DIMETHYL CARBONATE

(CAS #616-38-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: July 5, 2023

Expiration Date: July 5, 2028

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1526 New Hampshire Ave., N.W., Suite 350
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Dimethyl Carbonate (CAS #616-38-6)

Dimethyl carbonate (DMC, IUPAC name: dimethyl carbonate) belongs to the chemical class of carbonic acid diesters in which carbonic acid has two hydrogens substituted with methyl groups. It functions as a solvent, reagent, and a "green" methylating agent in the methylation and phosgenation in organic synthesis including pharmaceuticals and bisphenol A polycarbonates, cold-sterilizing agent in beverage production, blowing agent in the production of polyurethane foam, non-aqueous component in the production of chargeable lithium batteries, and as a solvent, fragrance, and propellant in cosmetics formulations.

Based on its boiling point of 90.35ºC, DMC is a volatile organic chemical (VOC). However, it is exempt as a VOC in the United States (U.S.) according to 40 CFR 51.100(s)(1) due to negligible photochemical reactivity. DMC is very water soluble (114,700 mg/L). DMC is not explosive or oxidizing, but it is highly flammable.

DMC was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Health Hazard (carcinogenicity-C, and developmental toxicity-D)
- Benchmark 2g
    - High Flammability-F

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DMC meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if DMC were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

ToxServices's GreenScreen® Benchmark Score for DMC has not changed over time. The original GreenScreen® assessment was performed in 2018 under version v1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in 2019. Most recently, reclassification of the carcinogenicity endpoint from *Low* (low confidence) to *Moderate* (low confidence) and the single exposure systemic toxicity endpoint from **Low** (high confidence) to *Moderate* (low confidence) following a weight of evidence evaluation of this chemical's dataset did not change the BM-2 score.

New Alternative Methods (NAMs) used in this assessment include use of QSAR modeling for carcinogenicity, endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and a variety of *in vitro* studies for genotoxicity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in DMC's NAMs dataset include lack or insufficient experimental data to assess carcinogenicity, endocrine activity, and respiratory sensitization, and lack of validated test methods for respiratory sensitization. DMC's Type II (extrapolation output) uncertainties include reliance on structural alerts or models with undefined applicability domains to assess carcinogenicity and respiratory sensitization, inability of OncoLogic to evaluate the structure of the compound, reliance

on *in vitro* genotoxicity studies that do not fully mimic *in vivo* metabolism or that have no validated guidelines, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, and lack of consideration of non-immunological mechanisms of respiratory sensitization.

GreenScreen® Hazard Summary Table for DMC

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**
						s	r*	s	r*	*	*								
M	**L**	**L**	*M*	DG	**L**	*M*	**L**	**M**	DG	**L**	*L*	**L**	*M*	**L**	*L*	**vL**	**vL**	*L*	**H**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. 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. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Dimethyl Carbonate (DMC) (CAS #616-38-6)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 10, 2018

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: October 11, 2018

GreenScreen® Assessment (v.1.4) Updated By:
Name: Sara Ciotti, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: May 24, 2019

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 29, 2019

GreenScreen® Assessment (v.1.4) Updated By:
Name: Deb Remeikas, M.A.
Title: Toxicologist
Organization: ToxServices LLC
Date: May 5, 2023; July 3, 2023

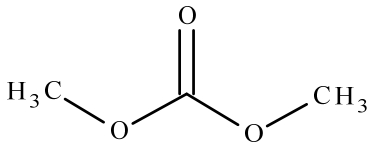
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: June 2, 2023; July 5, 2023

Expiration Date: July 5, 2028[2]

Chemical Name: Dimethyl Carbonate

CAS Number: 616-38-6

Chemical Structure(s):

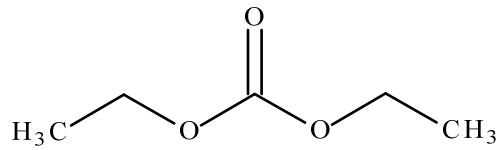


Also called:
Dimethyl carbonate; Methyl carbonate; Methyl carbonate ((MeO)2CO); Carbonic acid, dimethyl ester; Dimethyl carbonate, analytical standard; Dimethyl carbonate, anhydrous, >=99%; Dimethyl carbonate, ReagentPlus(R), 99% (PubChem 2023a).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A relatively complete toxicological dataset was identified for DMC; however, data gaps exist for DMC. Therefore, ToxServices used data for diethyl carbonate (CAS #105-58-8) to address the data gaps where

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

feasible. DMC and diethyl carbonate share a maximum common substructure (MCS) Tanimoto coefficient of 0.7500 (ChemMine 2023, Appendix C), differing only by one carbon in the length of the ester chains. Since the surrogate is larger in size than the target chemical, it is expected to be less reactive and hence a weak surrogate.



Surrogate: Diethyl carbonate (CAS #105-58-8) (PubChem 2023b)

Identify Applications/Functional Uses (PubChem 2023a, EC 2023)**:**
1. Solvent in multiple industries
2. Chemical intermediate
3. "Green" methylating agent in the methylation and phosgenation in organic synthesis
4. Cold-sterilizing agent in beverage production
5. Blowing agent in the production of polyurethane foams
6. Non-aqueous component in the production of chargeable lithium batteries
7. Fragrance in cosmetics formulations
8. Propellant in cosmetics formulations

Known Impurities[3]:
Methanol and water are the principle impurities of DMC (EFSA 2017). The current screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for DMC[4,5 6,7]: DMC was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Health Hazard (carcinogenicity-C, and developmental toxicity-D)
- Benchmark 2g
  - High Flammability-F

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), DMC meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if DMC were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] 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.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] 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 v1.4 Annex 2.

Figure 1: GreenScreen® Hazard Summary Table for DMC

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
						s	r*	s	r*	*	*								
M	L	L	*M*	DG	L	*M*	L	M	DG	*L*	*L*	L	*M*	L	*L*	vL	vL	*L*	H

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. 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. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). Although OECD QSAR Toolbox predicted 3 possible hydrolysis products, methanol (CAS #67-56-1), monomethyl carbonate (CAS #7456-87-3), and carbon dioxide (CAS #124-38-9), under neutral, basic, and acidic conditions (OECD 2022, Appendix D), DMC is readily biodegradable and, therefore, it is not expected to have relevant transformation products.

Introduction

DMC is manufactured by the carbonylation of methylnitrile via a catalytic redox process (PubChem 2023a).

ToxServices assessed DMC against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2023a). 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).

DMC is not listed on the 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 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for DMC can be found in Appendix E.

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

- DMC is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- DMC is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group II.
- DMC is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - GHS New Zealand – Hazardous to the aquatic environment – Chronic Category 2
    - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters

Hazard Statement and Occupational Control

A harmonized EU classification is available for DMC (ECHA 2023b), as shown in Table 1. The EU has classified this chemical as a GHS Category 2 flammable liquid (H225). Recommended personal protective equipment (PPE) and identified occupational exposure limits (OEL), if any, are summarized in Table 2.

Table 1: GHS H Statements for DMC (CAS #616-38-6) (ECHA 2023b)

H Statement	H Statement Details
H225	Highly flammable liquid and vapor.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for DMC (CAS #616-38-6)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Face shield/safety glasses, gloves, protective clothing, air-purifying respirator (when necessary)	Sigma-Aldrich 2022	None identified	Sigma-Aldrich 2022

Physicochemical Properties of DMC

DMC is a colorless liquid under standard temperature and pressure. It has a high vapor pressure (56.78 mmHg), indicating that it exists mostly in the vapor phase. DMC is highly soluble in water (114,700 mg/L), but is slightly more soluble in octanol than in water (log K_{ow} = 0.354). Its log K_{ow} value indicates that it is not likely to undergo bioaccumulation.

Table 3: Physical and Chemical Properties of DMC (CAS #616-38-6)

Property	Value	Reference
Molecular formula	$C_3H_6O_3$	PubChem 2023a
SMILES Notation	COC(=O)OC	PubChem 2023a
Molecular weight	90.08 g/mol	PubChem 2023a
Physical state	Liquid	PubChem 2023a
Appearance	Clear, colorless	PubChem 2023a
Melting point	4.65ºC (exp./lit.)	ECHA 2023a
Boiling point	90.35ºC (exp./lit., equivalent to OECD Guideline 103)	ECHA 2023a
Vapor pressure	7,570.4 Pa @ 23.8ºC (calculated as 56.78 mmHg) (exp., equivalent to OECD Guideline 104)	ECHA 2023a
Water solubility	114,700 mg/L @ 20ºC (exp., OECD Guideline 105 / EU Method A.6)	ECHA 2023a
Dissociation constant	Not applicable, lacks ionizable functional groups	ECHA 2023a

Table 3: Physical and Chemical Properties of DMC (CAS #616-38-6)		
Property	**Value**	**Reference**
Density/specific gravity	1.0633 g/cm^3 @ 25ºC (exp/lit., equivalent to OECD Guideline 109); 1.07 g/cm^3 at 20ºC (lit,)	ECHA 2023a
Partition coefficient	Log K_{ow} = 0.354 @ 20ºC (exp., OECD Guideline 107)	ECHA 2023a

Toxicokinetics

- *Absorption*: No direct data were identified for absorption via oral, dermal and inhalation routes of exposure.
    - *Oral:* Acute toxicity studies in rats exposed to single oral doses of 5,000 mg/kg DMC indicate that it is likely absorbed following oral exposure based on clinical signs of sedation (ECHA 2023a).
    - *Dermal:* Absorption via the dermal route is likely due to the physiochemical properties of the chemical including high water solubility and a log K_{ow} of 0.354; however, no conclusive evidence was found in *in vivo* dermal toxicology studies (ECHA 2023a).
    - *Inhalation:* Absorption via the inhalation route is likely due to the physiochemical properties of the chemical including volatility, water solubility, and log K_{ow}; however, no conclusive evidence was found in *in vivo* inhalation toxicology studies (ECHA 2023a).
- *Distribution:* No data were identified for distribution of DMC.
- *Metabolism:* DMC is metabolized via enzymatic hydrolysis into carbon dioxide and methanol which is further metabolized to formic acid ultimately resulting in carbon dioxide and water (OEHHA 2010, CIR 2017).
- *Excretion:* No data were identified for the elimination of DMC from the body.

Summary: Overall, limited data were available on the toxicokinetics of DMC. DMC is likely to be absorbed via oral, dermal, and inhalation routes based on its physiochemical properties; however, no definitive data was identified. In the environment and body, DMC is "readily hydrolyzed by esterases to carbon dioxide and methanol" and methanol is further metabolized to formic acid ultimately carbon dioxide and water (OEHHA 2010, CIR 2017).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

DMC was assigned a score of Moderate for carcinogenicity based on limited evidence of testicular tumors in a chronic oral toxicity study in rats exposed to surrogate diethyl carbonate and a positive VEGA prediction with high reliability for the target chemical. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals (CPA 2018b). The confidence in the score is low based on modeling of the target chemical and conflicting conclusions for results in a chronic oral study in mice exposed to the surrogate.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD Toolbox 2022
    - DMC lacks structural alerts for genotoxic or nongenotoxic carcinogenicity (Appendix D).

