and authors concluded that the substance is not sensitizing.
- Dimethyl sulfoxide was negative in a Buehler test that was not conducted according to guidelines (GLP status not reported). Animals (10/treatment) were induced topically 3 times (weekly intervals) with a 50 % solution of dimethyl sulfoxide (purity not reported) under occlusion, and challenged with a 100% solution under occlusion in the fourth week. The study was repeated 3 times. No positive sensitization responses were observed. Authors concluded that the substance is not sensitizing.
- In a split adjuvant test in guinea pigs (sex and strain not specified), 10 animals were induced with 0.2 mL of a 50% solution of dimethyl sulfoxide (purity not reported) under occlusion, followed by a second induction 2 days later. After an additional 2 days, animals received 2 injections of 0.0075 mL Freund's Complete Adjuvant to the induction site as well as another topical induction with 0.2 mL of 50% test substance. Animals received a fourth topical occlusive induction two days later. Animals were challenged topically on day 22 with undiluted dimethyl sulfoxide. The experiment was repeated 3 times. There were no positive responses in any of the animals, and authors concluded that the substance was not sensitizing.
- Dimethyl sulfoxide was tested in a mouse ear swelling test that was not conducted according to any recognized guidelines (GLP status not reported). Female CF-1 mice (10-15/test group, 5-10/control group) received 2 intradermal injections of Freund's Complete Adjuvant (FCA) totaling 5 mL into the stomach prior to topical induction with 0.1 mL undiluted dimethyl sulfoxide (>98% purity) to shaved stomach skin under occlusion. Animals were induced on 4 consecutive days, and then challenged after 7 days with 0.02 mL undiluted test substance applied to the ear. There were no positive responses in any of the animals. Authors concluded that the substance is not sensitizing.
- Dimethyl sulfoxide was negative in a cyclophosphamide/Freund's Complete Adjuvant (FCA) test in guinea pigs (sex and strain not specified). Animals (10/treatment) received a daily occlusive topical induction with 0.2 mL of a 50% solution of dimethyl sulfoxide (purity not reported) on days 0-4. On day 4 animals received 2 injections of 0.0075 mL Freund's Complete Adjuvant to the induction site, and on day 9 animals received a final topical induction. Animals were challenged on day 22 with undiluted dimethyl sulfoxide. The test was repeated 3 times. No positive responses were seen in any of the animals. Authors concluded that dimethyl sulfoxide is not sensitizing.

- Based on the weight of evidence, a high confidence score of Low was assigned. Although GLP status was not reported for any of the available studies, all were well reported and several were conducted according to or similar to guidelines. There was no evidence of sensitization in any of the assays, which include guinea pig maximization tests, a mouse LLNA, a mouse ear swelling test, a Buehler test, and several non-standard assays. Therefore, a score of Low was assigned.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): *L*

Dimethyl sulfoxide was assigned a score of Low for respiratory sensitization based on ECHA guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2017c). Confidence in this score is reduced because there are not validated test methods for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- No measured data were identified.
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2016). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2016). As dimethyl sulfoxide was not sensitizing to the skin in guinea pig maximization tests, a mouse LLNA, a mouse ear swelling test, a Buehler test, and several non-standard assays, and a literature search did not find any human evidence of respiratory sensitization by dimethyl sulfoxide, and as it does not contain any structural alerts for respiratory sensitization (OECD 2016), it is not expected to be a respiratory sensitizer. Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): *M*

Dimethyl sulfoxide was assigned a score of Moderate for skin irritation/corrosivity based on evidence of mild irritation in humans and classification to GHS Category 3 in New Zealand. GreenScreen® criteria classify chemicals as a Moderate hazard for skin irritation/corrosivity when available data indicate that GHS Category 3 classification is appropriate (CPA 2017c). The confidence in the score is low as it is based on the results of human studies with limited details and a screening list.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:*
        - New Zealand - GHS - 6.3B - Mildly irritating to the skin
            - Based on evidence of dermal irritation (erythema, scaling, contact urticarial, stinging, and burning) in 20 human volunteers that were dermally administered 9 mL of a 90% solution of dimethyl sulfoxide to the trunk twice daily for 3 weeks (CCID 207).
- ECHA 2017a
    - Dimethyl sulfoxide (99.98% purity) was slightly irritating in a GLP-compliant dermal irritation study that was conducted according to OECD Guideline 404 in 3 New Zealand White rabbits (sex not specified). The mean scores for erythema at 24, 48, and 72 hours were 0.3 for animal 1, 0 for animal 2, and 0.7 for animal 3, with an overall mean of 0.67. Effects were reversible within 48-72 hours. The mean scores for edema at 24, 48, and 72 hours were 0 for all animals.
        - Based on the results of this test, ToxServices would not classify dimethyl sulfoxide as a skin irritant under GHS criteria (UN 2015). GHS criteria define skin irritants as chemicals that produce mean erythema and/or edema scores ≥ 1.5 from gradings in at least 2 of 3 animals from grades at 24, 48, and 72 hours.