- VEGA 2023
    - ToxServices predicted the carcinogenicity potential of DMC using the following six VEGA v1.3.18 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/Antares v1.0.2, IRFMN/ISSCAN-CGX v1.0.2, IRFMN Oral Classification 1.0.1, and IRFMN Inhalation Classification 1.0.1 models. If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
    - The global ADI was < 0.70 for five out of the six models: ISS v.1.0.3, non-carcinogen (ADI = 0), IRFMN/ISSCAN-CGX v1.0.2, non-carcinogen (ADI = 0), IRFMN/Antares v1.0.0, possible non-carcinogen (ADI = 0), IRFMN Oral Classification 1.0.1, non-carcinogen (ADI = 0.38), and IRFMN Inhalation Classification 1.0.1, non-carcinogen (ADI = 0.38); therefore, the results of these models are not suitable for a weight of the evidence evaluation. The global ADI was > 0.70 for one of the six models: CAESAR v2.1.10, carcinogen (ADI = 0.761); therefore, the result of this model is suitable for a weight of the evidence evaluation (Appendix F).
- U.S. EPA 2019, 2021
    - ToxServices attempted to evaluate DMC using OncoLogic (v9.0) (U.S. EPA 2021). However, OncoLogic 9.0 could not evaluate the entire structure of the compound. In addition, it does not fall into any of the chemical classes of an earlier version of OncoLogic (v8.0) (U.S. EPA 2019)(Appendix G).
- DTU 2023
    - ToxServices evaluated DMC with the Danish (Q)SAR Database for carcinogenicity (DTU 2023). The QSAR modeling reports that DMC is in the domains of all seven E Ultra FDA RCA cancer models and it is predicted to be negative in all models (i.e., male rat, female rat, rat, male mouse, female mouse, mouse, and rodent). DMC is in the domains of one out of seven Leadscope FDA RCA cancer models and it is predicted to be negative by that model (i.e., mouse). Regarding the liver specific cancer in rat or mouse model, the SciQSAR and Leadscope models as well as the overall model battery predictions are negative and the compound is in their applicability domains; it is outside the applicability domain of the CaseUltra model (Appendix H).
- OEHHA 2010
    - OEHHA did not identify carcinogenicity or chronic data for the target chemical. Furthermore, no evidence of carcinogenicity was identified for the primary metabolite of DMC, methanol, which has a robust toxicological database and a long history of human exposure.
- ECHA 2023c
    - *Surrogate: Diethyl carbonate (CAS #105-58-8)*: In a chronic repeated dose toxicity test, ASH/CS1 mice (48 males and 50 females per group) were provided drinking water containing diethyl carbonate (greater than 99.5% purity) at 0, 50, 250, or 1,000 ppm (equivalent to 7, 35, and 140 mg/kg as identified by the authors of the ECHA dossier) for 83 weeks. The tumor incidence, including the 1-2 instances of testicular interstitial-cell tumors, was similar between each treatment group without comparable findings in the control group, but no dose-response relationship was identified. The study authors identified a no untoward effect of 140 mg/kg, the highest dose tested; however, the authors of the ECHA dossier identified a LOAEL of 50 ppm (7 mg/kg/day) for carcinogenicity based on testicular tumors identified in every dosed group (1 or 2 animals per dose) without similar findings in

the controls (Klimisch 2, reliable with restrictions). *Due to the conflicting conclusions from the study authors and authors of the ECHA dossier, the possible carcinogenic effect of diethyl carbonate cannot be excluded.*

- No data were identified for DMC; however, in a chronic oral study in mice exposed to surrogate diethyl carbonate, conflicting conclusions were made by the study authors, the authors of the IUCLID dossier, and the authors of the ECHA dossier regarding the 1 to 2 incidences (out of 48 animals, non-statistically significant) of testicular interstitial-cell tumors observed in treatment groups of all doses, but not in the control group. However, the testicular incidences are low, non-statistically significant, and non-dose-dependent; therefore, GHS classification is not warranted. However, due to the equivocal data on the surrogate, modeling with statistical based, and expert rule-based models (i.e., OECD Toolbox, VEGA, and Danish QSAR) were used to evaluate the carcinogenicity of DMC. One of the six carcinogenicity models in VEGA were within the applicability domain - the CAESAR v2.1.9 model that predicts DMC to be carcinogenic. OECD Toolbox did not identify structural alerts for genotoxic or nongenotoxic carcinogenicity. Danish QSAR predicted the target chemical to be non-carcinogenic in all models within their applicability domains. Overall, as no testicular tumors were found in the control mice, and predictions were mixed from models with in domain results for the target chemical, the carcinogenic potential could not be completely ruled out. Therefore, ToxServices conservatively assigned a score of Moderate.

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

DMC was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in a battery of *in vitro* assays and an *in vivo* test in mice. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate and negative results for mutagenicity and clastogenicity and no GHS classification are warranted (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted according to a Japanese guideline. *Salmonella typhimurium* tester strains TA 1535, TA 1537, TA 98, and TA 100 and *Escherichia coli* tester strain WP_2 *uvr* A were exposed to DMC (99.99% purity) in dimethyl sulfoxide (DMSO) at 313-5,000 µg/plate with and without metabolic activation. Positive, negative, and vehicle controls were reported as valid. No information on cytotoxicity or precipitation was reported, but the compound was tested up to guideline limit concentration. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471. *S. typhimurium* tester strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were exposed to DMC (purity not specified) in DMSO at 30-5,000 µg/plate with and without metabolic activation. Positive, negative, and vehicle controls were reported as valid. No cytotoxicity or precipitation were observed, but the substance was tested up to guideline limit concentration. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a reverse mutation assay conducted in a manner similar to OECD Guideline 471. *S. typhimurium* tester strains TA 98

and TA 100 were exposed to DMC (purity and vehicle not specified) at 2.5 and 5 mg/plate with and without metabolic activation. Positive controls were reported as valid. No cytotoxicity or precipitation were reported; however, the compound was tested up to guidance limit concentrations. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 2, reliable with restrictions).

- *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant OECD Guideline 476 mammalian cell gene mutation assay. Chinese hamster lung fibroblasts (V79) were exposed to DMC (purity not specified) in water at 1-1,000 µg/mL with and without metabolic activation. Positive and negative controls were reported as valid. No information on precipitation was provided, and no cytotoxicity was reported up to guideline limit concentration. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).
- *In vitro*: Negative results for clastogenicity were obtained in a GLP-compliant chromosome aberration test conducted according to OECD Guideline 473. Human lymphocytes were exposed to DMC (purity not specified) in water at 0.1-1,000 µg/mL with and without metabolic activation. Positive, negative, and vehicle controls were reported as valid. No cytotoxicity or precipitation were observed, but the compound was tested up to guideline limit concentration. No increase in the frequency of chromosome aberrations was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).
- *In vitro*: Negative results for genotoxicity were obtained in a comet assay. L 929 mouse fibroblasts were exposed to DMC (purity not specified) in DMSO at up to 150 mg/mL without metabolic activation. Vehicle controls were reported as valid. No information on cytotoxicity or precipitation was reported. No increase in DNA damage was detected in the comet assay following treatment in the absence of metabolic activation (Klimisch 2, reliable with restrictions).
- *In vivo*: Negative results for clastogenicity were obtained in a germ cell chromosome aberration assay conducted in a manner similar to OECD Guideline 483. Male mice (5 per group, strain not specified) were administered single oral doses of DMC (purity not specified) at 0, 0.99, 1.99, or 3.97 mg/kg. The incidence of chromosome aberrations was evaluated in spermatogonial mitoses. No increase in the incidence of chromosome aberrations was detected with treatment (Klimisch 2, reliable with restrictions).

Reproductive Toxicity (R) Score (H, M, or L): L

DMC was assigned a score of Low for reproductive toxicity based on the lack of reproductive toxicity identified in a one-generation oral reproduction toxicity study in rats on the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable data from a guideline study for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2023a
  - *Oral:* A GLP-compliant one-generation reproduction toxicity test conducted according to OECD Guideline 415 was performed with Sprague-Dawley rats (24/sex/group) administered gavage doses of DMC (99.99% purity) in water at 0, 5, 50, or 500 mg/kg/day. Males were treated for at least 10 weeks prior to mating and then thereafter until the day prior to

sacrifice (total exposure duration not specified), and females were dosed for at least 2 weeks prior to mating, through gestation, and until post-natal day (PND) 21 (total exposure duration not specified). For the parental generation, no treatment-related effects were observed on clinical signs of toxicity, body weight, estrous cyclicity, reproductive organ weight and pathology, and reproductive indices (i.e., copulatory index, fertility index, copulatory interval, pre-birth loss, pup loss at birth, cumulative pup loss on PND 4). The study authors identified a reproductive toxicity NOEL of 500 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
DMC was assigned a score of Moderate for developmental toxicity based on the developmental toxicity (increased post-implantation loss and malformations, decreased fetal body weight, and altered sex ratio) detected in an inhalation prenatal developmental toxicity test in mice in the presence of maternal toxicity. No effects were found in oral studies. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity in animals is available (CPA 2018b). The confidence in the score was low due to the differences in the results via the oral and inhalation routes of exposure.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - Japan - GHS - H361 - Suspected of damaging fertility or the unborn child [Toxic to reproduction - Category 2].
            - Based on developmental toxicity detected in mice administered inhalation exposures of 300-3,000 ppm (NITE 2008, 2009).
- ECHA 2023a
    - *Oral:* As previously described, a GLP-compliant one-generation reproduction toxicity test conducted according to OECD Guideline 415 was performed with Sprague-Dawley rats (24/sex/group) administered gavage doses of DMC (99.99% purity) in water at 0, 5, 50, or 500 mg/kg/day. Females were dosed for at least 2 weeks prior to mating, through gestation, and until PND 21 (total exposure duration not specified). The offspring were evaluated for litter size, viability, sex, weight, lactation index up to PND 21, and external malformations. No treatment-related effects were detected on these parameters and the study authors identified a developmental toxicity NOEL of 500 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
    - *Oral:* Two GLP-compliant prenatal developmental toxicity studies, including a range-finding study, were conducted according to OECD Guideline 414, and performed with pregnant female New Zealand White rabbits (study #1 = 22-23 per group and study #2 = 5-7 per group) administered gavage doses of DMC (99.91% purity) at nominal doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days (GD) 6-27. Maternal examinations included clinical signs of toxicity, body weight, and ovarian and uterine content. Fetal examinations included viability, sex ratio, and assessment of external, visceral, and skeletal malformations. No treatment-related effects were detected on these parameters and the study authors identified a maternal toxicity and developmental toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
- ECHA 2023a, Exxon Biomedical Sciences, Inc. 1992
    - *Inhalation:* A GLP-compliant prenatal developmental toxicity test conducted according to OECD Guideline 414 was performed with pregnant female CD-1 mice (30/group) administered whole body inhalation exposures to DMC (purity and form not specified) at 0,

300, 1,000, or 3,000 ppm 6 hours/day on GD 6-15. High concentration dams exhibited significant decreases in body weights and body weight gains, and food consumption was significantly decreased in the mid and high concentration groups. An increased resorption rate (post-implantation loss) and altered sex ratio (decreased proportion of male fetuses) was identified at 3,000 ppm. Decreased fetal body weights per litter and an increased number of stunted fetuses were detected in the high concentration group. A significant increase in the incidence of external, visceral, and skeletal malformations, including cleft palate, microtia, low set ears, multiple skull bone malformations and fused vertebral arches, was identified at 3,000 ppm. Additionally, the incidence of skeletal variations increased in the high concentration group. The study authors identified a NOAEC of 1,000 ppm (equivalent to 3.684 mg/L as identified by the authors of the ECHA dossier) for maternal toxicity based on decreased body weight gain and food consumption. Study authors identified a NOAEC of 1,000 ppm (equivalent to 3.684 mg/L as identified by the authors of the ECHA dossier) for developmental toxicity based on increased incidences of fetal malformations and developmental variations, as well as teratogenic effects (Klimisch 4, not assignable). Authors of the REACH dossier assigned this study a Klimisch score of 4 (not assignable) as only an abstract was available for review. The dossier authors noted that the study was previously reviewed by an expert panel in the SIDS 2003 (no reference provided). The REACH dossier authors also noted that some of all of the developmental effects may be attributable to the metabolite methanol at high DMC exposure concentrations, which saturated the catalase detoxification pathway. *ToxServices was able to obtain the full study (Exxon Biomedical Sciences, Inc. 1992) to confirm the details reported; therefore, the study was included in this assessment and considered reliable.*

- Based on this weight of evidence, a score of Moderate was assigned. Oral exposure to DMC at up to 1,000 mg/kg did not lead to developmental effects in an OECD Guideline 415 one-generation study in rats and an OECD Guideline 414 study in rabbits. However, effects on offspring including increased post-implantation loss, malformations, skeletal variations, decreased fetal body weight, and altered sex ratio, were observed in an OECD Guideline 414 developmental study in mice administered whole body inhalation exposures of DMC with a NOAEC of approximately 3.684 mg/L, in the presence of maternal toxicity (decreased body weight gain and food consumption). The REACH dossier authors stated that the metabolite methanol may be at least partially responsible for the developmental effects at very high exposure concentrations. In addition, the nature of the effects (e.g., malformation) indicated the developmental toxicity was unlikely to be secondary to maternal toxicity. Methanol is a known developmental toxicant (Proposition 65 developmental toxicant and U.S. National Institutes of Health (NIH) concludes it to have clear evidence of developmental toxicity (Pharos 2023). Therefore, methanol may be classified as GHS Category 1 for developmental toxicity. However, the extent of methanol formation after inhalation exposure to DMC is unknown. Therefore, ToxServices did not entirely rely on methanol's GHS classification for this endpoint and classified DMC to GHS Category 2.

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

DMC was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a

  - *Oral*: The previously described GLP-compliant one-generation reproduction toxicity test conducted according to OECD Guideline 415 was performed with Sprague-Dawley rats (24/sex/group) administered gavage doses of DMC (99.99% purity) in water at 0, 5, 50, or 500 mg/kg/day. Males were treated for at least 10 weeks prior to mating, and females were dosed for at least 2 weeks prior to mating, through gestation, and until PND 21. There were no treatment related effects on estrous cyclicity, reproductive organ weight and pathology, and reproductive indices (i.e., copulatory index, fertility index, copulatory interval, pre-birth loss, pup loss at birth, cumulative pup loss on PND 4). The study authors identified a reproductive toxicity NOEL of 500 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
- ECHA 2023a, Exxon Biomedical Sciences, Inc. 1992
  - *Inhalation*: The previously described GLP-compliant prenatal developmental toxicity test conducted according to OECD Guideline 414 was performed with pregnant female CD-1 mice (30/group) administered whole body inhalation exposures to DMC (purity and form not specified) at 0, 300, 1,000, or 3,000 ppm 6 hours/day on gestation days 6-15. An increased resorption rate (post-implantation loss) and altered sex ratio (decreased proportion of male fetuses) was identified at 3,000 ppm. Decreased fetal body weights per litter and an increased number of stunted fetuses were detected in the high concentration group. A significant increase in the incidence of external, visceral, and skeletal malformations, including cleft palate, microtia, low set ears, multiple skull bone malformations and fused vertebral arches, was identified at 3,000 ppm. Additionally, the incidence of skeletal variations increased in the high concentration group. No information on organ weights, gross pathology, histopathology on endocrine or reproductive parameters, or measurements of thyroid hormone were identified. Study authors identified a NOAEC of 1,000 ppm for developmental toxicity based on teratogenic effects (Klimisch 4, not assignable).
- U.S. EPA 2023b
  - DMC was not evaluated by and did not have ToxCast model information.
- DTU 2023
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models: 1) DMC is predicted to be negative for estrogen receptor α binding, full training set (human *in vitro*) by the SciQSAR model; 2) DMC is predicted to be negative for estrogen receptor α activation (human *in vitro*) by the model battery consisting of negative and in domain predictions by the Leadscope and SciQSAR models; 3) DMC is predicted to be negative for estrogen receptor activation, CERAPP data (*in vitro*) by the Leadscope model; 4) DMC is predicted to be negative for androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by CaseUltra, Leadscope, and SciQSAR models; 5) DMC is predicted to be negative for androgen receptor binding, inhibition and activation (CoMPARA data *in vitro*) by Leadscope (Appendix I).
- Available data from an oral reproductive/developmental toxicity screening test in rats reported no effects observed for endocrine organ weights (testis, adrenal glands, seminal vesicles, and ovary), estrous cycle, spermatogenic cycle, or sperm morphology; however, there were no measurements of thyroid, estrogen or androgen hormone levels reported. Developmental effects (i.e., increased post-implantation loss and malformations, and skeletal variations, decreased fetal body weight, and altered sex ratio) were observed in the presence of maternal toxicity (i.e., decreased body weight gain and food consumption) in rats exposed to DMC in an inhalation prenatal developmental toxicity study (see developmental toxicity section). The mechanisms causing these effects are not known. DMC was predicted negative by QSAR models in Danish QSAR database for estrogen

receptor binding and activation, and androgen receptor binding, inhibition, and activation. However, there are no data available regarding thyroid hormone pathways, steroidogenesis, or *in vivo* assays specifically addressing endocrine activity or reporting hormone levels. While reproductive /developmental toxicity effects were observed via the inhalation route, there is no evidence indicating an endocrine-related mechanism contributing to these effects. Therefore, ToxServices assigned a Data Gap 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 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

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

DMC was assigned a score of Low for acute toxicity based on oral LD_{50} values greater than 5,000 mg/kg, vapor inhalation LC_{50} values greater than 20 mg/L, and dermal LD_{50} values greater than 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/L and vapor LC_{50} values are greater than 20 mg/L (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- PubChem 2023a, HSDB 2014
  - *Oral*: LD_{50} (rat) = 13,000 mg/kg
  - *Oral*: LD_{50} (mouse) = 6,000 mg/kg
  - *Inhalation*: LC_{50} (rat) ≥ 140 mg/L/4 hours
  - *Dermal*: LD_{50} (rat) > 2,500 mg/kg
  - *Dermal*: LD_{50} (guinea pig) > 9,350 mg/kg
- ECHA 2023a
  - *Oral*: LD_{50} (Sprague-Dawley rat) > 5,000 mg/kg (GLP-compliant, similar to OECD Guideline 401) (Klimisch 1, reliable without restriction).
  - *Inhalation*: 4-hour whole body vapor LC_{50} (Sprague-Dawley rat) > 5.36 mg/L (GLP-compliant, similar to OECD Guideline 403) (Klimisch 1, reliable without restriction).
  - *Inhalation*: 7-hour whole body vapor LC_0 (Wistar-derived rat) > 37.5 mg/L (non-GLP-compliant) (Klimisch 2, reliable with restrictions due to low number of animals used in study). *The 4-hour LC_{50} is expected to be greater than the 7-hour value, and therefore is also > 37.5 mg/L.*
  - *Inhalation*: 6-hour whole body vapor LC_{50} (Alderley Park SPF rat) > 20 mg/L (non-GLP-compliant) (Klimisch 2, reliable with restrictions due to low number of animals used in study). *The 4-hour LC_{50} is expected to be greater than the 6-hour value, and therefore is also > 20 mg/L.*
  - *Dermal*: LD_{50} (New Zealand White rabbit) > 2,000 mg/kg (GLP-compliant) (Klimisch 1, reliable without restriction).

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

DMC was assigned a score of Moderate for systemic toxicity (single dose) based on ToxServices classifying it to GHS Category 3 for respiratory irritation. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation (CPA 2018b). The confidence in the score was reduced due to limited human evidence and inconsistent findings across animal studies for respiratory irritation.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral:* As previously described, a GLP-compliant oral acute toxicity study conducted in a manner similar to OECD Guideline 401 with male and female Sprague-Dawley rats, reported an LD_{50} of > 5,000 mg/kg. No mortalities or effects on body weights were reported. Clinical signs of toxicity included hypoactivity, sedation, and ataxia. Gross pathological findings were normal (Klimisch 2, reliable with restrictions).
  - *Inhalation*: As previously described, a GLP-compliant inhalation acute toxicity study conducted in a manner similar to OECD Guideline 403 with male and female Sprague-Dawley rats, reported a 4-hour whole body vapor LC_{50} of > 5.36 mg/L. No mortalities and no treatment related effects on body weights were observed at 5.36 mg/L, the only concentration tested. Clinical signs of toxicity were limited to redness around the nose in one male one hour after the exposure. Gross pathological changes observed included external hemorrhagic lung in one male and distended bladder in another male and one female; however, these findings are commonly detected in control animals and were not considered to be treatment-related (Klimisch 1, reliable without restriction).
  - *Inhalation*: As previously described, an inhalation acute toxicity study with male and female Wistar rats, reported a 7-hour whole body vapor LC_0 of > 37.5 mg/L. No mortalities and no treatment related effects on clinical signs of toxicity, histopathology (liver, lungs, and kidney only) and gross pathology were observed at 37.5 mg/L, the only concentration tested. No data on body weights were reported (Klimisch 2, reliable with restrictions).
  - *Inhalation*: As previously described, a non-GLP-compliant inhalation acute toxicity study with male and female Alderley Park SPF rats, reported a 6-hour whole body vapor LC_{50} of > 20 mg/L. No mortalities and no treatment related effects on gross pathology were observed at 20 mg/L, the only concentration tested. Clinical signs were reported including eye irritation, salivation, respiratory difficulty, and incoordination; all animals recovered quickly after exposure. No data on body weights were reported (Klimisch 2, reliable with restrictions). *Furthermore, clinical signs of eye irritation, salivation, respiratory difficulty, and incoordination were evaluated under other endpoints, and were not considered signs of systemic toxicity by ToxServices.*
  - *Dermal*: As previously described, a GLP-compliant dermal acute toxicity study with male and female New Zealand White rabbits (n=5) exposed to topical applications of DMC for 24 hours under occlusion and observed for 14 days, reported an LD_{50} of > 2,000 mg/kg. No mortalities and no treatment related effects on body weights, organ weights, and gross pathology were observed. Clinical signs of toxicity were limited to dermal irritation detected at up to 5 days into the observation period and then resolved. Body weight were measured immediately prior to dosing, once per week after dosing, and at the end of the study period; no further information was provided on body weights. Gross pathological findings included red foci of the lungs of two males, but this was not considered to be

treatment-related by the study authors. No information was provided on body weights (Klimisch 1, reliable without restriction). *Although no information was provided for specific body weights, ToxServices inferred that body weights were not affected by the treatment because no effects were reported on body weights.*

- HSDB 2014
  - DMC is reported to be a respiratory irritant; however, no further details were provided.
- DMC is reported to be a respiratory irritant to humans; however, no further details were provided. Respiratory effects (i.e., redness around the nose and eyes and respiratory difficulty) were observed in two acute inhalation toxicity studies in rats, and respiratory difficultly was quickly cleared up after exposure. Therefore, ToxServices classified DMC to GHS Category 3. However, no treatment related effects were observed in gross pathology findings of the respiratory system in the acute animal studies and no respiratory irritation effects based on clinical signs, organ weights, gross pathology, or histopathology were identified in a repeated exposure inhalation study on the surrogate diethyl carbonate (see repeated exposure systemic toxicity section). This leads to reduced confidence in the GHS classification.

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

DMC was assigned a score of Low for systemic toxicity (repeated dose) based on an oral NOAEL of > 500 mg/kg/day, the highest dose tested, in a 90-day OECD Guideline 408 subchronic repeated dose toxicity study in rats, which exceeds the GHS guidance value of 100 mg/kg/day for Category 2 classification (UN 2021), and based on a 28-day inhalation NOAEC of 13.16 mg/L in rats, which exceeds the duration-adjusted guidance value of 3 mg/L for vapors. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score was high as it was based on data from reliable, high quality studies for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral*: A GLP-compliant subchronic repeated dose toxicity study conducted according to OECD Guideline 408 was performed with Sprague-Dawley rats (15/sex/group) administered gavage doses of DMC (purity not specified) in water at 0, 1, 5, 50, or 500 mg/kg/day for 13 weeks. The animals were evaluated for clinical signs of toxicity, body weight, food and water consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. No treatment-related effects were detected on these parameters and the study authors identified a NOEL of 500 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction). *Based on the results of this study, ToxServices identified a NOAEL of > 500 mg/kg/day.*
- Seo 2021
  - *Inhalation*: A 28-day repeated dose toxicity study was performed with male and female F344 rats (5/sex/group) administered whole body inhalation exposures of 0, 600, 1,600, and 5,000 ppm (equivalent to 0, 2.21, 5.89, and 18.42 mg/L[9] as calculated by ToxServices) DMC vapor (purity and vehicle unspecified) for 6 hours per day, 5 days per week, for 4 weeks. The study authors identified the low, mid, and high dose test groups as T1, T2, and T3 respectively. No adverse treatment related effects were reported for mortality, clinical signs

[9] (Dose (ppm)*molecular (MW)) / 24,450 = Dose (mg/L); (600*90.08)/24,450 = 2.21 mg/L; (1,600*90.08)/24,450 = 5.89 mg/L; (5,000*90.08)/24,450 = 18.42 mg/L.