- In 500 patients treated therapeutically with dimethyl sulfoxide (90%) for up to 14 months, transient erythema, burning, stinging, and itching were observed.
- In a modified Draize test, 6 male Hartley guinea pigs were administered dimethyl sulfoxide (volume and purity not specified) to shaved skin for 4 hours under occlusion and were observed at 4, 24, 48, and 72 hours after application. The mean primary dermal irritation indices at 4, 24, 48, and 72 hours were 1.2, 0.4, 0, and 0, respectively. The mean erythema scores at 4, 24, 48, and 72 hours were 1.9, 0.8, 0.1, and 0, respectively. The mean edema scores at 4, 24, 48, and 72 hours were 0.4, 0, 0, and 0, respectively. All effects resolved within 72 hours. Authors concluded that the substance is slightly irritating.
- When 9 human volunteers were administered 0.75 mL of a 90% solution of dimethyl sulfoxide under occlusion for 30-35 days, dermatitis occurred within 24 hours, increased for 12 days, and then resolved. At the conclusion of the study, slight scaling, pigmentation change, hyperkeratosis, and acanthosis were seen.
- When 10 male guinea pigs (strain not specified) were administered 0.5 mL dimethyl sulfoxide (purity not specified) to shaved back and shoulder skin 4 times daily for up to 63 days, erythema became apparent after 2 days and gradually decreased. Scaling was observed by day 9 and edema was seen at day 12 and lessened within 5-7 days. Skin remained scaly throughout the experiment, and was mildly to moderately thickened 6 months after the conclusion of the study. Authors concluded that the substance is slightly irritating.
- When 29 human volunteers were openly administered 0, 30, 40, 50, 60, 70, 80, 90 or 100% medicinal grade dimethyl sulfoxide for 40-60 minutes, concentrations of 80-90% produced erythema and occasional whealing. Similar effects were seen in many individuals at concentrations of 70-80%. Authors concluded that the substance is slightly irritating.
- No evidence of dermal irritation was seen in 5 male AH mice that were painted with undiluted dimethyl sulfoxide on the dorsal scapula twice weekly for 30 weeks. No additional details were provided.
- Dimethyl sulfoxide produced mild irritation when an unspecified volume was administered to the abraded skin of 6 New Zealand White rabbits for 24 hours under occlusion. Slight erythema was seen, and faded after removal of the patch.
- In a poorly described study in humans, solutions of 50-90% produced death of the outer epidermis followed by rapid regeneration (within 4 days).
- Local irritation has been observed in 548 patients that were treated daily with dimethyl sulfoxide (60-90%) for 7 days-10 months. Erythema, itching, and local urticarial were seen and resolved within 2-3 hours.
- Dimethyl sulfoxide caused slight irritation in 91.9% of 1,097 patients that received therapeutic single or short-term applications of a 90% solution. Itching, warmth, and transient erythema were seen. In 33.2% of patients, burning, stinging, and erythema were seen for 3-4 hours. Occasional urticarial was seen in 56.5% of patients. Severe reactions were seen in 2.2% of patients.

- HSDB 2015
  - Erythema and pruritis have been observed in humans immediately upon contact with undiluted dimethyl sulfoxide. Solutions of 70% are not usually irritating but solutions of 10% may cause irritation in sensitive individuals.
- Based on the weight of evidence, a low confidence score of Moderate was assigned. Although scores for slight irritation in the GLP-compliant dermal irritation test in rabbits do not warrant GHS classification, numerous reports in humans indicate that mild but reversible irritation may occur following dermal exposure. Therefore, ToxServices conservatively classified dimethyl sulfoxide to

GHS Category 3 (causes mild skin irritation) based on effects seen in human studies. This is consistent with GHS classification in New Zealand, which is also based on effects seen in humans. Confidence in this score is reduced because the studies in humans are not reported in great detail, and because GHS New Zealand is a screening list.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): *M*