of toxicity, behavioral changes, body weight and weight change, food consumption, hematology, clinical chemistry, gross pathology, and histopathology (adrenal glands, lungs, brain, ovaries, epididymis, spleen, heart, testicles, kidneys, thymus, liver, uterus). Reductions in absolute and relative heart and liver weights for low dose females were reported. Additionally, reduced absolute liver and lung weights for mid dose males, reduced absolute liver and spleen weights for low dose males, and reduced relative liver weight for low and mid dose males were reported. Elevated partially active thromboplastin time (APTT) (T2 and T3 of males), and prothrombin time (PT) (T3 of males and T1, T2 and T3 of females)were reported and increased aspartate aminotransferase (AST) (T3 of females) and alanine aminotransferase (ALP) (T1, T2, and T3 of females) levels were reported; however, no adverse histological findings were reported and the changes compared to controls were slight, although statistically significant. The study authors concluded hematology and biochemistry effects are likely the effect of primary metabolite, methanol, on the liver. A NOAEC was not established; however, study authors established a NOEC of < 600 ppm (equivalent to 2.21 mg/L) based on elevated PT and ALP levels. *Based on the lack of dose-response, lack of concordance between genders, the low magnitude of changes in the organ weights, hematology, and clinical biochemistry findings, and the lack of corresponding histopathological changes, ToxServices did not consider the changes reported in this study to be toxicologically significant, and identified a NOAEC of 1,200 ppm (18.42 mg/L, or 18.42 mg/L * 5 days/7 days = 13.16 mg/L after adjustment for the less than daily exposure frequency).*

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): M
DMC was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposure for transient narcotic effects under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicant following single exposure for narcotic effects (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative list for this endpoint.
  - *Screening:*
    - Japan - GHS - Specific target organs/systemic toxicity following single exposure - Category 3
      - Based on narcotic effects detected in rats following single oral or inhalation exposures (NITE 2008). This classification was not reported in NITE (2009).
- ECHA 2023a
  - *Oral*: The previously described GLP-compliant oral acute toxicity study, conducted in a manner similar to OECD Guideline 401 with male and female Sprague-Dawley rats, reported an LD_{50} of > 5,000 mg/kg. No mortalities or effects on body weights were observed. Clinical signs of toxicity included hypoactivity, sedation, and ataxia. Gross pathological findings were normal (Klimisch 2, reliable with restrictions).
  - *Inhalation:* The previously described GLP-compliant inhalation acute toxicity study conducted in a manner similar to OECD Guideline 403 with male and female Sprague-Dawley rats, reported a 4-hour whole body vapor LC_{50} of > 5.36 mg/L. No treatment related effects on clinical signs or gross pathology indicative of neurotoxicity were observed at 5.36 mg/L, the only concentration tested (Klimisch 1, reliable without restriction).

  - *Inhalation:* The previously described inhalation acute toxicity study with male and female Wistar rats, reported a 7-hour whole body vapor LC_0 of > 37.5 mg/L. No mortalities and no treatment related effects on clinical signs of toxicity, histopathology (liver, lungs, and kidney only) and gross pathology were observed at 37.5 mg/L, the only concentration tested. No data on body weights were reported (Klimisch 2, reliable with restrictions).
  - *Inhalation:* The previously described non-GLP-compliant inhalation acute toxicity study with male and female Alderley Park SPF rats, reported a 6-hour whole body vapor LC_{50} of > 20 mg/L. No mortalities and no treatment related effects on gross pathology were observed at 20 mg/L, the only concentration tested. Clinical signs were reported including eye irritation, salivation, respiratory difficulty, and incoordination; all animals recovered quickly after exposure. No data on body weights were reported (Klimisch 2, reliable with restrictions).
  - *Dermal:* The previously described GLP-compliant dermal acute toxicity study, with male and female New Zealand White rabbits (n=5) exposed to topical applications of DMC for 24 hours under occlusion and observed for 14 days, reported an LD_{50} of > 2,000 mg/kg. No mortalities and no treatment related effects on clinical signs, organ weights and gross pathology were observed (Klimisch 1, reliable without restriction).
- Based on this weight of evidence, a Moderate score was assigned. An acute oral toxicity study in rats reported transient narcotic effects (i.e., hypoactivity, sedation, and ataxia) and an acute inhalation toxicity study in rats reported transient neurotoxicity indicative of narcosis (i.e., incoordination) at 20 mg/L after a single 6-hour exposure. However, no clinical signs or gross pathology findings indicative of neurotoxicity were found in two other acute inhalation toxicity studies at concentrations as high as 37.5 mg/L after a single 7-hour exposure and in the dermal acute toxicity study in rabbits exposed up to 2,000 mg/kg. Therefore, based on the transient narcotic effects detected following single oral and inhalation exposures to rats, ToxServices classified DMC as a Category 3 specific target organ toxicant following single exposure for narcotic effects under GHS criteria (UN 2017).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
DMC was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of repeated dose toxicity studies that specifically performed a neurotoxicity assessment, typically including a functional observation test on the target chemical or the surrogate.
- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
DMC was assigned a score of Low for skin sensitization based on the lack of sensitization reactions identified in a Magnusson-Kligman test in guinea pigs and a reduced local lymph node assay (rLLNA) in mice. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.
- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a

- A GLP-compliant Magnusson-Kligman guinea pig maximization test conducted in a manner similar to OECD Guideline 406 was performed with female Dunkin-Hartley guinea pigs (15 per group) administered dermal doses of DMC (purity not specified). The induction doses were administered as single 0.1 mL intradermal injections of 50:50 FCA in water, 100% DMC, and 25% DMC in 50:50 FCA in water. Seven days later, a topical induction dose of 0.25 mL 25% or 100% DMC was applied to the skin for 48 hours (coverage not specified). The challenge dose was applied 14 days after the topical induction dose as semi-occlusive patches saturated with 0.03 mL of 25%, 50%, or 100% DMC in ethanol for 24 hours. The dermal reactions were scored 24 and 48 hours after patch removal. No animals exhibited positive dermal reactions following the challenge dose, and the study authors concluded that DMC was not sensitizing to the skin in this study (Klimisch 2, reliable with restrictions).
- An rLLNA conducted in a manner similar to OECD Guideline 429 was performed with mice (strain, sex, and number not specified) administered topical applications of DMC (purity not specified) in acetone/olive oil (4:1 v/v) at 0.5%, 5%, or 50%. The resulting stimulation indices (SI) were 0.64, 0.69, and 1.71 for the 0.5%, 5%, and 50% solutions, respectively. As none of the SI values were greater than 3, the study authors concluded that DMC was not sensitizing to the skin in this study (Klimisch 2, reliable with restrictions).

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

DMC was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential and according to ECHA's guidance on respiratory sensitization evaluation. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). Confidence in the score was low as this evaluation did not include non-immunologic mechanisms of respiratory sensitization, and no specific data were available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative list for this endpoint.
  - *Screening:* Not listed on any screening list for this endpoint.
- OECD 2022
  - DMC does not contain any structural alerts for respiratory sensitization (Appendix D).
- DTU 2023
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models: DMC is predicted to be positive for respiratory sensitization in humans by the model battery consisting of positive and in domain predictions by Leadscope and SciQSAR (Appendix J).
- 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 2017). 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 2017). As DMC was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by DMC, and as DMC does not contain any structural alerts for respiratory sensitization (OECD 2022), DMC is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
DMC was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation detected in two rabbit studies testing undiluted DMC. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - A non-GLP-compliant dermal irritation test conducted in a manner similar to OECD Guideline 404 was performed with New Zealand White rabbits (3 females) administered topical applications of 0.5 mL undiluted DMC (purity not specified) to clipped skin under semi-occlusive dressing for 4 hours. A 72-hour observation period followed the exposure period. At 72 hours, the mean primary dermal irritation index (PDII) was 0. The edema and erythema scores for the three animals at 24, 48, and 72 hours were all 0. No adverse dermal reactions were detected following application of DMC, and the study authors concluded that it was not irritating to the skin under the tested conditions (Klimisch 2, reliable with restrictions).
  - A GLP-compliant dermal irritation test conducted in a manner similar to OECD Guideline 404 was performed with New Zealand White rabbits (3 females) administered 0.5 mL undiluted DMC (purity not specified) to clipped skin under semi-occlusive dressing for 4 hours. A 72-hour observation period followed the exposure period. After 1 hour, the mean PDII was 0/8. No further results were provided. The study authors concluded that DMC was not irritating to the skin in this study (Klimisch 2, reliable with restrictions).
- In summary, no evidence of dermal irritation was identified in two rabbit studies. Although the results are not presented in a format that allows for evaluation against GHS criteria (i.e., individual scores for erythema and/or edema at 24, 48, and 72 hours after application), the results indicate that no dermal irritation was elicited by topical application of undiluted DMC. Therefore, ToxServices considered these results to be suitable for no classification for dermal irritation under GHS criteria (UN 2021).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *M*
DMC was assigned a score of Moderate for eye irritation/corrosivity based on ToxServices classifying it as a Category 2B ocular irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for eye irritation/corrosivity when they are classified as GHS Category 2B ocular irritants (CPA 2018b). The confidence in the score was low due to the results of the critical study being presented in a manner that did not allow for direct comparison to the GHS criteria.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - A GLP-compliant ocular irritation test conducted according to a Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) testing guideline was performed with New Zealand White rabbits (6 without rinsing, 3 with rinsing) administered ocular instillations of 0.1 mL undiluted DMC (purity not specified). Three of the animals had their eyes rinsed 2-3 minutes after instillation (no further details provided). A 72-hour observation period followed the instillation. The eyes were scored using a modified Kay and Calandra

classification system. For the unrinsed eyes, the mean scores across 24, 48 and 72 hours for cornea opacity were 8.3, 0, 0, 0, 0, and 0 for each of the 6 animals; the mean scores for iris were 5, 0, 0, 0, 0, and 0; the mean scores for conjunctiva were 19.7, 0.7, 0.7, 0, 0, and 0.7; and the mean scores for chemosis were 2.7, 0, 0, 0, 0, and 0. All effects were reversible within 7 days. With rinsing, the overall irritation score was 1.3 1 hour after instillation and all irritation effects were fully reversible within 24 hours. The study authors concluded that DMC was not irritating to the eyes in this study (Klimisch 1, reliable without restriction).

- A GLP-compliant ocular irritation study conducted in a manner similar to OECD Guideline 405 was performed with New Zealand White rabbits (3 females) administered ocular instillations of 0.1 mL undiluted DMC (purity not specified). An observation period of up to 7 days followed the instillation. One hour after instillation, moderate conjunctival redness, and discharge and moderate to severe swelling was observed. One animal exhibited slight corneal opacity and iridial inflammation 1-3 days following treatment, whereas the other animals did not exhibit irritation to the cornea or iris. After 7 days, all eyes had fully recovered and the mean overall irritation score was 0/110. Scores for individual animals for individual endpoints were not reported. The study authors concluded that DMC was slightly irritating to the eyes in this study (Klimisch 2, reliable with restrictions) (Unnamed study 1984, 002 Key, ECHA, CAS #616-38-6, 2022). A second entry in the REACH dossier for this above study indicated that the maximum mean total score (MMTS) was 13.3 (max 14) at 1 hour, 6.7 (max 16) at day 1, 10.4 (max 29) at day 2, 10.4 (max 29) at day 3, and 0 (max 0) at day 7. All ocular irritation effects were fully reversible within 7 days of instillation. The study authors concluded that DMC was slightly irritating to the eyes and classified it as a Category 2B ocular irritant (mildly irritating to eyes) (Klimisch 2, reliable with restrictions).

- Based on the weight of evidence, a score of Moderate was assigned. No to slight ocular irritation were identified in two rabbit studies for DMC. The effects were not scored using a scale consistent with that used by GHS criteria, however the results indicated that slight ocular irritation was reversible within 7 days, and the REACH dossier authors classified it to GHS Category 2B based on the data presented. Therefore, ToxServices conservatively classified DMC as a Category 2B ocular irritant under GHS criteria (UN 2021).

Ecotoxicity (Ecotox)

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

DMC was assigned a score of Low for acute aquatic toxicity based on acute aquatic toxicity values greater than 100 mg/L for all trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 100 mg/L (CPA 2018b). The confidence in the score was high as it was based on reliable measured data for the target chemical and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2023a
  - 96-hour $LC_{50} \geq 100$ mg/L (nominal) (*Danio rerio*, zebrafish) (GLP-compliant, OECD Guideline 203/EU Method C.1) (Klimisch 1, reliable without restriction).
  - 48-hour mobility $EC_{50} > 100$ mg/L(*Daphnia magna*) (nominal) (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction).

  - 48-hour mobility EC_{50} > 74.16 mg/L (measured) (*D. magna*) (GLP-compliant, EU Method C.2) (Klimisch 1, reliable without restriction).
  - 72-hour growth rate and biomass EC_{50} > 100 mg/L (nominal) and > 57.29 mg/L (geometric mean measured) (*Pseudokirchneriella subcapitata*, green algae) (GLP-compliant, OECD Guideline 201/EU Method C.3) (Klimisch 1, reliable without restriction).
- ECHA 2023c
  - *Surrogate: Diethyl carbonate (CAS #105-58-8)*: 72-hour growth rate, yield and biomass EC_{50} > 100 mg/L (nominal) (*P. subcapitata*, green algae) (GLP-compliant, OECD Guideline 201/EU Method C.3) (Klimisch 1, reliable without restriction).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*
DMC was assigned a score of Low for chronic aquatic toxicity based on measured or modeled chronic aquatic toxicity values as low as 11.71 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2018b). The confidence in the score was low as no measured data were identified for the aquatic vertebrate trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening list for this endpoint.
- ECHA 2023a
  - 21-day mobility NOEC = 25 mg/L (nominal) (*D. magna*) (GLP-compliant, OECD Guideline 211) (Klimisch 1, reliable without restriction).
  - 72-hour growth rate and biomass NOEC > 100 mg/L (nominal) and > 57.29 mg/L (geometric mean measured) (*P. subcapitata*, green algae) (GLP-compliant, OECD Guideline 201/EU Method C.3) (Klimisch 1, reliable without restriction).
- U.S. EPA 2017a
  - DMC belongs to the Esters ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 11.7 mg/L in fish, 300 mg/L in daphnia, and 22.7 mg/L in green algae (see Appendix K).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL
DMC was assigned a score of Very Low for persistence based on it meeting the 10-day window in two OECD Guideline 301 ready biodegradability tests, and soil or water is the dominant environmental compartment. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil or water is the dominant environmental compartment and the 10-day window is met (CPA 2018b). The confidence in the score was high as it was based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative list for this endpoint.
  - *Screening:*
    - EC - CEPA DSL – Persistent
      - Based on an experimental atmospheric oxidation half-life of 34 days (CCR 2023).
- ECHA 2023a
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 C / EU Method C.4-F (MITI test) was performed with non-adapted activated sludge exposed to DMC (at least 99% purity) at 188 mg/L for 28 days. The mean level of degradation was

5% after 2 days, 38.8% after 3 days, 61.8% after 6 days, 79.1% after 13 days, and 86% after 28 days. As the 10-day window was met, the study authors concluded that DMC was readily biodegradable under the conditions of this test (Klimisch 1, reliable without restriction).
    - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 F (Manometric respirometry test) was performed with activated domestic sludge (adaptation not specified) exposed to DMC (99.95% purity) at 48 or 100 mg/L for 28 days. At the end of the exposure period, both solutions achieved 92% degradation. The study entry indicates that the 10-day window was met without providing data to support that conclusion. The study authors concluded that DMC was readily biodegradable in this study (Klimisch 1, reliable without restriction).
    - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 D (closed bottle test) was performed with non-adapted, activated sludge exposed to DMC (purity not specified) at 2 mg/L for 28 days. At the end of the exposure period, the level of degradation was 46.3%. The study authors concluded that DMC was not readily biodegradable but inherently biodegradable under the conditions of this study (Klimisch 1, reliable without restriction).
    - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 F was performed with non-adapted, domestic activated sludge exposed to DMC (purity not specified) at 100 mg/L for 50 days. After 28 days, the level of degradation was 35.5%. The study authors concluded that DMC was not readily biodegradable but inherently biodegradable in this study (Klimisch 1, reliable without restriction).
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that DMC is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 44.3% will partition to soil with a half-life of 30 days, 41.6% will partition to water with a half-life of 15 days, 14.1% will partition to air with a half-life of 34.5 days, and 0.0811% will partition to sediment with a half-life of 135 days (Appendix L).
- Although it is listed on the CEPA DSL as persistent, this classification is based on an experimental atmospheric oxidation half-life of 34 days (CCR 2023), while fugacity modelling by ToxServices indicates that DMC mainly partitions to water and soil compartments in the environment. Further, CEPA DSL's classification did not take into consideration biodegradation data included in the data summaries that ToxServices identified. In addition, DMC is not considered a VOC due to negligible photochemical reactivity under 40 CFR 51.100(s)(1). Therefore, ToxServices did not weigh the CEPA DSL classification heavily for evaluation of this endpoint, and assigned the score for this endpoint based on the results of the ready biodegradability tests and EPI Suite™ modeling.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
DMC was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 0.354 and an estimated BCF of 1.068. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4 and BCF values are no greater than 100 (CPA 2018b). The confidence in the score was high as it was based in part on measured data on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017b

  - BCFBAF predicts a BCF of 3.162 using the regression based model based on a measured log K_{ow} of 0.35, and a BCF of 1.068 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix L).
- ECHA 2023a
  - DMC has a log K_{ow} value of 0.354 at 20ºC as identified in an OECD Guideline 107 test (Klimisch 1, reliable without restriction).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
DMC 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 2018b). The confidence in the score was low as it was not based on an authoritative list or measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - The authors of the ECHA dossier stated that DMC was non-explosive and non-oxidizing due to a lack of chemical groups associated with explosive and oxidizing properties and non-oxidizing on the basis of its chemical structure. Furthermore, no evidence of pyrophoric properties was identified by the authors of the ECHA dosser. Lastly, DMC is not a peroxide.
  - In an auto-ignition temperature test, DMC does not self-ignite at temperatures up to 458°C (Klimisch 2, reliable with restrictions).
- Sigma Aldrich 2022
  - A safety data sheet for DMC reported that vapors may form explosive mixtures with air, and the chemical is stable under standard ambient conditions.
- HSDB 2014
  - DMC has a NFPA instability rating of 0 ("1 - Materials that in themselves are normally stable but that can become unstable at elevated temperatures and pressures").
- Based on the above data, ToxServices identified DMC as not reactive. DMC is not self-heating up to 458°C under standard pressure. It is not expected to be explosive or self-reactive based on chemical structure and an NFPA instability rating of 1. A safety data sheet reported that vapors may form explosive mixtures with air, but the chemical is stable under standard ambient conditions. DMC has no reactive functional groups that would make it oxidizing or explosive, and it is not a peroxide. As it is not explosive, it does not require desensitization. No data were found regarding corrosivity to metal.

Flammability (F) Score (vH, H, M, or L): H
DMC was assigned a score of High for flammability based on ToxServices classifying it to GHS Category 2 flammable liquid, and authoritative lists – EU harmonized H225, and U.S. DOT Class 3, Group 2. GreenScreen® criteria classify chemicals as a High hazard for flammability when they are classified as GHS Category 2 flammable liquids (H225) or DOT Class 3, Group 2 (CPA 2018b). The confidence in the score was high as it was based on authoritative lists with support from measured data.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H225 - Highly flammable liquid and vapour.

        - Quebec CSST – WHMIS 1988 – Class B2 – Flammable liquids.
        - U.S. DOT Hazard Class 3, Group 2.
    - *Screening:*
        - Australia - GHS - Highly flammable liquid and vapor [H225] (Flammable liquids – Category 2).
        - Japan - GHS - Highly flammable liquid and vapor [H225] (Flammable liquids – Category 2).
            - Based on a flash point of 14°C and boiling point of 90°C (NITE 2008).
        - New Zealand - GHS - Flammable liquids - Category 2.
            - Based on a flash point of 16°C and a boiling point of 90°C (CCID 2023).
- ECHA 2023a (Additional entries in the REACH dossier report similar flash points for DMC. Due to the large volume of data available, these studies were not individually summarized in this report.)
    - DMC (purity unspecified) has a measured flash point of 16.7°C at an assumed atmospheric pressure in a closed cup test conducted according to EU method A.9 (Klimisch 2, reliable with restrictions). *This value is within guidance values for GHS Category 2 (< 23ºC and a boiling point > 35ºC) for flammable liquids and therefore DMC is classified as a Category 2 flammable liquid under GHS (UN 2021)*.
    - The flash point of DMC was identified as 14ºC in a closed cup test (Klimisch 2, reliable with restrictions).
    - The flash point for DMC was identified as 18°C in an open cup test (Klimisch 2, reliable with restrictions).
    - In the previously described auto-ignition temperature test, DMC did not self-ignite at temperatures up to 458ºC (Klimisch 2, reliable with restrictions).
    - The authors of the ECHA dossier stated that DMC was not pyrophoric or flammable in contact with water.
- HSDB 2014
    - DMC has an NFPA fire rating of 3 (“Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials produce hazardous atmospheres with air under almost all ambient temperatures or, though unaffected by ambient temperatures, are readily ignited under almost all conditions”) (HSDB 2014).
- Based on the above data, ToxServices classified DMC as a Category 2 flammable liquid under GHS criteria (UN 2021). GHS criteria define Category 2 flammable liquids as chemicals with flash points less than 23°C and an initial boiling point greater than 35°C.

Use of New Approach Methodologies (NAMs)[10] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include use of QSAR modeling for carcinogenicity, endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and a variety of *in vitro* studies for genotoxicity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 4, Type I (input data) uncertainties in DMC's NAMs dataset include lack or insufficient experimental data to assess carcinogenicity, endocrine activity, and respiratory sensitization, and lack of validated test methods for respiratory sensitization. DMC's Type II (extrapolation output) uncertainties include reliance on structural alerts or models with undefined applicability domains to assess carcinogenicity and respiratory sensitization, inability of OncoLogic to evaluate the structure of the compound, reliance on *in vitro* genotoxicity studies that do not fully mimic *in vivo* metabolism or that have no validated guidelines, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of DMC's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: Limited experimental data are available only for oral exposure route. **Endocrine activity:** No *in vivo* data are available on circulating hormone levels. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: OECD Toolbox structural alerts screening does not define applicability domains. OncoLogic could not evaluate the structure of the compound. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation

[10] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

	system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[12] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[13]. There are no current OECD guidelines for *in vitro* comet assays. **Endocrine activity:** The *in vivo* relevance of *in silico* receptor binding modeling is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. The Danish QSAR predictions contradict the ECHA evaluation guidance (2017).	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**NAMs Data Available and Evaluated? (Y/N)**
Carcinogenicity	Y	*In silico* modeling: VEGA/ OncoLogic/OECD Toolbox/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay/*in vitro* comet assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	

[11] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[12] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[13] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/Danish QSAR
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301 C, D, F Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

References

Canadian Categorization Results (CCR). 2023. Categorization results from the Canadian Domestic Substance List for carbonic acid, dimethyl ester (CAS #616-38-6). Available: https://canadachemicals.oecd.org/ChemicalDetails.aspx?ChemicalID=2CCDB6EF-F5A6-4512-B4F2-E788A6CA046F

Chemical Classification and Information Database (CCID). 2023. Carbonic acid, dimethyl ester (CAS #616-38-6). New Zealand Environmental Protection Authority. Available: https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/view/09BA67CC-2134-47DE-9372-112809D185B0

ChemMine Tools (ChemMine). 2023. Available: https://chemminetools.ucr.edu/

Clean Production Action (CPA). 2018a. GreenScreen® Assessment Expiration Policy. October 2, 2018.

Clean Production Action (CPA). 2018b. The GreenScreen® for Safer Chemicals Guidance. Version 1.4 Guidance. Dated January, 2018. Available: https://www.greenscreenchemicals.org/static/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf

Cosmetic Ingredient Review (CIR). 2017. Safety assessment of dialkyl carbonates as used in cosmetics. Washington, D.C.: Cosmetic Ingredient Review.