Dimethyl sulfoxide was assigned a score of Moderate for eye irritation/corrosivity based on results in humans, and in several ocular irritation studies in rabbits that demonstrate at most slight irritation that does not warrant GHS classification. GreenScreen® criteria classify chemicals as a Moderate hazard for eye irritation/corrosivity when they are classified to GHS category 2B (CPA 2017c). The confidence in the score is low as there are limited details for the human study and they are inconsistent with the results observed in the animal studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:*
        - New Zealand - GHS - 6.4A - Irritating to the eye (Cat. 2A)
            - Based on the weight of evidence indicating irritation to the eye with high doses (CCID 2017).
- HSDB 2015
    - Administration of 2 drops of solutions of > 50% dimethyl sulfoxide into the eye produced temporary burning and vasodilation, while solutions of < 50% had no effects.
- ECHA 2017a
    - An ocular irritation test conducted according to OECD Guideline 405 was performed with rabbits (3 total, sex and strain not specified) administered ocular instillations of 0.1 mL undiluted dimethyl sulfoxide (purity not specified) for 24 hours. No details on washing of the eyes or duration of the observation period were provided. At 24, 48, and 72 hours, the mean chemosis score was 0.33/4 (individual scores of 0.3, 0.7, and 0), the mean conjunctival score was 1.13/3 (individual scores of 1, 1.7, and 0.7), the mean corneal opacity score was 0/4, and the mean iris score was 0/2. The chemosis resolved within 48 hours and the conjunctival effects resolved within 4 days. The study authors concluded that dimethyl sulfoxide was slightly irritating to the eyes in this study.
        - Based on the results of the above test, ToxServices would not classify dimethyl sulfoxide as an eye irritant under GHS criteria (UN 2015). Under GHS criteria, chemicals are classified as eye irritants if they produce mean scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following gradings at 24, 48, and 72 hours, and the irritant effects are fully reversible within 7 days.
    - An ocular irritation test conducted according to EU Method B.5 was performed with new Zealand White rabbits (6 total, sex not specified) administered ocular instillations of 0.1 mL undiluted dimethyl sulfoxide (purity not specified) for 24 hours. No information washing of the eyes was provided. An observation period of 7 days followed the instillation. At 24, 48, and 72 hours, the mean corneal opacity score was 0.06/4, the mean iris score was 0.11/2, the mean chemosis score was 0/4, and the mean conjunctival score was 0.95/3. The corneal, iris, and conjunctival effects were fully reversible within 48, 72, and 96 hours, respectively. The study authors concluded that dimethyl sulfoxide produces immediate and slight reversible effects on the conjunctiva, and that it does not warrant classification.
        - Based on the results of the above test, ToxServices would not classify dimethyl sulfoxide as an eye irritant under GHS criteria (UN 2015). Under GHS criteria,

chemicals are classified as eye irritants if they produce mean scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following gradings at 24, 48, and 72 hours, and the irritant effects are fully reversible within 7 days.
    - Dimethyl sulfoxide was slightly irritating in a Draize eye irritation test in 6 albino rabbits (strain not specified). Animals received a single instillation of 0.1 mL and were observed after 2 hours and daily for 11 days. The mean overall irritation scores (out of 110) were 8 at 2 hours, 2 at 24 hours, and 0 at 3 and 7 days. No additional details were provided.
    - In humans, 2 drops of up to 50% dimethyl sulfoxide produced no effects on the eye. A 50% solution caused transient burning, and a 90% solution caused temporary stinging and burning. Effects resolved within 24 hours. No additional details were provided.
    - When 0.2 mL of dimethyl sulfoxide at concentrations of 10, 15, 30, or 100% was instilled into the eyes of New Zealand White rabbits (number and sex not specified) 3 times/day for 6 months, there were no effects on the iris, cornea, lens, retina, conjunctiva, or lids. The only effect seen was temporary lacrimation in animals that were treated with undiluted dimethyl sulfoxide. Authors concluded that the substance is slightly irritating.
- Based on the weight of evidence, a low confidence score of Moderate was assigned. Numerous well conducted and reported studies report at most slight irritation in animals, and none of the studies indicate that GHS classification is warranted. The only study in humans indicate that concentrated dimethyl sulfoxide has the potential to induce transient eye irritation. The GHS Category 2A classification by New Zealand corresponds to a score of High, but the overall weight evidence suggests at most slight eye irritation.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L

Dimethyl sulfoxide was assigned a score of Low for acute aquatic toxicity based on numerous LC/EC_{50} values that exceed 100 mg/L in well conducted studies for all three trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when the most conservative LC/EC_{50} values are greater than 100 mg/L (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
    - Note: Due to the large number of studies available in the REACH Dossier, only those reported with a score of 1 (reliable) or 2 (reliable with restriction) for reliability were included in the assessment.
    - 96-hour LC_{50} (*Salvenilus fontinales*, brook trout) = 36.5 g/L
    - 96-hour LC_{50} (*Salvenilus namaycush*, lake trout) = 37.3 g/L
    - 96-hour LC_{50} (*Oncorhynchus mykis*, rainbow trout) = 32.3 g/L
    - 96-hour LC_{50} (*Cyprinus carpio*, carp) = 41.7 g/L
    - 96-hour LC_{50} (*Ictalurus melas*, black bullhead) = 36.5 g/L
    - 96-hour LC_{50} (*Ictalurus punctatus*, channel catfish) = 32.5 g/L
    - 96-hour LC_{50} (*Lepomis cyanellus*, green sunfish) = 43.0 g/L
    - 96-hour LC_{50} (*Lepomis macrochirus*, bluegill) = 33.5 g/L
    - 96-hour LC_{50} (*Perca flavascens*, yellow perch) = 37.0 g/L
    - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) = 34.0 g/L