Danish Technical University (DTU). 2023. National Food Institute. Danish QSAR Database. Available: http://qsar.food.dtu.dk/.

European Chemicals Agency (ECHA). 2017. Guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 6.0. Dated: July 2017. Available: https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f?t=1500286622893

European Chemicals Agency (ECHA). 2023a. REACH registration dossier for dimethyl carbonate (CAS #616-38-6). Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/14944

European Chemicals Agency (ECHA). 2023b. C&L Inventory for dimethyl carbonate (CAS #616-38-6). Available: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/43933

European Chemicals Agency (ECHA). 2023c. REACH registration dossier for diethyl carbonate (CAS #105-58-8). Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/14116

European Commission (EC). 2023. CosIng database. Available: https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple

European Food Safety Authority (EFSA). 2017. Safety assessment of the substance dimethyl carbonate for use in food contact materials. *EFSA J.* 15(7): 4901. Available: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4901

European Food Safety Authority (EFSA). 2018. Guidance on uncertainty analysis in scientific assessments. *EFSA J.* 16(1): e05123. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7009727/

Exxon Biomedical Sciences, Inc. 1992. Inhalation developmental toxicity study in mice with dimethylcarbonate. Prepared for Exxon Chemical Company. July 28, 1992. Available: www.toxplanet.com

Gad, S. 2016. QSAR Tools for Drug Safety. Chapter 10. In, Drug Safety Evaluation. Third Edition. New York: Wiley. 209-224.

Hazardous Substances Databank (HSDB). 2014. Entry for dimethyl carbonate (CAS #616-38-6). HSDB Number 6928. Last revision date: December 5, 2014. United States National Library of Medicine. Available: https://PubChem.ncbi.nlm.nih.gov/source/hsdb/6928

Madden, J.C., S.J. Enoch, A. Paini, and M.T.D. Cronin. 2020. A review of *in silico* tools as alternatives to animal testing: principles, resources, and applications. *Alt. Lab. Animals.* 1-27. Available: https://journals.sagepub.com/doi/pdf/10.1177/0261192920965977

National Institute of Technology and Evaluation (NITE). 2008. FY2008 GHS classification result for dimethyl carbonate (CAS #616-38-6). ID 20A2124. Incorporated Administrative Agency, Government of Japan. Available: http://www.safe.nite.go.jp/english/ghs/08-mhlw-0120e.html

National Institute of Technology and Evaluation (NITE). 2009. FY2009 GHS classification result for dimethyl carbonate (CAS #616-38-6). ID 21C0004. Incorporated Administrative Agency, Government of Japan. Available: http://www.safe.nite.go.jp/english/ghs/09-mhlw-2104e.html

Office of Environmental Health Hazard Assessment (OEHHA). 2010. OEHHA Final Revised Health Assessment for Dimethyl Carbonate. Appendix B. Available: http://www.valleyair.org/workshops/postings/2010/12-29-10/04%20AppB%20OEHHA%20assessment.pdf

Organisation for Economic Co-operation and Development (OECD). 2020. Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA), Series on Testing and Assessment, No. 329, Environment, Health and Safety, Environment Directorate. Available: https://www.oecd.org/chemicalsafety/risk-assessment/concepts-and-available-guidance-related-to-integrated-approaches-to-testing-and-assessment.pdf

Organisation for Economic Co-operation and Development (OECD). 2022. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 4.5. SP1. Available: http://toolbox.oasis-lmc.org/?section=download&version=latest.

Pharos. 2023. Pharos chemical and material library entry for dimethyl carbonate (CAS #616-38-6). Available: http://www.pharosproject.net/material/.

PubChem. 2023a. Entry for Dimethyl Carbonate (CAS #616-38-6). United States National Library of Medicine. Available: https://pubchem.ncbi.nlm.nih.gov/compound/12021

PubChem. 2023b. Entry for Diethyl Carbonate (CAS #105-58-8). United States National Library of Medicine. Available: https://pubchem.ncbi.nlm.nih.gov/compound/7766

Sahigara, F. 2007. Defining the Applicability Domain of QSAR models: An overview. Available: http://www.moleculardescriptors.eu/tutorials/T7_moleculardescriptors_ad.pdf

Sigma-Aldrich. 2022. Safety data sheet for dimethyl carbonate (CAS #616-38-6). Product number 517127. Version 6.6. Revision Date: September 8, 2022. Available: https://www.sigmaaldrich.com/US/en/sds/sial/517127

Seo, D. 2021. Toxicity assessment of dimethyl carbonate following 28 days repeated inhalation exposure. *Environ Anal Health Toxicol.* 36(2): e2021012. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8421751/

ToxServices. 2021. SOP 1.37: GreenScreen® Hazard Assessments. Dated: May 24, 2021.

United Nations (UN). 2021. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Ninth revised edition.

United States Department of Transportation (U.S. DOT). 2008a. Chemicals Listed with Classification. 49 CFR § 172.101. Available: http://www.gpo.gov/fdsys/pkg/CFR-2008-title49-vol2/pdf/CFR-2008-title49-vol2-sec172-101.pdf.

United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl

United States Environmental Protection Agency (U.S. EPA). 2015. Safer Choice Standard. Available: https://www.epa.gov/saferchoice/standard

United States Environmental Protection Agency (U.S. EPA). 2017. Estimation Programs Interface (EPI) Suite™ Web, v4.11, Washington, DC, USA. Available: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm.

United States Environmental Protection Agency (U.S. EPA). 2019. OncoLogic. Version 8.0.16 Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2020. New Approach Methods Workplan. Office of Research and Development. Office of Chemical Safety and Pollution Prevention. EPA 615B20001. June 2020. Available: https://www.epa.gov/sites/default/files/2020-06/documents/epa_nam_work_plan.pdf

United States Environmental Protection Agency (U.S. EPA). 2021. OncoLogic. Version 9.0 Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2023a. Safer Chemical Ingredients List (SCIL). Available: https://www.epa.gov/saferchoice/safer-ingredients

United States Environmental Protection Agency (U.S. EPA). 2023b. CompTox Dashboard. Available: https://comptox.epa.gov/dashboard

Virtual Models for Evaluating the Properties of Chemicals within a Global Architecture (VEGA). 2023. Predictive Model Platform version 1.2.3. Updated March 15, 2023. Available: https://www.vegahub.eu/portfolio-item/vega-qsar/

APPENDIX A: Hazard Classification 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 DMC (CAS #616-38-6)

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 / DMC / 616-38-6	*M*	L	L	*M*	DG	L	*M*	L	M	DG	L	*L*	L	*M*	L	*L*	vL	vL	*L*	H

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
DMC	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
DMC	2

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	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: MCS Tanimoto Coefficient Output for DMC (CAS #616-38-6)

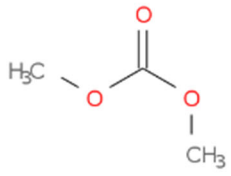
Compound Similarity

4 compound(s) in workbench

Select two compounds to compare from the grid below.

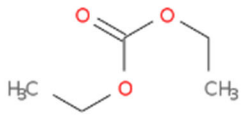
Selected Compounds

Target: Dimethyl carbonate (CAS #616-38-6)



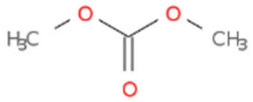
remove

Diethyl carbonate (CAS #105-58-8)

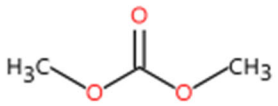


remove

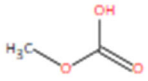
AP Tanimoto: 0.162162
MCS Tanimoto: 0.7500
MCS Size: 6
MCS Min: 1.0000
MCS Max: 0.7500
SMILES: C(=O)(OC)OC
Target: Dimethyl carbonate (CAS #616-38-6)



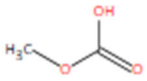
APPENDIX D: OECD Toolbox Profiling Results for DMC (CAS #616-38-6)

Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:2104784
CAS Number	616-38-6
CAS-SMILES relation	High
Chemical name(s)	Carbonic acid, dimethyl ester
Identity	Sources:16
Molecular formula	C3H6O3
Predefined substance type	Mono constituent
SMILES	COC(=O)OC
Profiling	
Predefined	
Database Affiliation	Acute Oral toxicity DB
Inventory Affiliation	AIIC
OECD HPV Chemical Categories	Not categorized
Substance type	Discrete chemical
US-EPA New Chemical Categories	Not categorized
General Mechanistic	
Toxic hazard classification by Cramer (...	Low (Class I)
Endpoint Specific	
Carcinogenicity (genotox and nongen...	No alert found
DNA alerts for AMES, CA and MNT by...	No alert found
in vitro mutagenicity (Ames test) alert...	No alert found
in vivo mutagenicity (Micronucleus) al...	No alert found
Oncologic Primary Classification	Not classified
Respiratory sensitisation	No alert found
Metabolism/Transformation	
Hydrolysis simulator (acidic)	3 metabolite(s)
Hydrolysis simulator (basic)	3 metabolite(s)
Hydrolysis simulator (neutral)	3 metabolite(s)

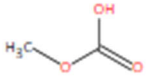
Hydrolysis simulator (acidic)

metabolite #1	metabolite #2	metabolite #3
No CAS number	No CAS number	No CAS number
		

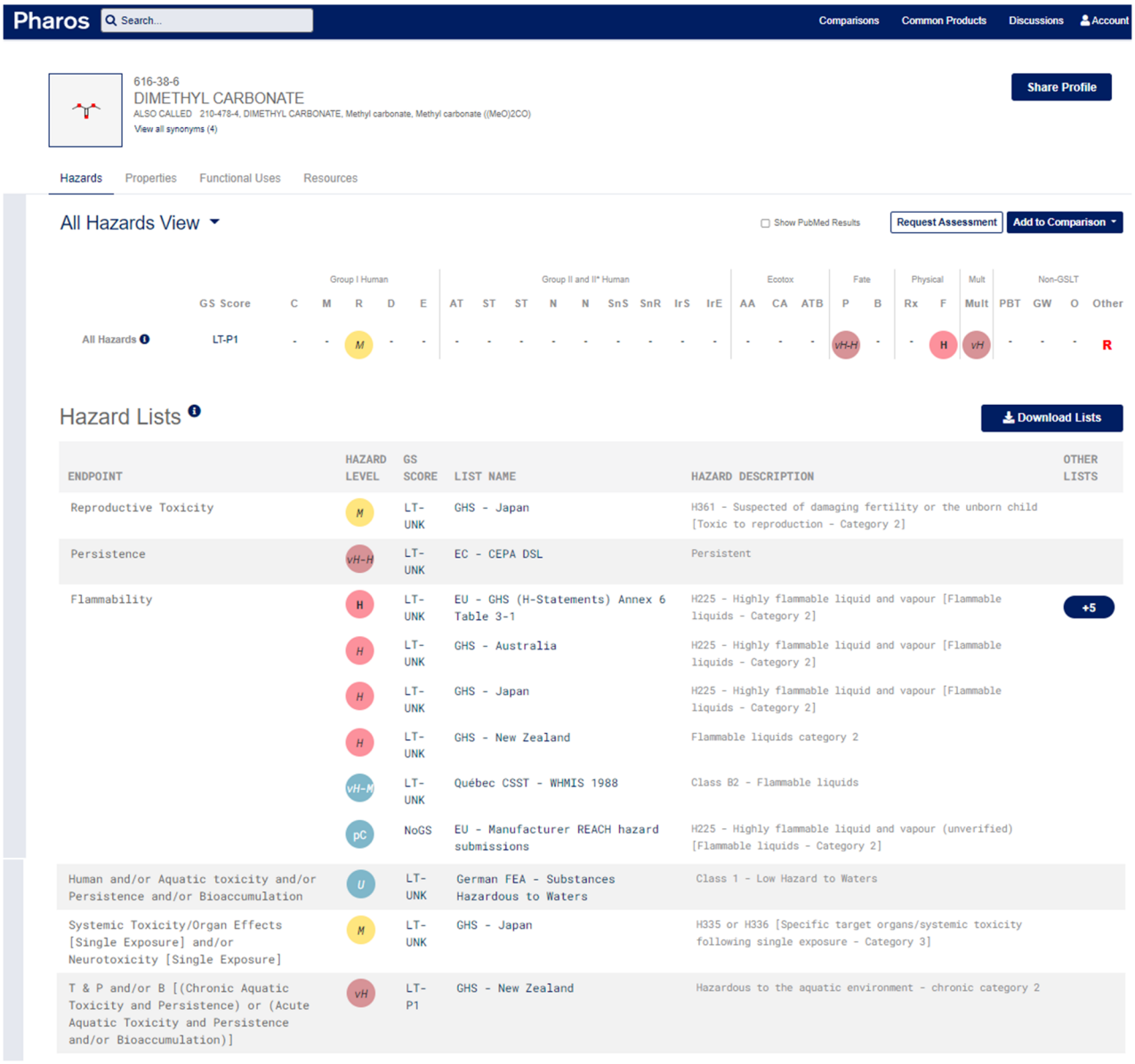
Hydrolysis simulator (basic)

metabolite #1	metabolite #2	metabolite #3
No CAS number	No CAS number	No CAS number
		

Hydrolysis simulator (neutral)

metabolite #1	metabolite #2	metabolite #3
No CAS number	No CAS number	No CAS number
		

APPENDIX E: Pharos Output for DMC (CAS #616-38-6)



Pharos | Search... | Comparisons | Common Products | Discussions | Account

616-38-6
DIMETHYL CARBONATE
ALSO CALLED 210-478-4, DIMETHYL CARBONATE, Methyl carbonate, Methyl carbonate ((MeO)2CO)
View all synonyms (4)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human									Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-P1	-	-	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	vH-H	-	-	H	vH	-	-	-	R

Hazard Lists

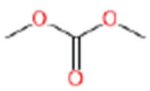
Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Reproductive Toxicity	M	LT-UNK	GHS - Japan	H361 - Suspected of damaging fertility or the unborn child [Toxic to reproduction - Category 2]	
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	
Flammability	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	+5
	H	LT-UNK	GHS - Australia	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Japan	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	
	vH-M	LT-UNK	Québec CSST - WHMIS 1988	Class B2 - Flammable liquids	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H225 - Highly flammable liquid and vapour (unverified) [Flammable liquids - Category 2]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	M	LT-UNK	GHS - Japan	H335 or H336 [Specific target organs/systemic toxicity following single exposure - Category 3]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	vH	LT-P1	GHS - New Zealand	Hazardous to the aquatic environment - chronic category 2	

APPENDIX F: VEGA Results for DMC (CAS #616-38-6)

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

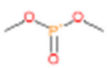
Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.585
P(NON-Carcinogen): 0.415
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

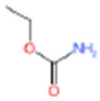
Compound #1

CAS: 598-55-0
Dataset id:445 (Training Set)
SMILES: O=C(OC)N
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Carcinogen



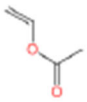
Compound #2

CAS: 868-85-9
Dataset id:264 (Training Set)
SMILES: O=[P+](OC)OC
Similarity: 0.796
Experimental value : Carcinogen
Predicted value : Carcinogen



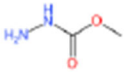
Compound #3

CAS: 51-79-6
Dataset id:792 (Training Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #4

CAS: 108-05-4
Dataset id:794 (Training Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 6294-89-9
Dataset id:446 (Training Set)
SMILES: O=C(OC)NN
Similarity: 0.742
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #6

CAS: 57-57-8
Dataset id:672 (Test Set)
SMILES: O=C1OCC1
Similarity: 0.733
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.761 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.802 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
⚠	Atom Centered Fragments similarity check ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..
✓	Model class assignment reliability Pos/Non-Pos difference = 0.169 Explanation: model class assignment is well defined..
✓	Neural map neurons concordance Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✗ The feature has a bad assessment, model is not reliable regarding this aspect.

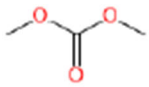
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

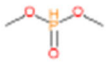
Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural Alerts: -
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

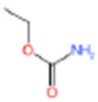
CAS: 598-55-0
Dataset id:270 (Training Set)
SMILES: O=C(OC)N
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA16 Alkyl carbamate and thiocarbamate



Compound #2

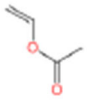
CAS: 868-85-9
Dataset id:620 (Training Set)
SMILES: O=P(OC)OC
Similarity: 0.788
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #3

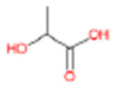
CAS: 51-79-6
Dataset id:24 (Training Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA16 Alkyl carbamate and thiocarbamate



Compound #4

CAS: 108-05-4
Dataset id:499 (Training Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 814-80-2
Dataset id:815 (Training Set)
SMILES: O=C(O)C(O)C
Similarity: 0.761
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #6

CAS: 756-79-6
Dataset id:739 (Training Set)
SMILES: O=P(OC)(OC)C
Similarity: 0.76
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA2 Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.798 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.508 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
⚠	Atom Centered Fragments similarity check ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

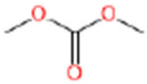
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

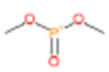
Prediction is Possible NON-Carcinogen, but the result may be not reliable.
A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

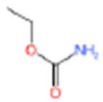
CAS: 598-55-0
Dataset id:221 (Training Set)
SMILES: O=C(OC)N
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

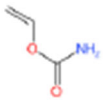
CAS: 868-85-9
Dataset id:512 (Training Set)
SMILES: O=[P+](OC)OC
Similarity: 0.796
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 15



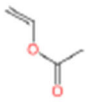
Compound #3

CAS: 51-79-6
Dataset id:20 (Training Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

CAS: 15805-73-9
Dataset id:921 (Training Set)
SMILES: O=C(OC=C)N
Similarity: 0.777
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 108-05-4
Dataset id:412 (Training Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #6

CAS: 298-14-6
Dataset id:897 (Training Set)
SMILES: O=C([O-])O
Similarity: 0.761
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.794 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.334 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
⚠	Atom Centered Fragments similarity check ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

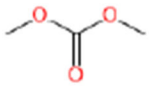
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

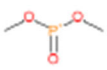
Prediction is Possible NON-Carcinogen, but the result may be not reliable.
A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

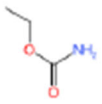
CAS: 598-55-0
Dataset id:445 (Training Set)
SMILES: O=C(OC)N
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

CAS: 868-85-9
Dataset id:264 (Training Set)
SMILES: O=[P+](OC)OC
Similarity: 0.796
Experimental value : Carcinogen
Predicted value : Carcinogen

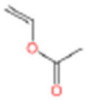
Alerts (not found also in the target): Carcinogenity alert no. 98



Compound #3

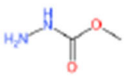
CAS: 51-79-6
Dataset id:792 (Training Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 118



Compound #4

CAS: 108-05-4
Dataset id:794 (Training Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 6294-89-9
Dataset id:446 (Training Set)
SMILES: O=C(OC)NN
Similarity: 0.742
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 2; Carcinogenity alert no. 44; Carcinogenity alert no. 55

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #6

CAS: 57-57-8
Dataset id:672 (Test Set)
SMILES: O=C1OCC1
Similarity: 0.733
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 114

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.794 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.659 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
⚠	Atom Centered Fragments similarity check ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.
⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.
✖ The feature has a bad assessment, model is not reliable regarding this aspect.

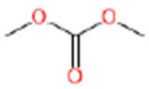
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

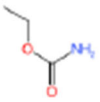
Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

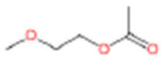
Compound #1

CAS: 79-20-9
Dataset id:578 (Training Set)
SMILES: O=C(OC)C
Similarity: 0.799
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



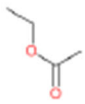
Compound #2

CAS: 51-79-6
Dataset id:316 (Test Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



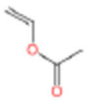
Compound #3

CAS: 110-49-6
Dataset id:576 (Training Set)
SMILES: O=C(OCCOC)C
Similarity: 0.777
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



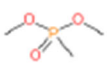
Compound #4

CAS: 141-78-6
Dataset id:501 (Test Set)
SMILES: O=C(OCC)C
Similarity: 0.767
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 108-05-4
Dataset id:740 (Training Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 756-79-6
Dataset id:121 (Training Set)
SMILES: O=P(OC)(OC)C
Similarity: 0.76
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.38 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.789 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.508 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.508 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✖	Atom Centered Fragments similarity check ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)..

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

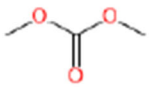
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has never been found in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

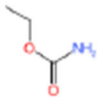
Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: O=C(OC)OC
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

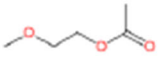
Compound #1

CAS: 79-20-9
Dataset id:557 (Training Set)
SMILES: O=C(OC)C
Similarity: 0.799
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



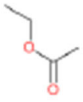
Compound #2

CAS: 51-79-6
Dataset id:261 (Training Set)
SMILES: O=C(OCC)N
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #3

CAS: 110-49-6
Dataset id:555 (Test Set)
SMILES: O=C(OCCOC)C
Similarity: 0.777
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

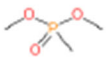


Compound #4

CAS: 141-78-6
Dataset id:473 (Training Set)
SMILES: O=C(OCC)C
Similarity: 0.767
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #5

CAS: 108-05-4
Dataset id:745 (Test Set)
SMILES: O=C(OC=C)C
Similarity: 0.761
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 756-79-6
Dataset id:431 (Training Set)
SMILES: O=P(OC)(OC)C
Similarity: 0.76
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.38 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.789 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.508 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.508 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✖	Atom Centered Fragments similarity check ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)..

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

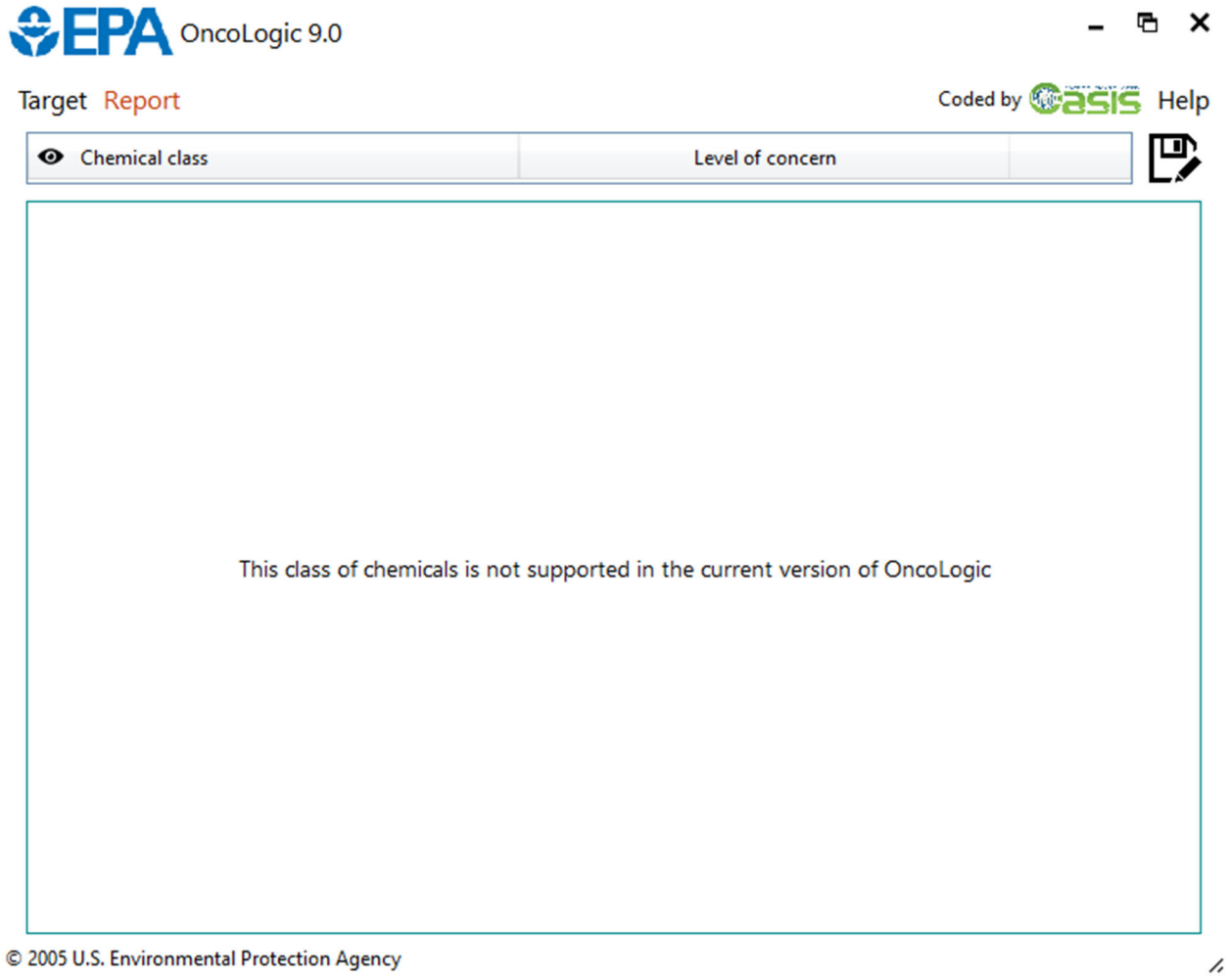
✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: OC(O)=O
The fragment has never been found in the model's training set