- 96-hour LC_{50} (*Danio rerio*, zebrafish)greater than 25 g/L (GLP-compliant, OECD Guideline 203)
- 48-hour mobility EC_{50} (*Daphnia magna*, water flea) = 24.6 g/L (OECD Guideline 202)
- 72-hour growth EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 17 g/L (GLP-compliant, OECD Guideline 201)
- 72-hour biomass EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 12 g/L (biomass) (GLP-compliant, OECD Guideline 201)

- Based on the weight of evidence, a high confidence score of Low was assigned. All LC/E_{50} values from numerous acute aquatic toxicity studies, including studies conducted according to GLP and OECD guidelines, greatly exceed 100 mg/L for all three trophic levels.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*

Dimethyl sulfoxide was assigned a score of Low for chronic aquatic toxicity based on numerous chronic aquatic toxicity values in fish, invertebrates, and algae that demonstrate a lack of effects below the guidance value. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L and the chemical is not present on authoritative or screening lists (CPA 2017c). Confidence in this score is reduced due to the lack of well reported chronic toxicity studies for invertebrates and fish.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2017a
  - 72-hour EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 17 g/L (growth), 12 g/L (biomass) (OECD Guideline 201, GLP) (NOEC not reported)
- U.S. EPA 2017b
  - The ECOTOX database reports on numerous chronic aquatic toxicity studies with NOEC values ranging from 0.22 g/L (the only dose tested) to 5.5 g/L in blue green algae, 0.19 mg/L (the only dose tested) to > 6 g/L in non-standard aquatic invertebrate species, 11 mg/L (the only dose tested) to > 42 g/L in standard aquatic invertebrate species, and < 100 mg/L (the only dose tested) to 100 g/L in standard fish test species. Experimental details were not reported in the ECOTOX database.
- U.S. EPA 2012a
  - Dimethyl sulfoxide is designated to the neutral organics ECOSAR chemical classes. The most conservative predicted ChV values are 4,443 mg/L in fish, 1,125 mg/L in daphnia, and 744 mg/L in green algae (Appendix E).
- Based on the weight of evidence, a low confidence score of Low was assigned. In a GLP-compliant study in green algae, the 96-hour EC_{50} was 12 g/L. Although no NOEC was reported, because this value exceeds the guidance value of 10 mg/L by 1,200-fold, no effects are expected below the guidance value. The ECOTOX database reported numerous chronic aquatic toxicity values for algae, invertebrates, and fish. None of these studies reported effects below the guidance value of 10 mg/L; however, few details were reported and the quality of the studies cannot be fully assessed due to the lack of experimental details provided. Modeling also reports ChVs that greatly exceed the guidance value of 10 mg/L, which also supports a score of Low. Therefore, a score of Low was assigned, but confidence in this score is reduced due to the lack of well reported chronic toxicity studies for invertebrates and fish.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *L*

Dimethyl sulfoxide was assigned a score of Low for persistence based on a weight of evidence evaluation that indicates that it meets the GHS criteria for rapid degradability. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they meet GHS rapid degradability criteria, and mainly partition to water, soil or sediment (CPA 2017c). Confidence in the score is reduced due to the conflicting data and use of modeling.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:*
        - EC - CEPA DSL - Persistent
- ECHA 2017a
    - In a GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 D (Closed Bottle Test), secondary effluent from a wastewater treatment plant was exposed to dimethyl sulfoxide (purity not specified) at 2 mg/L for 28 days. The level of degradation was 5% after 7 days, 7% after 14 days, 18% after 21 days and 31% after 28 days as measured by O_2 consumption. The study authors concluded that dimethyl sulfoxide was not readily biodegradable under the conditions of this test.
    - A ready biodegradability test conducted according to OECD Guideline 301 C (Modified MITI Test) was performed with activated sludge (adaptation not specified) exposed to dimethyl sulfoxide (purity not specified) at 100 mg/L for 14 days. At the end of the exposure period, the level of degradation was 3.1%. The study authors concluded that dimethyl sulfoxide was not readily biodegradable under the conditions of this test.
    - A biodegradability test conducted according to ISO 7827 (Evaluation in an Aqueous Medium of the "Ultimate" Aerobic Biodegradability of Organic Compounds - Method by Analysis of Dissolved Organic Carbon (DOC)) was performed with an inoculum (not identified) exposed to dimethyl sulfoxide (purity not specified) at 162 mg/L for 28 days. At the end of the exposure period, the level of degradation was 99% and the study authors concluded that dimethyl sulfoxide was readily biodegradable in this test.
    - In a non-GLP-compliant degradation test conducted according to EPA OPPTS 835.3170, adapted, activated industrial sludge was exposed to dimethyl sulfoxide (purity not specified) at 200, 400, 600, or 1,000 mg/L at 20, 25, 30, 35 or 40°C and pH of 3.0, 5.0, 7.0, 8.5, or 10. Optimal degradation of dimethyl sulfoxide occurred within 37 hours at pH 7.1-8.5 and 30°C. At 20, 25, and 35°C, complete degradation of DMSO required 80, 44, and 80 hours, respectively, and the optimum pH range for dimethyl sulfoxide degradation was 7.0-8.5.
- U.S. EPA 2009
    - Although conflicting results are available regarding rate of biodegradation, dimethyl sulfoxide is considered to have low persistence.
- OECD 2008
    - One biodegradation study according to AFNOR NF T 90 -312 concludes that dimethyl sulfoxide is readily biodegradable, but based on a weight of evidence approach, OECD considers dimethyl sulfoxide to be inherently but not readily degradable.
- U.S. EPA 2012b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that dimethyl sulfoxide is not expected to be readily biodegradable. Fugacity modeling predicts 62.8% will partition to soil with a half-life of 30 days, 37% will partition to water with a half-life of 15 days, and

0.071% will partition to sediment with a half-life of 135 days (Appendix F).

- Based on the weight of evidence, a low confidence score of Low was assigned. Although this chemical is classified as persistent on Environment Canada's DSL, numerous studies demonstrating a moderate to high degree of biodegradation suggest that the corresponding score of High to Very High may not be warranted. Results for biodegradation studies vary, but the majority of studies indicate that dimethyl sulfoxide meets the 28-day biodegradation window. It was not readily biodegradable in a GLP-compliant OECD Guideline 301D (Ready Biodegradability: Closed Bottle Test) study, achieving only 30% biodegradation in 22 days. However, it achieved 100% biodegradation within 80 hours in a ready biodegradability test according to EPA OPPTS 835.3170 (Shake Flask Die-away Test) and 99% biodegradation in 27 days (no information regarding the 10-day window was reported) in a biodegradation study according to ISO. In its review of dimethyl sulfoxide, OECD concluded that the weight of evidence indicates that dimethyl sulfoxide is inherently, but not readily, biodegradable. U.S. EPA concludes that dimethyl sulfoxide has low persistence. Modeling predicts that it will mainly partition to soil with a half-life of 30 days. Based on the majority of the studies reporting that it meets the 28-day window (but not necessarily the 10-day window), ToxServices classified dimethyl sulfoxide as GHS rapidly degradable, which warrants a score of Low for chemicals that mainly partition to soil, sediment or water.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

Dimethyl sulfoxide was assigned a score of Very Low for bioaccumulation based on a measured BCF less than 4 and a measured log K_{ow} of -1.35. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are no greater than 100 and log Kow values are no greater than 4 (CPA 2017c). The confidence in the score is high as it is based on measured values.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2009
  - Dimethyl sulfoxide has an experimental log K_{ow} of -1.35.
  - Dimethyl sulfoxide has low bioaccumulation potential based on a measured BCF of < 4
- ECHA 2017a
  - A bioaccumulation test conducted according to OECD Guideline 305C was performed in carp (*Cyprinus carpio*) exposed to dimethyl sulfoxide at 0.1 or 1 mg/L for 42 days in a continuous flow system. A BCF less than 4 was measured. No additional details were provided.
- U.S. EPA 2012
  - BCFBAF predicts a BCF of 0.8952 based on a log K_{ow} of -1.35 (Appendix F).
- Based on the weight of evidence, a high confidence score of Very Low was assigned based on an experimental log K_{ow} of -1.35, which indicates that this substance is highly hydrophilic and therefore unlikely to bioaccumulate. A measured BCF of 4 in carp supports the score of Very Low. Modeling also predicts a BCF of 0.8952, which corresponds to a Very Low.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*

Dimethyl sulfoxide was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2017c). The confidence in the score is low as it is not based on measured data or authoritative lists.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Sigma-Aldrich 2016
  - A safety data sheet for dimethyl sulfoxide indicates that it has a physical hazard score of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives") and a reactivity hazard score of 0 from NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water (e.g. helium, N2)").
- Based on the information presented in the safety data sheet, ToxServices did not classify dimethyl sulfoxide as a reactive chemical under GHS criteria (UN 2015).

Flammability (F) Score (vH, H, M, or L): M

Dimethyl sulfoxide was assigned a score of Moderate for flammability based on ToxServices classifying it as a Category 4 flammable liquid under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when they are classified as GHS Category 4 flammable liquids (CPA 2017c). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - New Zealand - GHS - 3.1D - Flammable Liquids: low hazard
      - Based on a flash point of 87°C in a closed cup test and a boiling point of 189°C (CCID 2017).
    - Québec CSST - WHMIS 1988 - Class B3 - Combustible liquids
- ECHA 2017a
  - Dimethyl sulfoxide has a flash point of 87°C in a closed cup test conducted according to ASTM D93.
  - Dimethyl sulfoxide has a flash point of 95°C in an open cup test.
  - Dimethyl sulfoxide has an auto-ignition temperature of 300-419°C.
- Based on the weight of evidence, a ToxServices classified dimethyl sulfoxide as a Category 4 flammable liquid under GHS criteria (UN 2015). GHS criteria define flammable liquids as chemicals that have a flash point > 60°C and ≤ 93°C. This GHS classification corresponds to a score of Moderate, which is consistent with the New Zealand GHS classification and WHMIS Class B3.

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Dimethyl Sulfoxide (CAS #67-68-5)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**Dimethyl Sulfoxide**	**67-68-5**	*L*	**L**	*L*	**L**	DG	**L**	**L**	**L**	**L**	**L**	**L**	*L*	*M*	*M*	**L**	*L*	*L*	**vL**	*L*	**M**

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	No	No	Yes	Yes			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Dimethyl Sulfoxide	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Dimethyl Sulfoxide	3

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

APPENDIX C: Pharos Output for Dimethyl Sulfoxide (CAS #67-68-5)

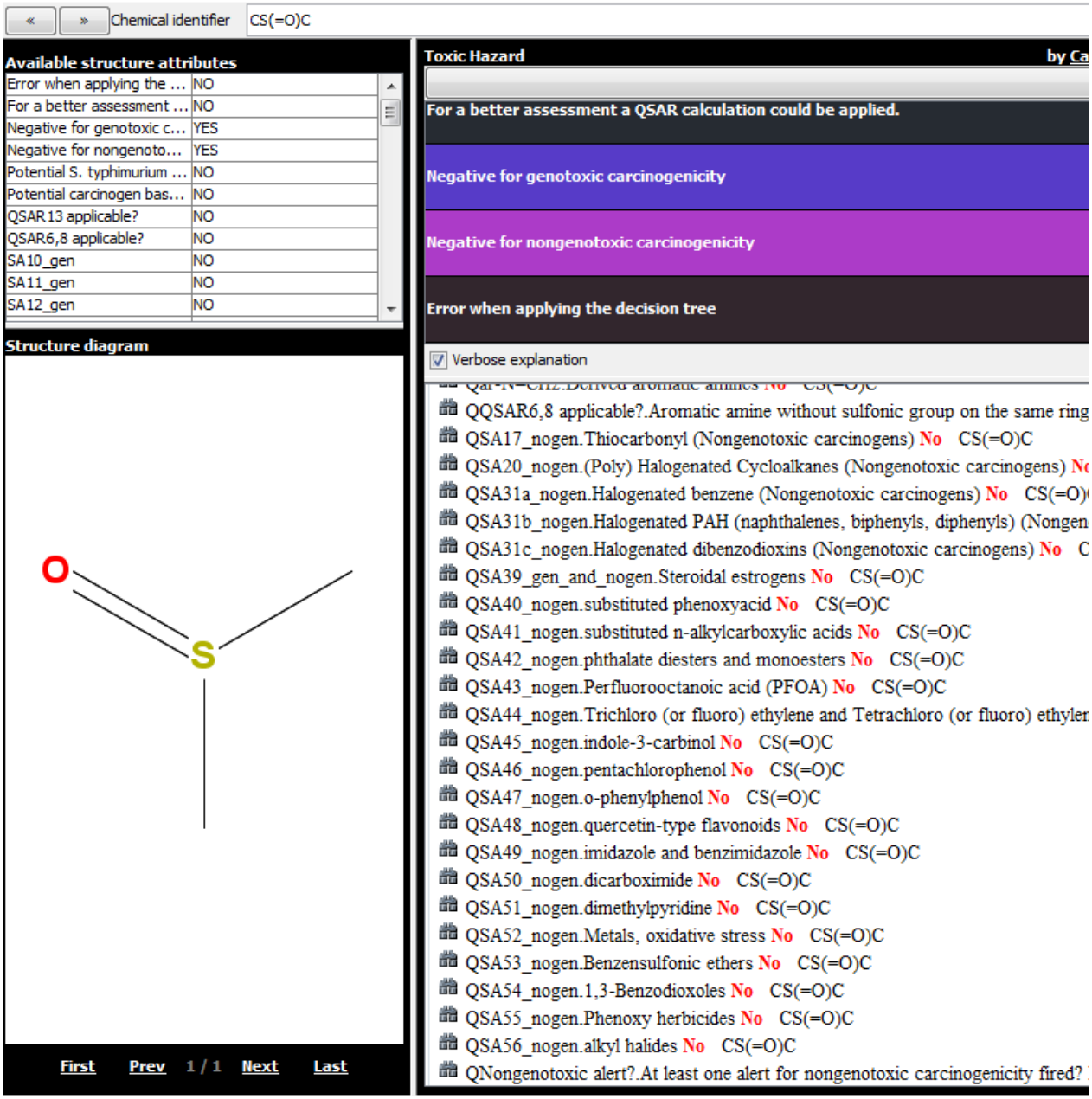
[67-68-5] DIMETHYL SULFOXIDE

General Information | Hazards | Process Chemistry Research | GreenScreen | C2C

Direct Hazards:

DEVELOPMENTAL	MAK - Pregnancy Risk Group B
EYE IRRITATION	New Zealand - GHS - 6.4A - Irritating to the eye (Cat. 2A)
SKIN IRRITATION	New Zealand - GHS - 6.3B - Mildly irritating to the skin
TERRESTRIAL	New Zealand - GHS - 9.3B - Ecotoxic to terrestrial vertebrates
FLAMMABLE	Québec CSST - WHMIS 1988 - Class B3 - Combustible liquids +1 New Zealand - GHS - 3.1D - Flammable Liquids: low hazard
RESTRICTED LIST	Health Canada - Cosmetic Ingredient Hotlist - Ingredients that are Prohibited for Use in Cosmetic Products +1 EU - Cosmetics Regulation Annex II - Prohibited in Cosmetic Products
MULTIPLE	German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters
PERSISTENT	EC - CEPA DSL - Persistent

APPENDIX D: Toxtree Skin Carcinogenicity Results for Dimethyl Sulfoxide (CAS #67-68-5)



APPENDIX E: ECOSAR Modeling Results for Dimethyl Sulfoxide (CAS #67-68-5)

ECOSAR Version 1.11 Results Page

SMILES: O=S(C)C
CHEM: Methane, sulfinylbis-
CAS Num: 000067-68-5
ChemID1:
MOL FOR: C2 H6 O1 S1
MOL WT: 78.13
Log K_{ow}: -1.222 (EPISuite K_{ow}win v1.68 Estimate)
Log K_{ow}: -1.350 (User Entered)
Log K_{ow}: -1.35 (PhysProp DB exp value - for comparison only)
Melt Pt: 18.50 (deg C, User Entered for Wat Sol estimate)
Melt Pt: 18.50 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 1E+006 (mg/L, EPISuite WSK_{ow}win v1.43 Estimate)
Wat Sol: 1E+006 (mg/L, User Entered)
Wat Sol: 1E+006 (mg/L, PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log K_{ow}: -1.350 (User Entered)
Wat Sol: 1E+006 (mg/L, User Entered)

Available Measured Data from ECOSAR Training Set

CAS No	Organism	Duration	End Pt	Measured mg/L (ppm)	Ecosar Class	Reference
000067-68-5	Fish	96-hr.	LC50	34000	Neutral organics	DUL

ECOSAR v1.1 Class-specific Estimations

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	: Fish	96-hr.	LC50	65471.262
Neutral Organics	: Daphnid	48-hr.	LC50	27284.473

Neutral Organics	: Green Algae	96-hr.	EC50	5656.993
Neutral Organics	: Fish		ChV	4443.197
Neutral Organics	: Daphnid		ChV	1125.008
Neutral Organics	: Green Algae		ChV	743.928
Neutral Organics	: Fish (SW)	96-hr.	LC50	80786.852
Neutral Organics	: Mysid	96-hr.	LC50	5.81e+005
Neutral Organics	: Fish (SW)		ChV	1133.759
Neutral Organics	: Mysid (SW)		ChV	1.35e+005
Neutral Organics	: Earthworm	14-day	LC50	302.281

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

Class Specific LogK_{ow} Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Neutral Organics:

Maximum LogK_{ow}: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogK_{ow}: 6.0 (Earthworm LC50)
Maximum LogK_{ow}: 6.4 (Green Algae EC50)
Maximum LogK_{ow}: 8.0 (ChV)

APPENDIX F: EPISuite Modeling Results for Dimethyl Sulfoxide (CAS #67-68-5)

CAS Number: 67-68-5
SMILES : O=S(C)C
CHEM : Methane, sulfinylbis-
MOL FOR: C2 H6 O1 S1
MOL WT : 78.13
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log K_{ow} (octanol-water): -1.35
Boiling Point (deg C): 85.00
Melting Point (deg C): 18.50
Vapor Pressure (mm Hg): 0.61
Water Solubility (mg/L): 1E+006
Henry LC (atm-m^3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{OW}WIN v1.68 estimate) = -1.22
Log K_{ow} (Exper. database match) = -1.35
Exper. Ref: HANSCH, C. ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 128.63 (Adapted Stein & Brown method)
Melting Pt (deg C): -49.71 (Mean or Weighted MP)
VP (mm Hg, 25 deg C): 70.8 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C): 9.44E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): 18.5 deg C
BP (exp database): 189 deg C
VP (exp database): 6.10E-01 mm Hg (8.13E+001 Pa) at 25 deg C

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 1e+006
log K_{ow} used: -1.35 (user entered)
melt pt used: 18.50 deg C
Water Sol (Exper. database match) = 1e+006 mg/L (deg C)
Exper. Ref: DORIGAN, J. ET AL. (1976A);@2ND

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method: 4.96E-008 atm-m^3/mole (5.02E-003 Pa-m^3/mole)
Group Method: 1.90E-003 atm-m^3/mole (1.92E+002 Pa-m^3/mole)
Exper Database: 1.51E-09 atm-m^3/mole (1.53E-004 Pa-m^3/mole)

For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 6.271E-008 atm-m^3/mole (6.354E-003 Pa-m^3/mole)
VP: 0.61 mm Hg (source: User-Entered)
WS: 1E+006 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: -1.35 (user entered)
Log K_{aw} used: -7.209 (exp database)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 5.859
Log K_{oa} (experimental database): 4.960

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model): 0.7104
Biowin2 (Non-Linear Model): 0.8698
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0265 (weeks)
Biowin4 (Primary Survey Model): 3.7350 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model): 0.4805
Biowin6 (MITI Non-Linear Model): 0.5766
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6769
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 81.3 Pa (0.61 mm Hg)
Log K_{oa} (Exp database): 4.960
Kp (particle/gas partition coef. (m^3/ug)):
Mackay model: 3.69E-008
Octanol/air (K_{oa}) model: 2.24E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model: 1.33E-006
Mackay model: 2.95E-006
Octanol/air (K_{oa}) model: 1.79E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 62.1216 E-12 cm^3/molecule-sec
Half-Life = 0.172 Days (12-hr day; 1.5E6 OH/cm^3)
Half-Life = 2.066 Hrs.
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

2.14E-006 (Junge-Pankow, Mackay avg)
1.79E-006 (K_{oa} method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc}: 2.082 L/kg (MCI method)
Log K_{oc}: 0.319 (MCI method)
K_{oc}: 1.877 L/kg (K_{ow} method)
Log K_{oc}: 0.273 (K_{ow} method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.6621 days (HL = 0.02177 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.048 (BCF = 0.8952)
Log BAF Arnot-Gobas method (upper trophic) = -0.048 (BAF = 0.8952)
log K_{ow} used: -1.35 (user entered)

Volatilization from Water:
Henry LC: 1.51E-009 atm-m^3/mole (Henry experimental database)
Half-Life from Model River: 3.427E+005 hours (1.428E+004 days)
Half-Life from Model Lake: 3.739E+006 hours (1.558E+005 days)

Removal in Wastewater Treatment:
Total removal: 75.06 percent
Total biodegradation: 74.44 percent
Total sludge adsorption: 0.62 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0325	4.14	1000
Water	37	360	1000
Soil	62.8	720	1000
Sediment	0.071	3.24e+003	0

Persistence Time: 573 hr

Licensed GreenScreen® Profilers

Dimethyl Sulfoxide GreenScreen® Evaluation Prepared by:

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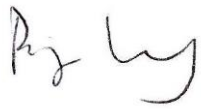
ToxServices LLC

Dimethyl Sulfoxide GreenScreen® Evaluation QC'd by:



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Dimethyl Sulfoxide GreenScreen® Update Prepared by:

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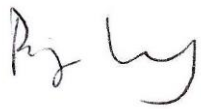

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