APPENDIX G: Oncologic Results for DMC (CAS #616-38-6)



APPENDIX H: Danish QSAR Carcinogenicity Results for DMC (CAS #616-38-6)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_IN	INC_OUT
FDA RCA Cancer Female Rat	NEG_IN	NEG_OUT
FDA RCA Cancer Rat	NEG_IN	NEG_OUT
FDA RCA Cancer Male Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Female Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Rodent	NEG_IN	NEG_OUT

Commercial models from CASE Ultra and Leadscope

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	POS_OUT	NEG_IN	NEG_IN

DTU-developed models

APPENDIX I: Danish QSAR Endocrine Results for DMC (CAS #616-38-6)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_OUT	NEG_OUT	NEG_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_OUT	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	INC_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			14408.82	1575.029	25.62291

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- µM			159955.8	17484.78	284.4461
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			2914.933	26.21371	104.3106
- µM			32359.38	291.0048	1157.977
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
DTU-developed models					
Estrogen Receptor Binding, alerts in:					
- parent only		Non binder, non cyclic structure			
- metabolites from *in vivo* Rat metabolism simulator only		Non binder, non cyclic structure			
- metabolites from Rat liver S9 metabolism simulator only		Non binder, non cyclic structure			
rtER Expert System - USEPA, alerts in:					

- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

APPENDIX J: Danish QSAR Sensitization Results for DMC (CAS #616-38-6)

Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		NEG_OUT	NEG_OUT	POS_OUT	NEG_IN
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Respiratory Sensitisation in Humans		POS_IN	POS_OUT	POS_IN	POS_IN

DTU-developed models

**Based on commercial training set*

	VEGA	ADI
Skin Sensitization (CAESAR)	POS_Low	0.438

CAESAR skin sensitization model is version 2.1.6 contained in VEGA command line version 1.1.2 BETA 5 with calculation core version 1.2.4

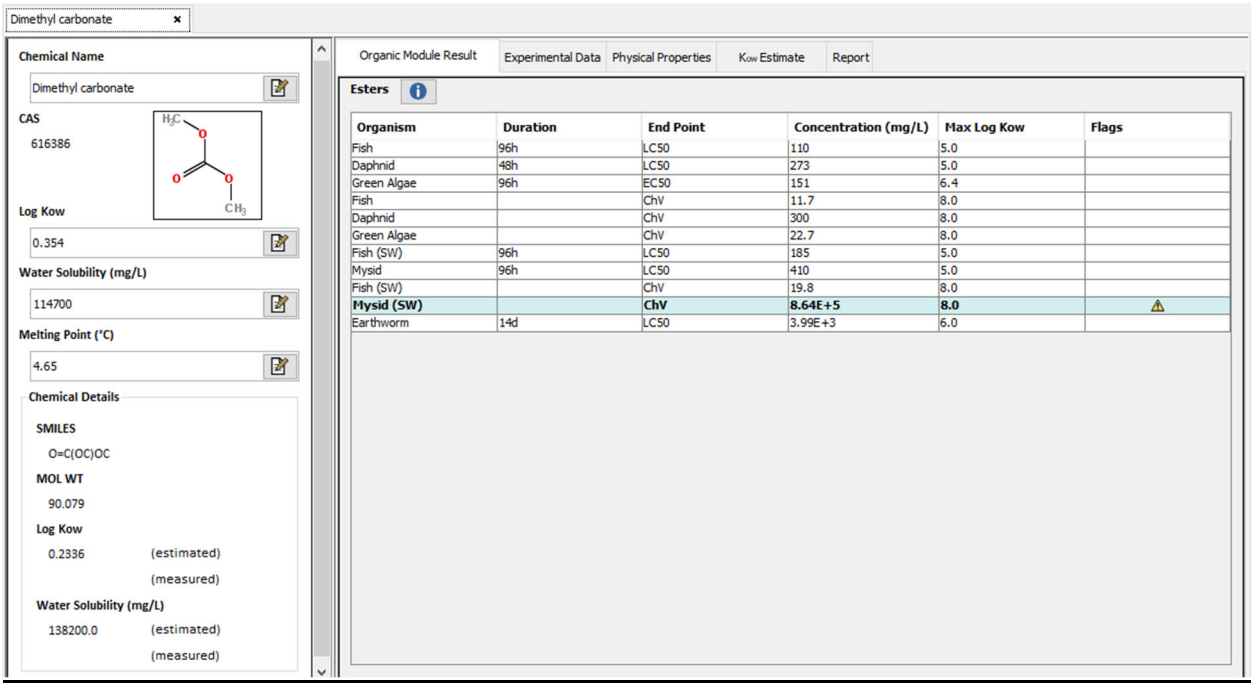
Prediction: POS = Sensitizer, NEG = Non-sensitizer, SUSP.POS = Suspected sensitizer, POSS.NEG = Possible Non-sensitizer, Exp = experimental value, Good = Good reliability, Mod = Moderate reliability, Low = Low reliability.

Protein binding by OASIS, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	No alert found
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	No alert found
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Alcohols
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Alcohols
- metabolites from auto-oxidation simulator only	
Keratinocyte gene expression, alerts in:	
- parent only	Not possible to classify according to these rules
- metabolites from skin metabolism simulator only	Not possible to classify according to these rules
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	Not possible to classify according to these rules (GSH)

OECD QSAR Toolbox v.4.1 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

APPENDIX K: ECOSAR Modeling Results for DMC (CAS #616-38-6)



Dimethyl carbonate

Chemical Name

Dimethyl carbonate

CAS

616386

Log Kow

0.354

Water Solubility (mg/L)

114700

Melting Point (°C)

4.65

Chemical Details

SMILES

O=C(OC)OC

MOL WT

90.079

Log Kow

0.2336 (estimated)

(measured)

Water Solubility (mg/L)

138200.0 (estimated)

(measured)

Organic Module Result | Experimental Data | Physical Properties | Kow Estimate | Report

Esters

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	110	5.0	
Daphnid	48h	LC50	273	5.0	
Green Algae	96h	EC50	151	6.4	
Fish		ChV	11.7	8.0	
Daphnid		ChV	300	8.0	
Green Algae		ChV	22.7	8.0	
Fish (SW)	96h	LC50	185	5.0	
Mysid	96h	LC50	410	5.0	
Fish (SW)		ChV	19.8	8.0	
Mysid (SW)		**ChV**	**8.64E+5**	**8.0**	⚠
Earthworm	14d	LC50	3.99E+3	6.0	

APPENDIX L: EPI Suite™ Modeling Results for DMC (CAS #616-38-6)

(Estimations Used for Hazard Classification Are Highlighted and Bolded)

CAS Number: 000616-38-6
SMILES : O=C(OC)OC
CHEM : Carbonic acid, dimethyl ester
MOL FOR: C3 H6 O3
MOL WT : 90.08
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 0.35
Boiling Point (deg C) : 90.50
Melting Point (deg C) : 0.50
Vapor Pressure (mm Hg) : 55.4
Water Solubility (mg/L): 1.147E+005
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.23

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 97.75 (Adapted Stein & Brown method)
Melting Pt (deg C): -120.12 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 56.2 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 7.49E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): 0.5 deg C
BP (exp database): 90.5 deg C
VP (exp database): 5.54E+01 mm Hg (7.39E+003 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1.059e+005
log Kow used: 0.35 (user entered)
melt pt used: 0.50 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 84977 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 6.20E-004 atm-m3/mole (6.29E+001 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 5.725E-005 atm-m3/mole (5.801E+000 Pa-m3/mole)
VP: 55.4 mm Hg (source: User-Entered)
WS: 1.15E+005 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 0.35 (user entered)
Log Kaw used: -1.596 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 1.950
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7047
Biowin2 (Non-Linear Model) : 0.8494
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0001 (weeks)
Biowin4 (Primary Survey Model) : 3.7178 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4922
Biowin6 (MITI Non-Linear Model): 0.6397
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): 7.39E+003 Pa (55.4 mm Hg)
Log Koa (Koawin est): 1.950
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 4.06E-010
Octanol/air (Koa) model: 2.19E-011
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.47E-008
Mackay model : 3.25E-008
Octanol/air (Koa) model: 1.75E-009

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 0.4352 E-12 cm3/molecule-sec
Half-Life = 24.577 Days (12-hr day; 1.5E6 OH/cm3)
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
2.36E-008 (Junge-Pankow, Mackay avg)
1.75E-009 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc : 2.877 L/kg (MCI method)
Log Koc: 0.459 (MCI method)
Koc : 7.792 L/kg (Kow method)
Log Koc: 0.892 (Kow 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) = -1.1691 days (HL = 0.06776 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.029 (BCF = 1.068)
Log BAF Arnot-Gobas method (upper trophic) = 0.029 (BAF = 1.068)
log Kow used: 0.35 (user entered)

Volatilization from Water:
Henry LC: 5.72E-005 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 10.68 hours
Half-Life from Model Lake : 196 hours (8.168 days)

Removal In Wastewater Treatment:
Total removal: 4.77 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.72 percent
Total to Air: 2.96 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**14.1**	**828**	**1000**
Water	**41.6**	**360**	**1000**
Soil	**44.3**	**720**	**1000**
Sediment	**0.0811**	**3.24e+003**	**0**

Persistence Time: 316 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	14.1	828	1000
Water	41.6	360	1000
water	(41.6)		
biota	(4.7e-006)		
suspended sediment	(0.000179)		
Soil	44.3	720	1000
Sediment	0.0811	3.24e+003	0

Persistence Time: 316 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	14.7	828	1000
Water	43.3	360	1000
water	(43.3)		
biota	(4.89e-006)		
suspended sediment	(6.02e-005)		
Soil	41.9	720	1000
Sediment	0.0809	3.24e+003	0

Persistence Time: 307 hr

APPENDIX M: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for DMC. The GreenScreen® Benchmark Score for DMC has not changed over time. The original GreenScreen® assessment was performed in 2018 under version v1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in 2019. Most recently, reclassification of the carcinogenicity endpoint from *Low* (low confidence) to *Moderate* (low confidence) and the single exposure systemic toxicity endpoint from **Low** (high confidence) to *Moderate* (low confidence) following a weight of evidence evaluation of this chemical's dataset did not change the BM-2 score.

Table 5: Change in GreenScreen® Benchmark™ for DMC

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October, 11, 2018	BM-2	v. 1.4	Original report
May 29, 2019	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with an updated v.1.4 template.
June 2, 2023	BM-2	v. 1.4	BM-2 score was maintained; however, there was a reclassification of carcinogenicity endpoint from *Low* (low confidence) to *Moderate* (low confidence), and of single exposure systemic toxicity endpoint from **Low** (high confidence) to *Moderate* (low confidence).
July 5, 2023	BM-2	v. 1.4	Minor changes were made to correct typos and to clarify information without affecting any hazard scores.

Licensed GreenScreen® Profilers

DMC GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Zach Guerrette, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC

DMC GreenScreen® Evaluation Updated by:

SIGNATURE BLOCK

Sara M. Ciotti, Ph.D.
Toxicologist
ToxServices LLC

SIGNATURE BLOCK

Deb Remeikas, M.A.
Toxicologist
ToxServices LLC

DMC GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC