DIMETHYL GLUTARATE (DMG)

(CAS #1119-40-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: June 3, 2021

Expiration Date: June 3, 2026

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GreenScreen® Executive Summary for Dimethyl Glutarate (DMG) (CAS #1119-40-0)

Dimethyl glutarate (DMG) is used as solvent in personal care products and fragrances, as a chemical intermediate in the production of resins, and as a plasticizer. It is a clear, colorless liquid at room temperature with moderate vapor pressure and boiling point, and may be considered a semi-volatile compound. DMG is water soluble, and is not flammable or reactive.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (endocrine activity-E)

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, use of *in vitro* data for genotoxicity, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation. 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 DMG's NAMs dataset include lack of experimental data for carcinogenicity and respiratory sensitization, lack of validated test methods for respiratory sensitization, and lack of chronic aquatic toxicity for two trophic levels. DMG's Type II (extrapolation output) uncertainties include lack of defined applicability domains for some models, limited reliability in some carcinogenicity predictions, conflicting predictions by different carcinogenicity models, limited relevance of *in vitro* data to mimic complex *in vivo* conditions with the assessment of genotoxicity, and structural alerts for respiratory sensitization do not capture non-immunologic mechanisms. Some of DMG's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for DMG

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*	*	*								
L	*L*	*L*	*L*	*M*	**L**	**M**	**L**	*L*	**L**	**L**	*L*	**L**	*L*	**M**	*M*	**vL**	**vL**	*L*	**L**

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 Glutarate (DMG) (CAS #1119-40-0)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: June 2, 2021

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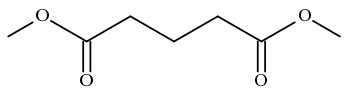
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: June 3, 2021

Expiration Date: June 3, 2026[2]

Chemical Name: Dimethyl Glutarate (DMG)

CAS Number: 1119-40-0

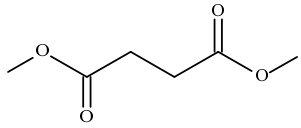
Chemical Structure(s):



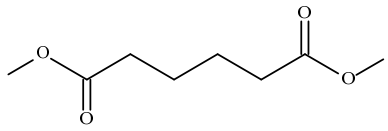
(Biovia 2018)

Also called: DMG (U.S. EPA 2008)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s): Dibasic esters (DBE) is a blend of approximately 55-65% DMG, 15-25% dimethyl succinate (DMS) (CAS #106-65-0), and 10-25% dimethyl adipate (DMA) (CAS #627-93-0) (U.S. EPA 2008). DMG is the major constituent of DBE, and the other constituents, DMS and DMA are structurally similar to DMG. Therefore, they are expected to have similar toxicological properties to DMG.



Surrogate: Dimethyl succinate (DMS) (CAS #106-65-0) (Biovia 2018)



Surrogate: Dimethyl adipate (DMA) (CAS #627-93-0) (Biovia 2018)

[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).

Identify Applications/Functional Uses (Pharos 2021)**:**
1. Antistatic agent and emollient in cosmetics
2. Chemical intermediate in the production of epichlorohydrin-polyamide resins, polyamide resins, and polyester resins
3. Fragrance
4. Plasticizer
5. Solvent

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for DMG[4,5 6,7]: DMG 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:

- Benchmark 2e
    - Moderate Group I Human Toxicity (endocrine activity-E)

Figure 1: GreenScreen® Hazard Summary Table for DMG

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*	*	*								
L	*L*	*L*	*L*	*M*	**L**	**M**	**L**	*L*	**L**	**L**	*L*	**L**	*L*	**M**	*M*	**vL**	**vL**	*L*	**L**

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). As DMG is readily biodegradable (see persistence section below), it is not expected to have relevant transformation products.

Introduction

DMG is manufactured by esterification of methyl alcohol with glutaric acid (HSDB 2002).

[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.

ToxServices assessed DMG against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

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 2020a). 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).

DMG is on the SCIL with a full green circle, indicating it has been verified to be of low concern based on experimental and modeled data.

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 2021) 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 DMG can be found in Appendix C.

- DMG is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- DMG is not listed on the U.S. DOT list.
- DMG 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.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters
    - Environment Canada (EC) – Canadian Environmental Protection Agency (CEPA) Dangerous Substances List (DSL) – Inherently Toxic to Humans (iTH)

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements that are harmonized in the EU or assigned by its REACH dossier authors were identified for DMG, and as of the date of this GreenScreen®, DMG is not appearing on the C&L Inventory. However, some unverified H statements by EU manufactures were identified in Pharos (Pharos 2021, Appendix C) as indicated in Table 1. As shown in Table 2, below, recommendations for use of personal protective equipment (PPE) were identified, but no occupational exposure limits (OEL) were identified.

Table 1: GHS H Statements for DMG (CAS #1119-40-0) (Pharos 2021)

H Statement	H Statement Details
H302	Harmful if swallowed
H331	Toxic if inhaled
H373	May cause damage to organs through prolonged or repeated exposure
H315	Causes skin irritation
H319	Causes serious eye irritation

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for DMG (CAS #1119-40-0)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Use respirators with combination filter for vapor/particulate only when ventilation is insufficient; Wear solvent-resistant gloves of permeation rate > 480 min and thickness of 0.5 mm (avoid nitrile rubber gloves); Wear safety glasses or chemical goggles if there is splashing potential; Wear solvent-resistant apron and boots	ECHA 2021	None	OSHA 2018

Physicochemical Properties of DMG

DMG is a clear, colorless liquid at room temperature. It is soluble in water, with similar density to water, and is not expected to dissociate. DMG is expected to be more soluble in octanol than in water, based on the log K_{ow} of 0.49. It has a moderate boiling point and vapor pressure and may be considered semi-volatile.

Table 3: Physical and Chemical Properties of DMG (CAS #1119-40-0)		
Property	**Value**	**Reference**
Molecular formula	C7H12O4	ChemIDplus 2021
SMILES Notation	COC(=O)CCCC(=O)OC	ChemIDplus 2021
Molecular weight	160.1678 g/mol	ChemIDplus 2021
Physical state	Liquid	ECHA 2021
Appearance	Clear, colorless	ECHA 2021
Melting point	-38ºC	ECHA 2021
Boiling point	216ºC	ECHA 2021
Vapor pressure	0.063 mmHg at 20°C, 0.1 mmHg at 25°C	ECHA 2021
Water solubility	63.1 g/L @ 20ºC	ECHA 2021
Dissociation constant	Not identified	
Density/specific gravity	1.09 g/cm^3	ECHA 2021
Partition coefficient	Log K_{ow} = 0.49 (exp.) Koc = 10 (est., MCI method) Koc – 13.07 (est., K_{ow} method)	ECHA 2021; U.S. EPA 2017a

Toxicokinetics

- ECHA 2021
    - No toxicokinetic studies were identified for DMG, however, based on its low molecular weight and good water solubility, it is expected to be absorbed following ingestion. Based on its low measured log K_{ow}, DMG is expected to be poorly soluble in lipids, and have low potential to bioaccumulate. Observations of local effects in the nasal epithelium in both acute and repeated dose inhalation toxicity studies, suggest DMG is absorbed through the respiratory tract. The estimated dermal permeability coefficient of 4.9 x 10^{-4} cm/hour using

EPA Dermwin v2.01 by REACH dossier authors indicates that DMG can be absorbed through the skin. Based on analogy to other dibasic esters, DMG is expected to be readily metabolized to methanol, monomethyl glutarate, and glutaric acid, and subsequently excreted in the urine.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

DMG was assigned a score of Low for carcinogenicity based on modeling using statistical and rule-based methods supported by lack of mutagenicity, and lack of preneoplastic lesions in sub-chronic inhalation exposure studies on DMG and surrogate compound DBE. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low based on lack of chronic data.

- 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 experimental data were found for the target compound or a close surrogate.
- VEGA 2021
  - QSAR modeling in VEGA results in a negative prediction for carcinogenicity. Six of six models predict the compound to be non-carcinogenic. The models encompass rule-based and statistical/expert-based methods. While all the expert rule-based methods provided global applicability domain (AD) index values >0.7, indicating high reliability[9], the CAESAR model, which is the only statistical-based method, provided an AD value of 0.632, indicating lower reliability (Appendix D).
- DTU 2021
  - Modeling in the Danish QSAR Database resulted in negative predictions for carcinogenicity with E Ultra and Leadscope models using all 7 databases, and the compound was in the applicability domain for each model. Modeling for liver-specific cancer in rat or mouse resulted in a positive prediction with the CASE Ultra method, and negative for Leadscope, and was within the applicability domain of both models (results for Battery and SciQSAR were outside the applicability domain and are not considered in the weight of evidence) (Appendix E).
- U.S. EPA 2019, 2021
  - Modeling could not be performed using Oncologic v. 8.0 or v. 9.0, as the structure (i.e., a primary ester, or carboxylic acid ester) is not within the domain of applicable compounds at this time.
- Toxtree 2018
  - No structural alerts for genotoxic or nongenotoxic carcinogenicity were identified in Toxtree using the ISS rulebase (Appendix F).

[9] If an external compound is beyond the defined scope of a given model, it is considered outside that model's AD and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD range from 0 (worst case) to 1 (best case). Generally, AD values of >0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).

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

DMG was assigned a score of Low for mutagenicity/genotoxicity based on the weight of evidence including negative results in *in vitro* mutagenicity assays in bacterial and mammalian cells, equivocal results for clastogenicity *in vitro*, and negative results for clastogenicity *in vivo*. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is low as the *in vivo* clastogenicity studies had limited details reported and therefore unknown reliability.

- 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 2008
  - DMG tested negative in an Ames assay (method and GLP not specified) using *Salmonella typhimurium* (strains not specified) in the presence and absence of metabolic activation at up to 20,000 µg/plate. Cytotoxicity was observed at the high doses, but results were negative for the induction of reverse mutations at all concentrations for all strains.
  - DMG tested negative in an *in vivo* mammalian bone marrow micronucleus assay (method and GLP not specified). CD-1 mice were exposed to the test substance (route of exposure not disclosed). Results were negative for the induction of micronucleated polychromatic erythrocytes in the bone marrow.
  - *Surrogate: DBE*: DBE tested negative in an Ames assay (method and GLP not specified) using *S. typhimurium* (strains not specified) in the presence and absence of metabolic activation at up to 20,000 µg/plate. Cytotoxicity was observed at the high doses, but results were negative for the induction of reverse mutations at all concentrations for all strains.
  - *Surrogate: DBE*: DBE tested negative in an *in vivo* mammalian bone marrow micronucleus assay (method and GLP not specified). CD-1 mice were exposed to the test substance (route of exposure not disclosed). Results were negative for the induction of micronucleated polychromatic erythrocytes in the bone marrow.
- ECHA 2021
  - DMG (99.61% purity) was evaluated in an *in vitro* gene mutation study in mammalian cells (OECD 476, GLP compliant). Chinese hamster ovary cells were exposed to the test substance in DMSO, at concentrations up to 5,000 ug/L in 2 trials, with and without metabolic activation. Results were negative for the induction of mutations at the HPRT locus at all concentrations, with and without activation. Cytotoxicity was observed at the highest doses in both trials, with and without activation, and controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Klimisch 1, reliable without restriction).
  - *Surrogate: DBE*: DBE tested negative in a bacterial reverse mutation assay (equivalent or similar to OECD 471, GLP compliant). *S. typhimurium* TA98, TA100 and TM677 were exposed to the test substance in DMSO, with and without metabolic activation, at concentrations up to 10.66 mM in TA98 and TA100, and up to 5.63 mM for TM677. Activation for TA98 and TA100 was from the liver fraction of Aroclor 1254-induced rats (S9 mix); activation for TM677 was olfactory tissue homogenate fractions of uninduced female Crl:CDBR BR rats (S9 mix). Results were negative for increased mutations in all strains, with and without activation, at all concentrations. Cytotoxicity was not observed, controls performed as expected (Klimisch 1, reliable without restriction, although only 2 of the recommended 5 strains were tested).

- *Surrogate: DBE*: DBE tested negative in a bacterial reverse mutation assay (equivalent or similar to OECD 471, GLP not specified). *S. typhimurium* TA98, TA100, TA1535, and TA1537 were exposed to the test substance in DMSO, with and without metabolic activation, at concentrations up to 10,000 µg/plate. Results were negative for the induction of reverse mutations at all concentrations, with and without activation. Cytotoxicity was not observed, and controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Klimisch 2, reliable with restrictions as only 4 of the 5 recommended strain types were tested).
- *Surrogate: DBE*: DBE was evaluated in an *in vitro* chromosome aberration assay in mammalian cells (OECD 473, GLP compliant). Cultured human primary lymphocytes were exposed to the test substance in DMSO, with and without metabolic activation, at concentrations up to 0.6% v/v (6.6 mg/mL). Without activation, results were negative for the induction of chromosomal aberrations at all concentrations, and cytotoxicity was observed based on reduced mitotic indices at the highest concentration. With activation, results were positive for the induction of chromosomal aberrations at 0.3 and 0.4% in Trial 1 with cytotoxicity at 0.4%; results were positive in Trial 2 at 0.4% with cytotoxicity starting at 0.3% (Klimisch 1, reliable without restriction).

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

DMG was assigned a score of Low for reproductive toxicity based on a lack of adverse effects on reproductive endpoints in a one-generation reproductive toxicity study for the surrogate DBE. Additionally, no reproductive effects were observed in a subchronic inhalation toxicity study on the target compound, DMG, in which there were examinations of some reproductive parameters. It is noted there were observed effects on hormones related to the reproductive system, however, they were not associated with adverse pathological observations; and therefore, are of unknown relevance. 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 low based on unknown relevance of observed hormonal effects of DMG.

- 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 2021, U.S. EPA 2008
  - DMG was evaluated in a subchronic inhalation toxicity study (equivalent or similar to OECD 413, GLP compliant) in which some reproductive endpoints were examined. Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed to the DMG as aerosol via whole body exposure at concentrations of 0, 10, 50 or 400 mg/m^3, 6 hours/day, 5 days/week for 90 days, followed by a 1-month recovery period. Standard parameters were evaluated, as well as neurobehavioral test battery, estrus cycle, and hormonal analyses in both sexes. No effects were observed based on clinical signs, mortality, ophthalmology, hematology, urinalysis, behavior (functional observations and motor activity), or organ weights. Male rats at 400 mg/m^3 had lower mean body weight gain through day 84, and during recovery, male rats at 50 and 400 mg/m^3 had decreased mean body weights compared to controls. Male rats at 400 mg/m^3 had decreased food consumption from day 49 through the end of the recovery period; females at 400 mg/m^3 had decreased food consumption through day 84. For reproductive and endocrine effects, there were statistically significant decreases in serum testosterone and increased epididymal sperm counts at 50 mg/m^3 and higher. Serum LH concentrations were decreased in a dose-dependent manner with statistical significance at 400 mg/m^3 (71% of controls). Serum FSH was not affected by treatment. There were no corresponding

histopathological findings and no changes in reproductive organ weights. Authors noted decreased male sex hormones is generally associated with decreased sperm counts, but the opposite was observed, therefore the effects were considered not toxicologically significant. There were no effects on sperm motility, morphology or testicular spermatid counts. In females, there were no changes in serum estradiol, serum progesterone, or estrus cycling. Authors concluded a systemic toxicity NOEC at 10 mg/m^3 (Klimisch 1, reliable without restriction). Based on the guideline not being intended to evaluate reproductive toxicity, and because effects on hormone levels were not associated with adverse pathological effects, the significance of minimal effects levels for reproductive toxicity cannot be determined (U.S. EPA 2008).

- *Surrogate: DBE*: DBE was evaluated in a one-generation reproductive toxicity study (equivalent or similar to OECD 415, EU Method B.34, GLP compliant). Male and female Crl:CD(SD)BR rats (20/sex/dose) were exposed to DBE vapor by whole body exposure at 0, 0.16, or 0.40 mg/L, or aerosol at 1 mg/L, 6 hours/day. Animals were exposed 5 days/week from pre-breeding for 14 weeks, and 7 days/week for 8 weeks through breeding, gestation, and lactation. Females however were not exposed from gestation days 19 through postpartum day 3. There were no effects on clinical signs. Body weights were reduced in females at 0.40 mg/L and 1.0 g/L. No treatment-related differences were observed between the control and test groups with regard to male or female fertility, gestation length, litter sizes, viability, or lactation performance. Histopathology for parental rats demonstrated squamous metaplasia primarily in the olfactory epithelium in all groups exposed to DBE. The nasal effect was minimal at 0.16 mg/L, and mild to moderate at 0.40 and 1.0 mg/L. The squamous metaplasia was characterized by a flattening and pavementing of epithelial cells which replaced the normal architecture of the olfactory epithelium. In some cases, particularly in the 0.40 and 1.0 mg/L rats, this squamous change was accompanied by a very minimal to mild suppurative inflammation. The squamous metaplasia was present primarily in the olfactory epithelium of the dorsal meatus, along the dorsal portion of the nasal septum, and on the tips of the ecto- and endoturbinates in the nasal cavity. There was also an increase in squamous metaplasia of the respiratory epithelium in the nasal cavity in high-dose rats. The severity of the lesions ranged from absent to moderate in some rats. One male at 1.0 mg/L had a meningeal sarcoma surrounding the olfactory region of the brain. Because the tumor did not communicate with the nasal cavity and the tumor cell type was unrelated to any nasal epithelial cell types, the tumor was considered to be unrelated to inhalation of DBE. In parental rats, relative liver weights were slightly lower 0.40 and 1.0 mg/L compared to controls. Other incidental differences between test and control rats included slight decreases in absolute heart and kidney weights in females at 0.40 and 1.0 mg/L, slight decrease in absolute spleen weight and a slight increase in relative brain weight in females at 1.0 mg/L. These differences were not dose-related and may have been related to the slight body weight differences between the test and control groups and were considered of minimal biological significance. There were no macroscopic findings in pups, however high dose pup body weights were reduced at birth and weaning on day 21 post-partum. A NOAEC could not be determined based on nasal histopathology at all concentrations. The NOEC for reproductive toxicity was 1 mg/L, the highest concentration tested (Klimisch 1, reliable without restriction). EPA evaluated this same study and concluded a NOAEC at 0.4 mg/L, and a LOAEC at 1.0 mg/L based on decreased pup body weights.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
DMG was assigned a score of Low for developmental toxicity based on data for DMG in rabbits, and surrogate data for DBE in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low because the severity and incidence of delayed sternebral ossifications in high dose pups (in the presence of parental systemic toxicity) and concurrent and historical controls is not provided in the DMG study in rabbits, rather ToxServices relies on the authors' conclusions that such effects were not toxicologically significant.

- 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 2021, U.S. EPA 2008
  - DMG was evaluated in a prenatal developmental toxicity study (EPA OPPTS 870.3700, GLP compliant). Hra:(NZW)SPF rabbits (22/dose) were exposed to the test substance as aerosol (no vehicle) via whole body inhalation at concentrations of 0, 30, 100, 300 or 1,000 mg/m^3, 6 hours/day during gestation days (GD) 7-28. The measured high dose vapor concentrations were 450-590 mg/m^3, and the mean daily aerosol concentrations were 410-580 mg/m^3. At 1,000 mg/m^3, one animal was found dead on GD 13, and another was sacrificed in extremis on day GD 22. Reduced mean body weights were observed at 300 and 1,000 mg/m^3, and reduced food consumption at 1,000 mg/m^3. Clinical observations included clear ocular discharge at 300 and 1,000 mg/m^3. There were no compound-related gross postmortem findings for any dose group. Authors concluded a NOAEC of 100 mg/m^3 for maternal toxicity, and a LOAEC of 300 mg/m^3. There were no treatment related findings on mortality, mean number of live fetuses, body weights, or malformations. At 1,000 mg/m^3 there was a significant increase in delayed sternebral ossification compared to concurrent controls, however concurrent control values were significantly less than historical control values. Authors concluded a NOAEC for developmental toxicity at 1,000 mg/m^3 (Klimisch 1, reliable without restriction). EPA evaluated this study and concluded a NOAEC of 300 mg/m^3 and LOAEC at 1,000 mg/m^3 based on the effects on sternebral ossifications. *ToxServices agrees with ECHA authors' conclusion that because they were not significant compared to historical controls, and because concurrent control values were less than historical controls, they are not necessarily an indicator of developmental toxicity. Accordingly, ToxServices concludes the NOAEC for developmental effects is 1,000 mg/m^3.*
- ECHA 2021
  - <u>*Surrogate: DBE*</u>: DBE was evaluated in a prenatal developmental toxicity study (equivalent or similar to OECD 414, GLP compliant). Crl:CD BR rats (24/dose) were exposed to the test substance by whole body inhalation (no vehicle) at 0, 0.16, 0.4, or 1.0 mg/L (nominal) or 0, 0.15, 0.38, and 0.99 mg/L (measured), 6 hr/day on GD 7-16. There were no mortalities throughout the study. Body weights were reduced at 0.4 and 1.0 mg/L and corresponded with reduced food consumption. Clinical observations included perinasal staining in 1 rat at 0.16 mg/L, 4 rats at 0.4 mg/L, and 15 rats at 1.0 mg/L. There were no significant differences in absolute or relative liver weights. There were no significant differences in the incidence of external, visceral, or skeletal malformations or variations compared to controls. Authors concluded a NOAEC of 1 mg/L for developmental toxicity, and 0.16 mg/L for maternal toxicity based on reduced food consumption and body weight gain at 0.4 mg/L (Klimisch 1, reliable without restriction).

Endocrine Activity (E) Score (H, M, or L): *M*
DMG was assigned a score of Moderate for endocrine activity based on decreased serum testosterone, increased epididymal sperm counts, and decreased serum luteinizing hormone concentrations in a subchronic inhalation toxicity study. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when endocrine activity is observed but there are no corresponding adverse pathological findings (CPA 2018b). The confidence in the score is low based on lack of a more robust study, such as a multi-generational study and/or examination of endocrine activity in a second species.

- 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 2021
  - DMG was evaluated in a subchronic inhalation toxicity study (equivalent or similar to OECD 413, GLP compliant), and some endocrine-related endpoints were included. Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed to the DMG as aerosol via whole body exposure at concentrations of 0, 10, 50 or 400 mg/m^3, 6 hours/day, 5 days/week for 90 days, followed by a 1-month recovery period. Standard parameters were evaluated, as well as neurobehavioral test battery, estrus cycle, and hormonal analyses in both sexes. No effects were observed based on clinical signs, mortality, ophthalmology, hematology, urinalysis, behavior (functional observations and motor activity), or organ weights. Male rats at 400 mg/m^3 had lower mean body weight gain through day 84, and during recovery, male rats at 50 and 400 mg/m^3 had decreased mean body weights compared to controls. Male rats at 400 mg/m^3 had decreased food consumption from day 49 through the end of the recovery period; females at 400 mg/m^3 had decreased food consumption through day 84. For reproductive and endocrine effects, there were statistically significant decreases in serum testosterone and increased epididymal sperm counts at 50 mg/m^3 and higher. Serum luteinizing hormone concentrations were decreased in a dose-dependent manner with statistical significance at 400 mg/m^3 (71% of controls). Serum FSH was not affected by treatment. There were no corresponding histopathological findings and no changes in reproductive organ weights. Authors noted decreased male sex hormones is generally associated with decreased sperm counts, but the opposite was observed, therefore the effects were considered not toxicologically significant. There were no effects on sperm motility, morphology or testicular spermatid counts. In females, there were no changes in serum estradiol, serum progesterone, or estrus cycling. Authors established a systemic toxicity NOEC at 10 mg/m^3 (Klimisch 1, reliable without restriction). *As effects on hormone levels were not associated with adverse pathological effects, ToxServices concludes there is evidence of endocrine activity but not endocrine disruption.*

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>
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
DMG was assigned a score of Low for acute toxicity based on oral LD_{50} values > 5,000 mg/kg for the target compound DMG, a dermal LD_{50} >2,000 mg/kg for surrogate compound DBE, and an inhalation LC_{50} > 11 mg/kg for the surrogate DBE. These values meet the GreenScreen® criteria for Low hazard classification (CPA 2018b). The confidence in the score is high based on high quality data for the target compound and a strong 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.
- ECHA 2021
    - *Oral:* Female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 423, GLP compliant). Rats were exposed by a single gavage (no vehicle) at 5,000 mg/kg and observed for 14 days. There were no deaths. Clinical signs included hunched posture and piloerection in two animals, but effects reversed within 4 days. There were no effects on body weight gain, and no abnormalities found at necropsy. Authors concluded the test substance exceeded the criteria for GHS classification (Klimisch 1, reliable without restriction).
    - *Oral:* Male and female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 401, GLP compliant). Rats were exposed to a single gavage (no vehicle) at 2,000 mg/kg and observed for 14 days. There were no deaths, no observed clinical signs, no effect on body weight gain, and no abnormalities found at necropsy. Authors concluded the test substance exceeded the criteria for GHS classification (Klimisch 1, reliable without restriction).
    - *Oral:* Male ChR-CD rats were exposed to DMG in an Oral Class B Poison Test (US Department of Transportation 173.333-173.343, non-GLP). Rats were exposed to a single gavage in water at 50 mg/kg as 1% aqueous solution and observed for 48 hours. There were no deaths or clinical signs. Authors concluded the test substance did not warrant classification as a Class B poison (Klimisch 2, reliable with restrictions).
    - *Dermal:* Male albino rabbits were exposed to DMG in a standard acute toxicity test (US Department of Transportation 173.343, similar to OECD 402, non-GLP). Animals were exposed to neat substance under occlusion at 200 mg/kg for 24 hour and were observed for another 24 hours before sacrifice. There were no deaths or clinical signs. Authors concluded the test substance did not warrant classification as a Class B poison by skin absorption (Klimisch 2, reliable with restrictions).
    - *Dermal: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute dermal toxicity study (OECD 402, GLP compliant). Rats (5/sex) were exposed under semi-occlusion at 2,000 mg/kg for 24 hours, then observed for 14 days. There were no deaths, no clinical signs of toxicity, no effects on body weight gain, and no signs of gross pathology at necropsy. Authors concluded the test substance exceeded the criteria for GHS classification (Klimisch 1, reliable without restriction).
    - *Inhalation: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute inhalation toxicity study (OECD 403, non-GLP). Rats were exposed to DBE aerosol nose only at 0, 3.5, 5.6, or 11.0 mg/L mg/L for 4 hours, and then observed for 14 days. There were no mortalities in the study. Clinical signs included red nasal, ocular, or oral discharges, wet, yellow-stained perineum, and hunched posture, but all signs resolved by day 4. Slight to severe body weight losses in all exposure groups were measured 1 day after exposure, and transient weight loss was measured during the first or second weeks of recovery in both sexes. There were no effects on corneal and pupillary reflexes for the low- and high-dose groups, however mid-dose rats had bilateral mild chemosis (edema/swelling) in the bulbar conjunctiva, and one mid-dose rat had a subepithelial corneal opacity. Authors concluded the LC_{50} was > 11 mg/L and exceeded the criteria for GHS classification (Klimisch 2, reliable with restrictions).

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

DMG was assigned a score of Moderate for systemic toxicity (single dose) based on respiratory tract irritation in an acute inhalation toxicity study. No systemic toxicity was observed in acute oral and dermal studies, and DMG does not present an aspiration hazard. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when data support GHS Category 3 classification (CPA 2018b). The confidence in the score is high based on reliable data on DMG and a strong 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.
- ECHA 2021
  - *Oral:* Female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 423, GLP compliant). Rats were exposed to a single gavage (no vehicle) at 5,000 mg/kg, then observed for 14 days. There were no deaths. Clinical signs included hunched posture and piloerection in two animals, but effects reversed within 4 days. There were no effects on body weight gain and no abnormalities found at necropsy (Klimisch 1, reliable without restriction).
  - *Oral:* Male and female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 401, GLP compliant). Rats were exposed to a single gavage (no vehicle) at 2,000 mg/kg and observed for 14 days. There were no deaths, no observed clinical signs, no effect on body weight gain, and no abnormalities found at necropsy (Klimisch 1, reliable without restriction).
  - *Oral:* Male ChR-CD rats were exposed to DMG in an Oral Class B Poison Test (US Department of Transportation 173.333-173.343, non-GLP). Rats were exposed to a single gavage in water at 50 mg/kg as 1% aqueous solution and observed for 48 hours. There were no deaths or clinical signs (Klimisch 2, reliable with restrictions).
  - *Dermal:* Male albino rabbits were exposed to DMG in a standard acute toxicity test (US Department of Transportation 173.343, similar to OECD 402, non-GLP). Animals were exposed to neat substance under occlusion at 200 mg/kg for 24 hour and were observed for another 24 hours before sacrifice. There were no deaths or clinical signs (Klimisch 2, reliable with restrictions).
  - *Dermal: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute dermal toxicity study (OECD 402, GLP compliant). Rats (5/sex) were exposed under semi-occlusion at 2,000 mg/kg for 24 hours, then observed for 14 days. There were no deaths, no clinical signs of toxicity, no effects on body weight gain, and no signs of gross pathology at necropsy (Klimisch 1, reliable without restriction).
  - *Inhalation: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute inhalation toxicity study (OECD 403, non-GLP). Rats were exposed to DBE aerosol nose only at 0, 3.5, 5.6, or 11.0 mg/L mg/L for 4 hours, then observed for 14 days. There were no mortalities in the study. Clinical signs included red nasal, ocular, or oral discharges, wet, yellow-stained perineum, and hunched posture, but all signs resolved by day 4. Slight to severe body weight losses in all exposure groups were measured 1 day after exposure, and transient weight loss was measured during the first or second weeks of recovery in both sexes. There were no effects on corneal and pupillary reflexes for the low- and high-dose groups, however mid-dose rats had bilateral mild chemosis (edema/swelling) in the bulbar conjunctiva, and one mid-dose rat had a subepithelial corneal opacity (Klimisch 2, reliable with restrictions). *ToxServices notes that red nasal discharge is plausibly an early indicator*

of respiratory tract irritation, particularly because more significant symptoms were observed in repeated dose studies (e.g., olfactory mucosa degeneration / atrophy were observed in rats exposed to DMG in a 90-day inhalation toxicity study, and squamous metaplasia was observed in the olfactory epithelium in rats exposed to surrogate compound DBE in a one-generation inhalation reproductive toxicity study). These data meet the criteria for GHS category 3 for transient target organ effects (UN 2019).

- *Aspiration:* The kinematic viscosity was 2.53 mm^2/s at 20°C, and 1.70 mm^2/s at 40°C. *GHS criteria classify chemicals as aspiration hazards Category 2 when they are hydrocarbons, alcohols or ketones with a kinematic viscosity of 14 mm^2/s at 40°C along with consideration of surface tension, water solubility, boiling point and volatility (UN 2019). DMG is not a hydrocarbon, alcohol or ketone, it has a high vapor pressure, a low boiling point, high water solubility, and a low kinematic viscosity. Accordingly, if inhaled or ingested, it can be readily cleared from the airways and is unlikely to create an aspiration hazard. There are no signs of aspiration in animal studies described previously.*

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

DMG was assigned a score of Low for systemic toxicity (repeated dose) based on decreased bodyweight gain and food consumption and a corresponding adjusted LOAEC of 0.29 mg/L/6hr/day in a subchronic inhalation toxicity study. The LOAEC of 0.29 mg/L/6hr/day exceeds the GHS classification criteria. Data are insufficient to evaluate the oral and dermal routes of exposure; however, there is no reason to expect toxicity would be higher for these routes compared to the inhalation route of exposure. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound, DMG, for the inhalation route of exposure.

- 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 2008
  - *Oral: <u>Surrogate: DBE</u>*: EPA reported a very brief summary for an oral repeated dose toxicity study in which rats were exposed to DBE by gavage at 0, 100, 300 or 1,000 for 1 month. The only effect noted was a small decrease in urine pH in male and female rats at 1,000 mg/kg/day. The reported NOAEL was 1,000 mg/kg/day. *As no further details were provided, such as if testing were performed equivalently or similarly to a specific guideline, which parameters were evaluated, if the testing was done according to GLP, etc., ToxServices does not consider this study reliable for the assessment of oral repeated dose toxicity.*
- ECHA 2021
  - *Dermal:* DMG was evaluated in a sub-acute dermal toxicity study (OECD 410, GLP compliant). Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed for 14 days, followed by a 14-day recovery period. The test article was applied undiluted, 6 hours/day, 7 days/week, for two weeks under occlusion (no vehicle) at 0, 100, 300 or 1,000 mg/kg. Application sites were washed following each exposure period. Animals were evaluated for the standard parameters including ophthalmology and behavior. There were no effects on clinical signs, mortality, body weight changes, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, behavior, organ weights, gross pathology, or hematology. Local effects in males and females included minimal to mild erythema, edema, focal eschar, and

desquamation. Authors concluded a NOEL for systemic toxicity at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).

- *Inhalation:* DMG was evaluated in a subchronic inhalation toxicity study (equivalent or similar to OECD 413, GLP compliant). Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed to DMG as aerosol via whole body exposure at concentrations of 0, 10, 50 or 400 mg/m^3, 6 hours/day, 5 days/week for 90 days, followed by a 1-month recovery period. Standard parameters were evaluated, as well as neurobehavioral test battery, estrus cycle, and hormonal analyses in both sexes. No effects were observed based on clinical signs, mortality, ophthalmology, hematology, urinalysis, behavior (functional observations and motor activity), or organ weights. Male rats at 400 mg/m^3 had lower mean body weight gain through day 84, and during recovery, male rats at 50 and 400 mg/m^3 had decreased mean body weights compared to controls. Male rats at 400 mg/m^3 had decreased food consumption from day 49 through the end of the recovery period; females at 400 mg/m^3 had decreased food consumption through day 84. For reproductive and endocrine effects, there were statistically significant decreases in serum testosterone and increased epididymal sperm counts at 50 mg/m^3 and higher. Serum LH concentrations were decreased in a dose-dependent manner with statistical significance at 400 mg/m^3 (71% of controls). Serum FSH was not affected by treatment. There were no corresponding histopathological findings and no changes in reproductive organ weights. Authors noted decreased male sex hormones is generally associated with decreased sperm counts, but the opposite was observed, therefore the effects were considered not toxicologically significant. There were no effects on sperm motility, morphology or testicular spermatid counts. In females, there were no changes in serum estradiol, serum progesterone, or estrus cycling. Authors concluded a systemic toxicity NOEC at 10 mg/m^3 based on decreased serum testosterone concentrations and increased epididymal sperm counts with no toxicological significance. For local effects, olfactory mucosa degeneration / atrophy was observed in both sexes at 400 mg/m^3; authors concluded a NOEC for respiratory local toxicity at 50 mg/m^3 (Klimisch 1, reliable without restriction). *ToxServices inferred a NOAEC at 50 mg/m^3 (0.05 mg/L), and LOAEC at 400 mg/m^3 (0.4 mg/L) based on decreased bodyweight gain and food consumption. The adjusted LOAEC, based on exposure 6 hr/day, 5 days/week, is equivalent to 0.29 mg/L/6h/day and exceeds the GHS Category 2 classification criteria (0.2 mg/L/6h/day for aerosols). The NOAEC of 0.05 mg/L is equivalent to 0.036 mg/L/6h/day that is above the GHS Category 1 classification cutoff of 0.02 mg/L/6h/day.*
- *Inhalation: Surrogate: DBE*: DBE was evaluated in a subchronic inhalation toxicity study (equivalent or similar to OECD 413 GLP compliant). Crl:CD BR rats were exposed to DBE vapor by whole body exposure at 0, 20, 76, or 390 mg/m^3, 6 hr/day, 5 days/week, 10/sex/dose for 7 weeks, 20/sex/dose for 13 weeks, and 10/sex/dose for a 6-week recovery period. There were no effects on mortality, hematology, clinical chemistry, or urinalysis. Serum sodium was slightly decreased in all treated males, and the mid- and high-dose females at the end of the 13-week exposure period. At the end of the recovery period, sodium concentrations were still elevated in high-dose males and females. High dose females had decreased absolute liver and brain weights at 13 weeks, and decreased body weight gain compared to controls, and these effects were no longer significant at the end of the recovery period. Degeneration of the olfactory epithelium was observed in male and female rats at 76 and 390 mg/m^3 at 7 weeks, in all treated females at 13 weeks, and in males at 76 and 390 mg/m^3 at 13 weeks. At the end of the 6-week recovery period, signs of tissue repair included disorganization of the olfactory epithelium, decreased numbers of neuronal cells, and respiratory metaplasia. Authors concluded a systemic toxicity NOAEC at 390 mg/m^3, the highest concentration tested. Authors concluded a LOAEC for local respiratory

toxicity at 20 mg/m^3 based on olfactory epithelium degeneration/atrophy, the lowest concentration tested (Klimisch 1, reliable without restriction). *ToxServices notes no definitively adverse systemic effects were reported.*

- *Inhalation: Surrogate: DBE*: DBE was evaluated in a subchronic inhalation toxicity study (equivalent or similar to OECD 413 GLP compliant). Crl:CD BR rats (10/sex/dose) were exposed to DBE aerosol (MMAD 5.6 µm ±0.3 µm); 72% (±2%) < 10 µm) by whole body exposure at 0, 160, 400 or 1,000 mg/m^3, 6 hr/day, 5 days/week, for 90 days. Animals were evaluated for clinical signs, clinical chemistry, urinalysis, hematology, histopathology and gross pathology. A slight decrease in serum sodium concentration compared to control rats was observed in all male rats and high dose females. There was a statistically significant slight increase in serum calcium in female rats in the 400 mg/m^3 and 1000 mg/m^3 groups at the midpoint and near the end of the study. Decreased absolute liver weights were measured in all treated females and decreased absolute and relative liver weights were measured in high dose males. Minimal to mild squamous cell metaplasia was observed in the olfactory epithelium in all treatment groups, and the incidence was dose-related. A NOAEC for systemic toxicity was not determined (Klimisch 1, reliable without restriction).
- *Inhalation: Surrogate: DBE*: DBE was evaluated in a previously described one-generation reproductive toxicity study (equivalent or similar to OECD 415, EU Method B.34, GLP compliant). Male and female Crl:CD(SD)BR rats (20/sex/dose) were exposed to DBE vapor by whole body exposure at 0, 0.16, or 0.40 mg/L, or aerosol at 1 mg/L, 6 hours/day. Animals were exposed 5 days/week from pre-breeding for 14 weeks, and 7 days/week for 8 weeks through breeding, gestation, and lactation. Females however were not exposed from GD 19 through postpartum day 3. There were no effects on clinical signs. Histopathology for parental rats demonstrated squamous metaplasia primarily in the olfactory epithelium in all groups exposed to DBE. The nasal effect was minimal at 0.16 mg/L, and mild to moderate at 0.40 and 1.0 mg/L. The squamous metaplasia was characterized by a flattening and pavementing of epithelial cells which replaced the normal architecture of the olfactory epithelium. In some cases, particularly in the 0.40 and 1.0 mg/L rats, this squamous change was accompanied by a very minimal to mild suppurative inflammation. The squamous metaplasia was present primarily in the olfactory epithelium of the dorsal meatus, along the dorsal portion of the nasal septum, and on the tips of the ecto- and endoturbinates in the nasal cavity. There was also an increase in squamous metaplasia of the respiratory epithelium in the nasal cavity in high-dose rats. The severity of the lesions ranged from absent to moderate in some rats. One male at 1.0 mg/L had a meningeal sarcoma surrounding the olfactory region of the brain. Because the tumor did not communicate with the nasal cavity and the tumor cell type was unrelated to any nasal epithelial cell types, the tumor was considered to be unrelated to inhalation of DBE. A NOAEC could not be determined based on nasal histopathology at all concentrations (Klimisch 1, reliable without restriction). *ToxServices notes the squamous metaplasia and suppurative inflammation were local effects, and no definitively adverse systemic effects were reported.*

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

DMG was assigned a score of Low for neurotoxicity (single dose) in animals exposed to the target compound DMG in acute oral toxicity studies at doses up to 5,000 mg/kg, in animals exposed to surrogate compound DBE in an acute dermal toxicity study at 2,000 mg/kg, and in animals exposed to surrogate compound DBE as aerosol in an acute inhalation study for 4 hours at up to 11 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low

because the rating is based on clinical observations and none of the studies included a comprehensive neurological battery.

- 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 2021
  - *Oral:* Female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 423, GLP compliant). Rats were exposed to a single gavage (no vehicle) at 5,000 mg/kg, and then observed for 14 days. There were no deaths. Clinical signs included hunched posture and piloerection in two animals, but effects reversed within 4 days. There were no effects on body weight gain and no abnormalities found at necropsy (Klimisch 1, reliable without restriction).
  - *Oral:* Male and female Sprague-Dawley rats were exposed to DMG in an acute oral toxicity study (OECD 401, GLP compliant). Rats were exposed to a single gavage (no vehicle) at 2,000 mg/kg and observed for 14 days. There were no deaths, no observed clinical signs, no effect on body weight gain, and no abnormalities found at necropsy (Klimisch 1, reliable without restriction).
  - *Oral:* Male ChR-CD rats were exposed to DMG in an Oral Class B Poison Test (US Department of Transportation 173.333-173.343, non-GLP). Rats were exposed to a single gavage in water at 50 mg/kg as 1% aqueous solution and observed for 48 hours. There were no deaths or clinical signs (Klimisch 2, reliable with restrictions).
  - *Dermal:* Male albino rabbits were exposed to DMG in a standard acute toxicity test (US Department of Transportation 173.343, similar to OECD 402, non-GLP). Animals were exposed to neat substance under occlusion at 200 mg/kg for 24 hour and were observed for another 24 hours before sacrifice. There were no deaths or clinical signs (Klimisch 2, reliable with restrictions).
  - *Dermal: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute dermal toxicity study (OECD 402, GLP compliant). Rats (5/sex) were exposed under semi-occlusion at 2,000 mg/kg for 24 hours, and then observed for 14 days. There were no deaths, no clinical signs of toxicity, no effects on body weight gain, and no signs of gross pathology at necropsy (Klimisch 1, reliable without restriction).
  - *Inhalation: Surrogate: DBE*: Crj: CD(SD) rats were exposed to DBE in an acute inhalation toxicity study (OECD 403, non-GLP). Rats were exposed to DBE aerosol nose only at 0, 3.5, 5.6, or 11.0 mg/L mg/L for 4 hours, then observed for 14 days. There were no mortalities in the study. Clinical signs included red nasal, ocular, or oral discharges, wet, yellow-stained perineum, and hunched posture, but all signs resolved by day 4. Slight to severe body weight losses in all exposure groups were measured 1 day after exposure, and transient weight loss was measured during the first or second weeks of recovery in both sexes. There were no effects on corneal and pupillary reflexes for the low- and high-dose groups, however mid-dose rats had bilateral mild chemosis (edema/swelling) in the bulbar conjunctiva, and one mid-dose rat had a subepithelial corneal opacity (Klimisch 2, reliable with restrictions).

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

DMG was assigned a score of Low for neurotoxicity (repeated dose) based on lack of adverse effects in a neurobehavioral analysis for functional observations and motor activity in a 90-day inhalation toxicity study in rats exposed to DMG at up to 400 mg/m^3 (0.4 mg/L) 6 hr/day, 5 days/week. The NOAEC is equivalent to 0.29 mg/L/6h/day when adjusted for the treatment frequency, and exceeds the GHS guidance values. Data are insufficient to evaluate the oral and dermal routes of exposure; however,

there is no reason to expect neurotoxicity would be higher for these routes compared to the inhalation route of exposure. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data.

- 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 2021
  - *Dermal:* DMG was evaluated in a sub-acute dermal toxicity study (OECD 410, GLP compliant). Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed for 14 days, followed by a 14-day recovery period. The test article was applied undiluted, 6 hours/day, 7 days/week, for two weeks under occlusion (no vehicle) at 0, 100, 300 or 1,000 mg/kg. Application sites were washed following each exposure period. Animals were evaluated for the standard parameters including ophthalmology and behavior (details not specified). There were no effects on clinical signs, mortality, body weight changes, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, behavior, organ weights, gross pathology, or hematology. Local effects in males and females included minimal to mild erythema, edema, focal eschar, and desquamation. Authors concluded a NOEL for systemic toxicity at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
  - *Inhalation:* DMG was evaluated in a previously described subchronic inhalation toxicity study (equivalent or similar to OECD 413, GLP compliant). Crl:CD (SD)IGS BR rats (10/sex/dose) were exposed to the DMG as aerosol via whole body exposure at concentrations of 0, 10, 50 or 400 mg/m^3, 6 hours/day, 5 days/week for 90 days, followed by a 1-month recovery period. Standard parameters were evaluated, as well as neurobehavioral test battery, estrus cycle, and hormonal analyses in both sexes. The neurobehavioral examinations included forelimb and hindlimb grip strength, hindlimb foot splay, and motor activity. No effects were observed based on clinical signs and behavior, or organ weights (Klimisch 1, reliable without restriction). *ToxServices assigned a NOAEC of 400 mg/m^3 for neurotoxicity, which is equivalent to 0.29 mg/L/6h/day when adjusted for the treatment frequency, and exceeds the GHS Category 2 guidance value of 0.2 mg/L/6h/day for aerosols.*

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

DMG was assigned a score of Low for skin sensitization based on negative results for sensitization in two *in vivo* assays for surrogate DBE. Results from each study exceed the criteria for GHS classification. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for a strong 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.
- ECHA 2021
  - <u>*Surrogate: DBE*</u>: An *in vivo* local lymph node assay (LLNA) (OECD 429, GLP compliant) was performed using Rhodasolv RPDE (DBE) (purity not specified). Female CBA mice were exposed at 0, 5, 10, 25, 50 or 100% v/v in acetone/olive oil solution (4:1 v/v). The stimulation index (SI) was 0.6, 0.6, 1.0, 0.6, and 0.5 for the 5, 10, 25, 50 and 100% groups, respectively. Controls performed as expected. As the SI was <3 at all tested concentrations, authors concluded the test substance was not sensitizing (Klimisch 1, reliable without restriction).

- *Surrogate: DBE*: DBE (purity not specified) was evaluated in a guinea pig maximization test (OECD 406, EU Method B.6, GLP compliant). Male and female Dunkin-Hartley guinea pigs were exposed epicutaneously (once) and intradermally (4 times) and at 10% (v/v) in water, and 100% for induction. The challenge was performed 2 weeks later via epicutaneous application at 10% (v/v) in water, and 100%. There were no mortalities, body weight gain was unaffected by treatment, and there were no observations of skin reactions in any exposed animals at any dose. Authors concluded DBE was not sensitizing under the conditions of the test (Klimisch 2, reliable with restrictions).

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

DMG was assigned a score of Low for respiratory sensitization based on guidance from ECHA with extrapolation from negative skin sensitization data, and lack of structural alerts for respiratory sensitization. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- 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 2020a
  - DMG does not have any structural alerts for respiratory sensitization when modeled in the OECD Toolbox (Appendix G).
- 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 DMG was not sensitizing to the skin based on surrogate data (see skin sensitization section above), a literature search did not find any human evidence of respiratory sensitization by DMG, and DMG does not contain any structural alerts for respiratory sensitization (Appendix G), it is not expected to be a respiratory sensitizer.

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

DMG was assigned a score of Low for skin irritation/corrosivity based on lack of irritation/corrosivity in rabbits exposed to surrogate DBE in a GLP-compliance guideline (OECD 404) study. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). Confidence is high based on high quality data for a strong 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.
- ECHA 2021
  - *Surrogate: DBE*: New Zealand White rabbits were exposed to DBE in a skin irritation study (OECD 404, GLP-compliant). Animals were exposed to 0.5 mL for 4 hours under semi-occlusion, and observations were recorded at 1, 24, 48 and 72 hours after exposure. The means scores for erythema and edema were 0 for all time points. The primary irritation index was 0. No other signs of intoxication were observed (Klimisch 1, reliable without restriction).

- *Surrogate: DBE*: New Zealand White rabbits were exposed to DBE in a skin irritation study (equivalent or similar to OECD 404, GLP-compliant). Animals were exposed to 0.5 mL for 24 hours under occlusion, and observations were recorded at 24, 48 and 72 hours after exposure. At 24 hours, there was moderate erythema in one rabbit; mild erythema in 4 rabbits, no erythema in one rabbit, and no edema for any rabbits. At 48 hours 2 rabbits had moderate erythema and 4 rabbits had no-to-mild erythema; one rabbit had slight edema. At 72 hours, one rabbit had severe erythema with fissuring and slight edema, and there was no-to-mild erythema and no edema in the other 5 rabbits. One rabbit exhibited no dermal irritation throughout the study. All rabbits exhibited red swollen nictitating membranes and a milky-white ocular discharge during the study. The mean 24, 48 and 72 hours erythema scores were 2,3, 2, 0, 1.7, 1 and 3.3 for animal # 1 – 6, respectively. No edema was observed except in one animal with a 24, 48 and 72 hours mean score of 0.67. Authors concluded the test substance meets the criteria for GHS category 2 classification (Klimisch 2, reliable with restrictions as the 24-hour occlusive application is more stringent). *ToxServices notes the current guideline requires semi-occlusion and a 4-hour exposure period (OECD 2002), therefore results from this study, performed under more strenuous exposure conditions, are not suitable for comparison to the GHS classification criteria.*
- *Surrogate: DBE*: Six Albino rabbits were exposed to DBE in a skin irritation study (US Department of Transportation 173.240, non-GLP). Rats were exposed to neat substance at 0.5 mL under semi-occlusive conditions for 4 hours, and observations were recorded at 24 and 48 hours post exposure. No incidences of corrosion were observed. Authors concluded the test substance was not corrosive to the skin under the conditions of the test (Klimisch 2, reliable with restrictions as the study examined only corrosion and not irritation).

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

DMG was assigned a score of Low for eye irritation/corrosivity based on a GLP-compliant, guideline study on surrogate DBE, in which results exceed the criteria for GHS classification. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low as there are some non-guideline studies that demonstrated mild irritation, but because the exposure conditions were not in accordance with recommended guidelines and/or critical details were not reported, the data suggest possible concerns but are not sufficient for GHS classification purposes.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – New Zealand – 6.4A – Irritating to the eye (Cat. 2A)
- ECHA 2021
  - *Surrogate: DBE*: New Zealand White rabbits were exposed to DBE in an acute eye irritation and corrosion study (OECD 405, GLP-compliant). Animals were exposed to 0.1 mL in the eye and observations were recorded at 1 hour after application, and daily thereafter for 3-21 days. At 1 hour, chemosis scores in the three rabbits were 0, 1, and 3, respectively, and effects were fully reversed within 1 day. At 1 hour, conjunctiva scores were 2, 2, and 3, respectively, and effects were fully reversed within 2 days. Scores at 24, 48 and 72 hours were not reported. Study authors concluded DBE to be non-irritating to the eye (Klimisch 1, reliable without restriction).
  - *Surrogate: DBE*: New Zealand White rabbits were exposed to DBE in an acute eye irritation and corrosion study (equivalent or similar to OECD 405, GLP-compliant). Animals were exposed in three trials. Trial 1 consisted of exposure to DBE vapor by whole

body exposure at 60 ppm, or by dermal application at 200 µL (equivalent to 60 mg/kg), or 10 µl DBE in the conjunctival sac of the eye, for 4 hours. Trial 2 consisted of exposure to DBE vapor by whole body exposure at 60 ppm for 4 hours, 200 µl (60 mg/kg) applied to the skin for 6 hours, or application to the conjunctival sac of the eye at 50 µL. Trial 3 was dermal exposure at 200 µL for 6 hours. This study explored possible alterations in intraocular distances, corneal thickness and ophthalmoscopic appearance of the eye that could be attributed to direct contact or systemic absorption of DBE. Compound-related increases in slight or mild conjunctival chemosis and/or redness was observed 1 hour after treatment in rabbits exposed at 15 and 60 ppm. A slight (approximately 10%) but significant increase in anterior chamber depth in the eyes was noted in the 60 ppm group. All rabbits exposed in the conjunctival sac exhibited moderate iritis in the treated eye; and conjunctival chemosis and redness were also seen in some of these rabbits. Due to the low instillation volume used (0.1 mL) and the absence of an observation timepoint at 72 hours, no reliable conclusion can be drawn from this study regarding eye irritation potential (Klimisch 2, reliable with restrictions as the administration volume was low (10 µL) and there was no observation at 72 hours).

- *Surrogate: DBE*: Two Albino rabbits were exposed to DBE in an eye irritation study (equivalent or similar to OECD 405, non-GLP). Animals were exposed to neat substance at 0.1 mL in the eye. One animal had an eye wash 20 seconds after exposure, the other animal did not have the eye washed, and the animals were observed for 7 days. Slight, mild, and moderate effects were reported for the cornea, iris, conjunctiva, and chemosis, however the scoring system was not disclosed. All effects were fully reversed by day 7. Authors concluded the test substance was slightly irritating to the eye under the conditions of the test (Klimisch 2, reliable with restrictions as the test substance purity was not provided, and the scoring system was not provided).

Ecotoxicity (Ecotox)

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

DMG was assigned a score of Moderate for acute aquatic toxicity based on the most sensitive species, fish, having an LC_{50} value >18 and < 24 ppm following 96 hours exposure to the target compound, DMG. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when the most sensitive trophic level has an LC/EC_{50} value in the range of 10-100 mg/L (CPA 2018b). The confidence in the score is high based on high quality data for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – New Zealand – 9.1D (algal) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action.
    - GHS – New Zealand – 9.1D (fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action.
- ECHA 2021
  - 96 hr LC_{50} in *Lepomis macrochirus* (Bluegill) was 30.9 ppm (v/v), or 33.7 mg/L (equivalent or similar to EPA OTS 797.1400, non-GLP). Fish were exposed to DMG at 0.1 mL/mL solution in acetone, under static conditions (Klimisch 2, reliable with restrictions).
  - *Surrogate: DBE*: 96 hr LC_{50} in *Pimephales promelas* (Fathead minnow) was >18 and < 24 ppm (v/v) (equivalent or similar to EPA OTS 797.1400, non-GLP). Fish were exposed to DBE under static conditions (Klimisch 2, reliable with restrictions).

- 48 hr EC_{50} in *D. magna* was > 112 and < 150 ppm (v/v) (equivalent or similar to EPA OTS 797.1300, non-GLP). Daphnia were exposed to DMG under static conditions (Klimisch 2, reliable with restrictions, similar to guideline).
- 24 hr EC_{50} in *D. magna* was 180 mg/L, based on mobility (EU Method C.2, GLP compliant). Daphnia were exposed to DMG in acetone to facilitate dispersion at 0.1 mL/kg, under static conditions (Klimisch 2, reliable with restrictions, guideline study to GLP but only 24 hours exposure).
- <u>*Surrogate: DBE*</u>: 72 hr EC_{50} for DBE in *Pseudokirchneriella subcapitata* was > 85 mg/L (measured concentration at the nominal concentration of 100 mg/L), based on growth rate and yield (OECD 201, EU Method C.3, GLP compliant). Algae were exposed to DBE under static conditions (Klimisch 1, reliable without restriction).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
DMG was assigned a score of Moderate for chronic aquatic toxicity based on a predicted chronic value (ChV) for the most sensitive trophic level, fish, at 8.96 mg/L. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when the most sensitive trophic level has chronic toxicity values in the range of >1 to 10 mg/L (CPA 2018b). The confidence in the score is low as it is based on reliance on modeling in the absence of chronic aquatic toxicity data on the target compound or a strong 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.
- ECHA 2021
  - <u>*Surrogate: DBE*</u>: 72 hr NOEC for DBE in *P. subcapitata* was 36 mg/L, based on growth rate and yield (OECD 201, EU Method C.3, GLP compliant). Algae were exposed to DBE under static conditions (Klimisch 1, reliable without restriction).
- U.S. EPA 2017a
  - DMG is designated to the ECOSAR Esters chemical class. The predicted ChVs are 8.96 mg/L in fish, 208 mg/L in daphnia, and 20.1 mg/L in green algae (Appendix H).

<u>Environmental Fate (Fate)</u>

Persistence (P) Score (vH, H, M, L, or vL): vL
DMG was assigned a score of Very Low for persistence based predicted partitioning primarily to soil and water, data demonstrating >70% degradation in 7 days in a ready biodegradability test, and a predicted half-life of 30 days in soil. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when the dominant compartment is soil or water, and data demonstrate >60% degradation in 28 days, and within the 10-day window, in a ready biodegradation test (CPA 2018b). The confidence in the score is high based on high quality data.

- 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 2021
  - DMG was evaluated in a ready biodegradability, closed-bottle test (equivalent or similar to OECD 301D, non-GLP). The test substance was exposed in city water, and biodegradation was measured as loss of dissolved oxygen. DMG reached 70% degradation within 7 days based on oxygen consumption. Authors concluded the test substance is readily

biodegradable under the conditions of the test (Klimisch 2, reliable with restrictions based on method similar to guideline, and purity of the test substance was not disclosed).

- U.S. EPA 2017b
    - BIOWIN of EPI Suite™ predicts DMG to be readily biodegradable. Level III fugacity model using the default MCI method predicts 59.6% to partition to soil with a half-life of 30 days, 36.8% to water with a half-life of 15 days, 3.52% to air with a half-life of 3.2 days, and 0.0828% to sediment with a half-life of 135 days (Appendix I).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
DMG was assigned a score of Very Low for bioaccumulation based on its highest estimated BCF of 3.162 L/kg wet-wt, and its highest measured log K_{ow} of 0.62. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF is ≤100, and log K_{ow} is ≤4 (CPA 2018b). The confidence in the score is high based on measured data.

- 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
    - EPI Suite™'s BCFBAF (v3.01)'s Meylen et al. (1997/1999) regression model estimates a BCF of 3.162 L/kg wet-wt based on an experimental log K_{ow} of 0.62. Using the Arnot-Gobas method including biotransformation, the BCF for the upper trophic level was estimated to be 0.9515. DMG is within the applicability domain of both models in BCFBAF (Appendix I).
- ECHA 2021
    - DMG has an experimentally derived log K_{ow} of 0.49.
- U.S. EPA 2017a
    - DMG has an experimentally derived log K_{ow} of 0.62.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
DMG was assigned a score of Low for reactivity based on lack of reactive functional groups associated with oxidation, explosivity, or self-reactivity. Additionally, the surrogate DBE has NFPA and HMIS reactivity scores of 0, indicating low reactivity concerns. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low based on lack of experimental data on explosivity.

- 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 2021
    - The self-ignition temperature was 440°C; DMG is soluble in water, does not have functional groups likely to ignite on contact with water or emit flammable gas in contact with water, and does not have pyrophoric properties based on testing. *These data exceed the criteria for GHS classification (UN 2019)*.
- UN 2019
    - Based on the structure of its components or moieties, DMG is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (Appendix J).

  - Based on the structure of its components or moieties, DMG is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.
- ITW TRANS TECH 2006
  - *Surrogate: DBE*: DBE has a NFPA reactivity score of 0 (i.e., "materials that are stable even under exposure to fire" (Colorado State University Undated)) and HMIS physical rating of 0 (i.e., chemicals that are "normally stable even under fire exposure conditions and that are not reactive with water" (NIEHS Undated).

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

DMG was assigned a score of Low for flammability based on a measured flash point of 109°C. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score was high based on measured data.

- 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 2021
  - The flash point was 109°C in a closed-cup test; the self-ignition temperature was 440°C; DMG is soluble in water, does not have functional groups likely to ignite on contact with water or emit flammable gas in contact with water, and does not have pyrophoric properties based on testing. *A flash point of >93° C exceeds the criteria for GHS classification (UN 2019).*

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 *in silico* modeling for carcinogenicity, use of *in vitro* data for genotoxicity, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation. 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 2020b, OECD 2020b). 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 2020b):

- 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 DMG's NAMs dataset include lack of experimental data for carcinogenicity and respiratory sensitization, lack of validated test methods for respiratory sensitization, and lack of chronic aquatic toxicity for two trophic levels. DMG's Type II (extrapolation output) uncertainties include lack of defined applicability domains for some models, limited reliability in some carcinogenicity predictions, conflicting predictions by different carcinogenicity models, limited relevance of *in vitro* data to mimic complex *in vivo* conditions with the assessment of genotoxicity, and structural alerts for respiratory sensitization do not capture non-immunologic mechanisms. Some of DMG'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 2020b)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Respiratory sensitization**: No experimental data are available and no validated test methods are available. **Chronic aquatic toxicity:** Experimental data are not available for fish and aquatic invertebrate trophic levels.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). The only statistical based model in VEGA platform has an inadequate AD index (i.e., < 0.7), limiting the reliability of the prediction (VEA 2021). The liver-specific cancer in rat or mouse model in Danish QSAR database produced conflicting results from Case Ultra and Leadscope, with are both in domain results. **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 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]. **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.

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/ /Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	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
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Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301D aerobic biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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Virtual Models for Evaluating the Properties of Chemicals within a Global Architecture (VEGA). 2021. Predictive Model Platform version 1.1.5-b58. Available: http://www.vega-qsar.eu/index.php.

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 DMG (CAS #1119-40-0)

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	DMG	1119-40-0	*L*	*L*	*L*	*L*	*M*	L	M	L	*L*	L	L	*L*	L	*L*	M	*M*	vL	vL	*L*	L

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	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
DMG	2

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

Table 6

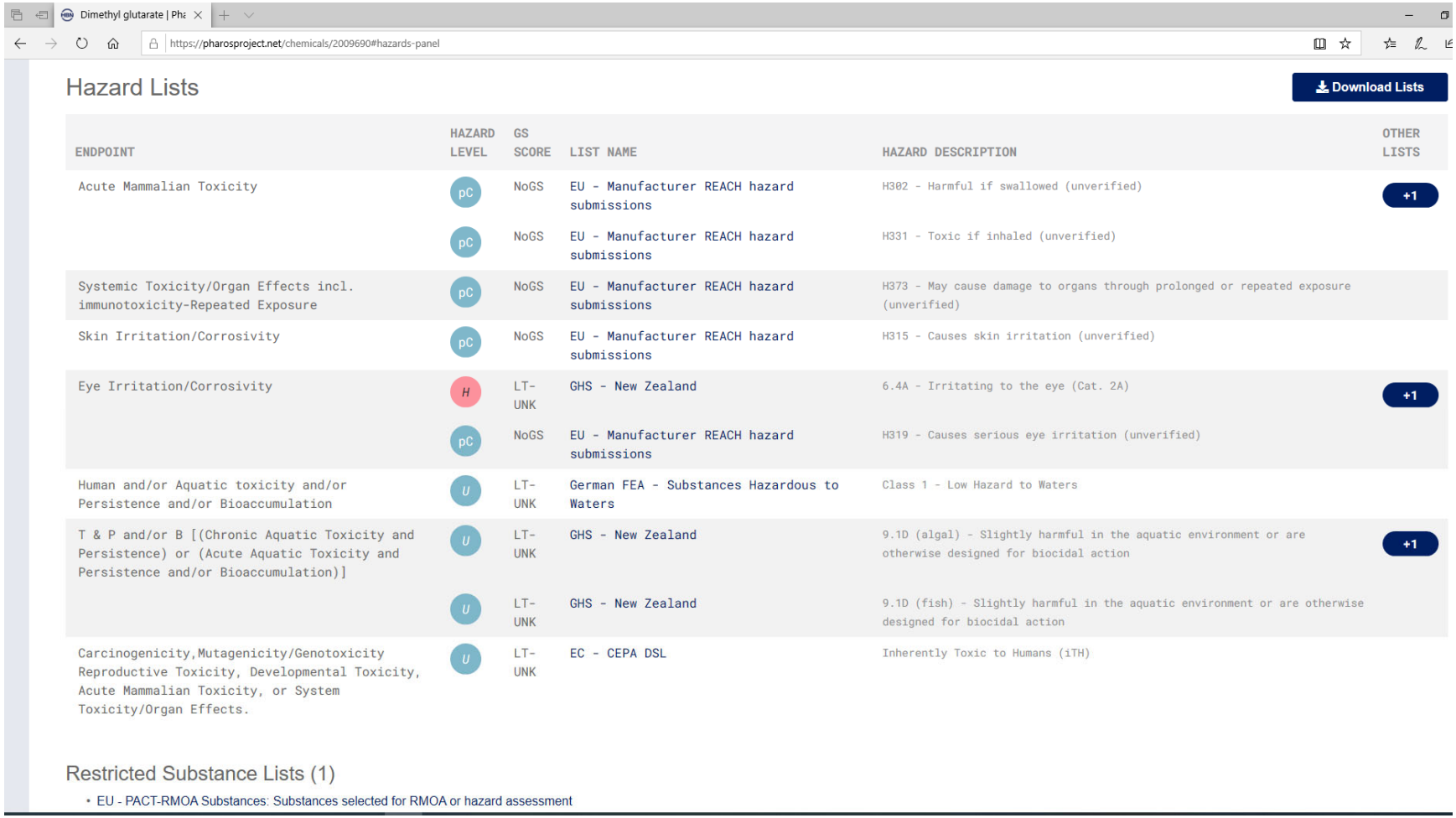
Chemical Name	Final GreenScreen® Benchmark Score
DMG	2

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: Pharos Output for DMG (CAS #1119-40-0)



Dimethyl glutarate | Pha

https://pharosproject.net/chemicals/2009690#hazards-panel

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H302 - Harmful if swallowed (unverified)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H331 - Toxic if inhaled (unverified)	
Systemic Toxicity/Organ Effects incl. immunotoxicity-Repeated Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H373 - May cause damage to organs through prolonged or repeated exposure (unverified)	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
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	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - New Zealand	9.1D (algal) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	+1
	U	LT-UNK	GHS - New Zealand	9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (iTH)	

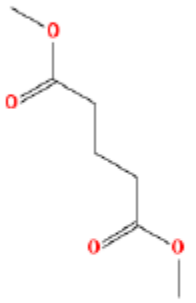
Restricted Substance Lists (1)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment

APPENDIX D: VEGA Carcinogenicity Modeling Results for DMG (CAS #1119-40-0)

1. Prediction Summary

Prediction for compound Molecule 0

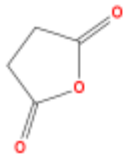


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- 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
- some similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(OC)CCCC(=O)OC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.193
P(NON-Carcinogen): 0.807
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

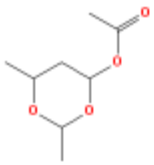
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-30-5
Dataset id: 710 (Training set)
SMILES: O=C1OC(=O)CC1
Similarity: 0.797

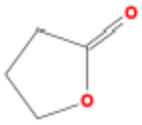
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 828-00-2
Dataset id: 254 (Test set)
SMILES: O=C(OC1OC(OC(C)C1)C)C
Similarity: 0.786

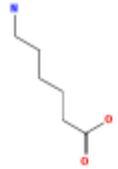
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 96-48-0
Dataset id: 120 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.779

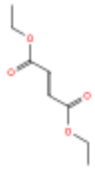
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 60-32-2
Dataset id: 47 (Training set)
SMILES: O=C(O)CCCCCN
Similarity: 0.774

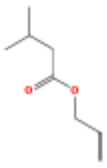
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 141-05-9
Dataset id: 242 (Training set)
SMILES: O=C(OCC)C=CC(=O)OCC
Similarity: 0.771

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 2835-39-4
Dataset id: 33 (Test set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.767

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.632 Explanation: the predicted compound could be out of the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.791 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.505 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
⚠	**Concordance for similar molecules** Concordance index = 0.505 Explanation: some 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 = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.
✓	**Model class assignment reliability** Pos/Non-Pos difference = 0.614 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:

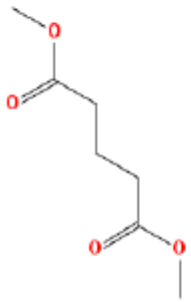
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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.

1. Prediction Summary

Prediction for compound Molecule 0

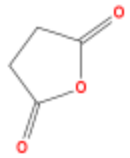


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- only moderately similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value

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

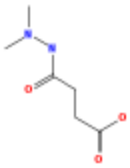
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-30-5
Dataset id: 702 (Training set)
SMILES: O=C1OC(=O)CC1
Similarity: 0.797

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

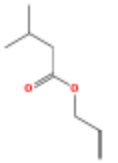


Compound #2

CAS: 1596-84-5
Dataset id: 225 (Training set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.769

Experimental value: Carcinogen
Predicted value: Carcinogen

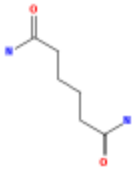
Alerts (not found in the target): SA13 Hydrazine



Compound #3

CAS: 2835-39-4
Dataset id: 35 (Training set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.767

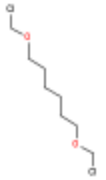
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 628-94-4
Dataset id: 782 (Training set)
SMILES: O=C(N)CCCCC(=O)N
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

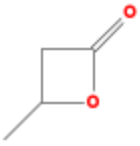


Compound #5

CAS: 56894-92-9
Dataset id: 804 (Training set)
SMILES: O(CCCCCCOCCl)CCl
Similarity: 0.761

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA8 Aliphatic halogens



Compound #6

CAS: 3068-88-0
Dataset id: 15 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA6 Propiolactones and propiosultones

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.748 Explanation: the predicted compound could be out of the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.782 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✓	**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 = 0.512 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

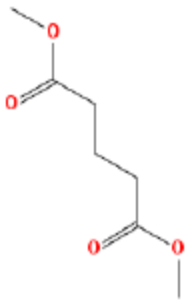
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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.

1. Prediction Summary

Prediction for compound Molecule 0

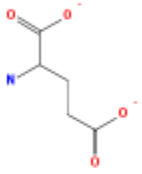


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

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

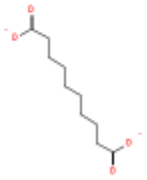
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 1115 (Training set)
SMILES: O=C([O-])CCC(N)C(=O)[O-]
Similarity: 0.836

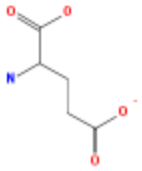
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 1213 (Training set)
SMILES: O=C([O-])CCCCCCCCC(=O)[O-]
Similarity: 0.83

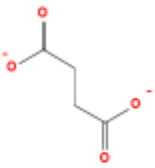
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: N.A.
Dataset id: 1155 (Training set)
SMILES: O=C([O-])CCC(N)C(=O)O
Similarity: 0.824

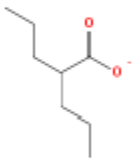
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: N.A.
Dataset id: 1079 (Training set)
SMILES: O=C([O-])CCC(=O)[O-]
Similarity: 0.811

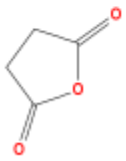
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: N.A.
Dataset id: 1216 (Training set)
SMILES: O=C([O-])C(CCC)CCC
Similarity: 0.802

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: N.A.
Dataset id: 714 (Training set)
SMILES: O=C1OC(=O)CC1
Similarity: 0.797

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.911
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.83
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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.

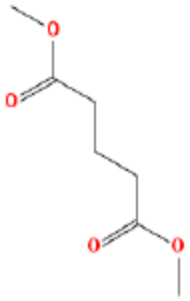
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

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.

1. Prediction Summary

Prediction for compound Molecule 0

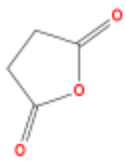


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal:
- only moderately similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value

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

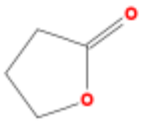
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-30-5
Dataset id: 698 (Training set)
SMILES: O=C1OC(=O)CC1
Similarity: 0.797

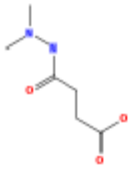
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: 96-48-0
Dataset id: 931 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.779

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

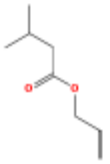


Compound #3

CAS: 1596-84-5
Dataset id: 183 (Training set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.769

Experimental value: Carcinogen
Predicted value: Carcinogen

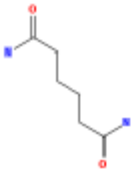
Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28



Compound #4

CAS: 2835-39-4
Dataset id: 28 (Training set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.767

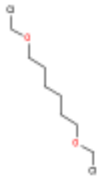
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 628-94-4
Dataset id: 602 (Training set)
SMILES: O=C(N)CCCCC(=O)N
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: 56894-92-9
Dataset id: 736 (Training set)
SMILES: O(CCCCCCOCCl)CCl
Similarity: 0.761

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	**Global AD Index** AD index = 0.801 Explanation: the predicted compound is into the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.781 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✓	**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 = 0.674 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

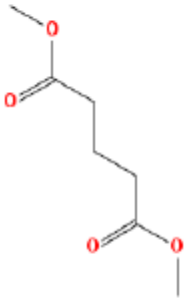
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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.

1. Prediction Summary

Prediction for compound Molecule 0

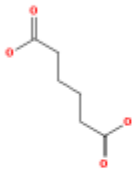


Prediction: Reliability:

Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

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

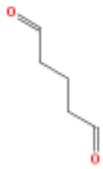
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 124-04-9
Dataset id: 541 (Training set)
SMILES: O=C(O)CCCCC(=O)O
Similarity: 0.844

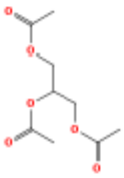
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-30-8
Dataset id: 529 (Training set)
SMILES: O=CCCCC=O
Similarity: 0.773

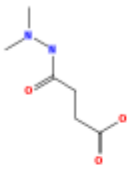
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 102-76-1
Dataset id: 706 (Test set)
SMILES: O=C(OCC(OC(=O)C)COC(=O)C)C
Similarity: 0.771

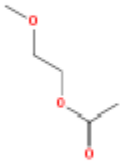
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 1596-84-5
Dataset id: 88 (Training set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.769

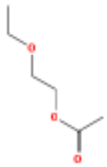
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 576 (Training set)
SMILES: O=C(OCCOC)C
Similarity: 0.765

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 111-15-9
Dataset id: 499 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.897
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.804
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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.

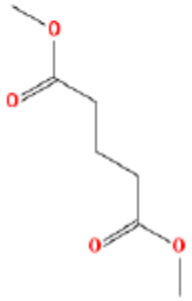
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

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.

1. Prediction Summary

Prediction for compound Molecule 0

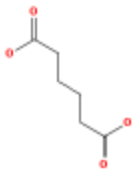


Prediction: Reliability:

Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

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

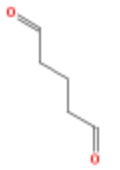
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 124-04-9
Dataset id: 517 (Training set)
SMILES: O=C(O)CCCCC(=O)O
Similarity: 0.844

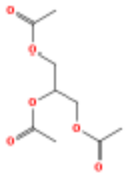
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-30-8
Dataset id: 504 (Training set)
SMILES: O=CCCCC=O
Similarity: 0.773

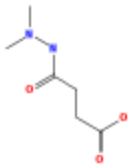
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 102-76-1
Dataset id: 701 (Training set)
SMILES: O=C(OCC(OC(=O)C)COC(=O)C)C
Similarity: 0.771

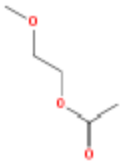
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 1596-84-5
Dataset id: 74 (Training set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.769

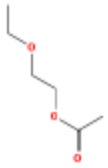
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 555 (Test set)
SMILES: O=C(OCCOC)C
Similarity: 0.765

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 111-15-9
Dataset id: 471 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.897
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.804
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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 = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

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.

APPENDIX E: Danish QSAR Carcinogenicity Modeling Results for DMG (CAS #1119-40-0)

Carcinogenicity

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

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

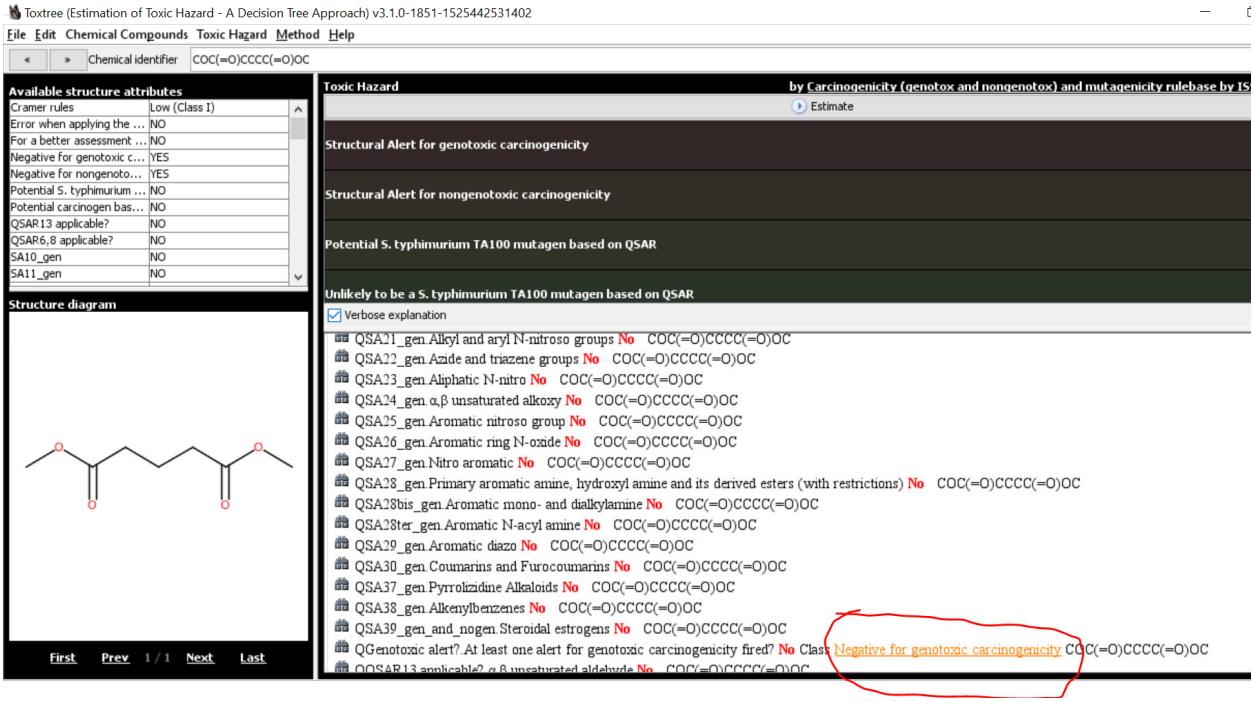
OECD QSAR Toolbox v.4.2 profilers

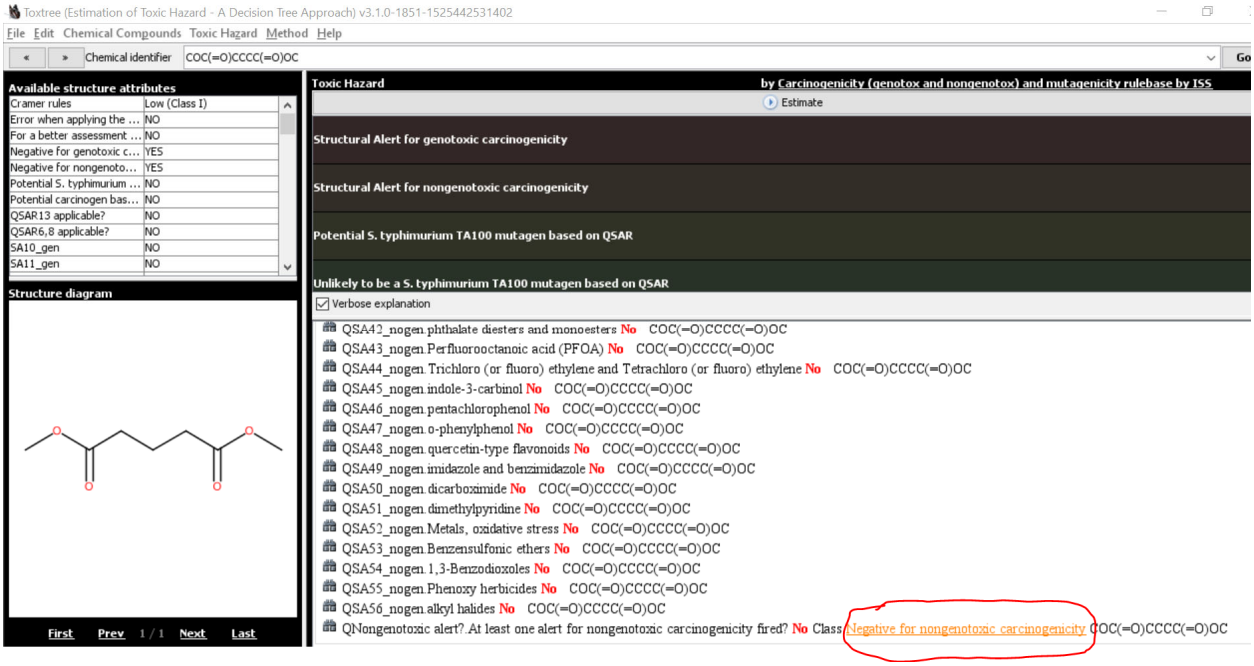
Profiler predictions are supporting information to be used together with the relevant QSAR predictions

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		INC_OUT	POS_IN	NEG_IN	NEG_OUT

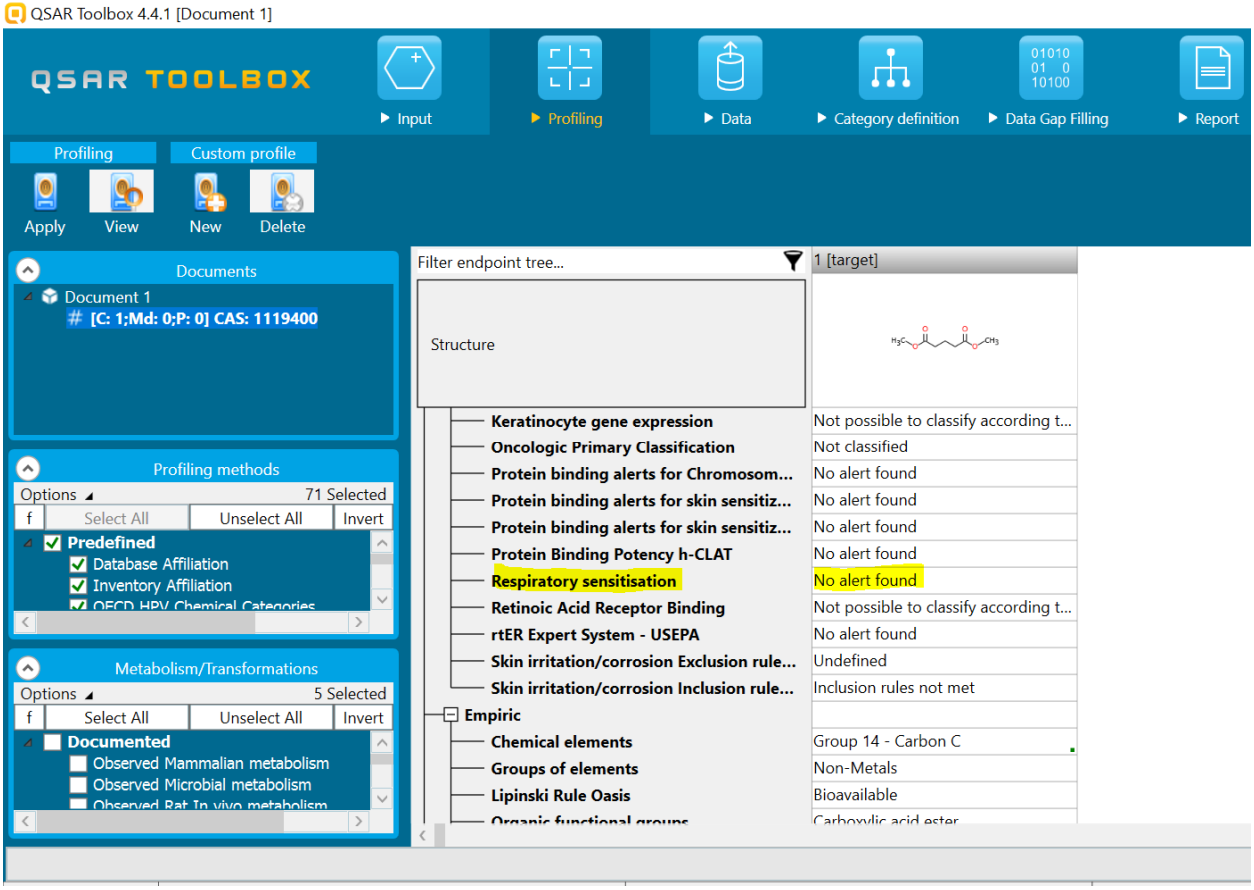
DTU-developed models

APPENDIX F: Toxtree Structural Alerts for Carcinogenicity of DMG (CAS #1119-40-0)

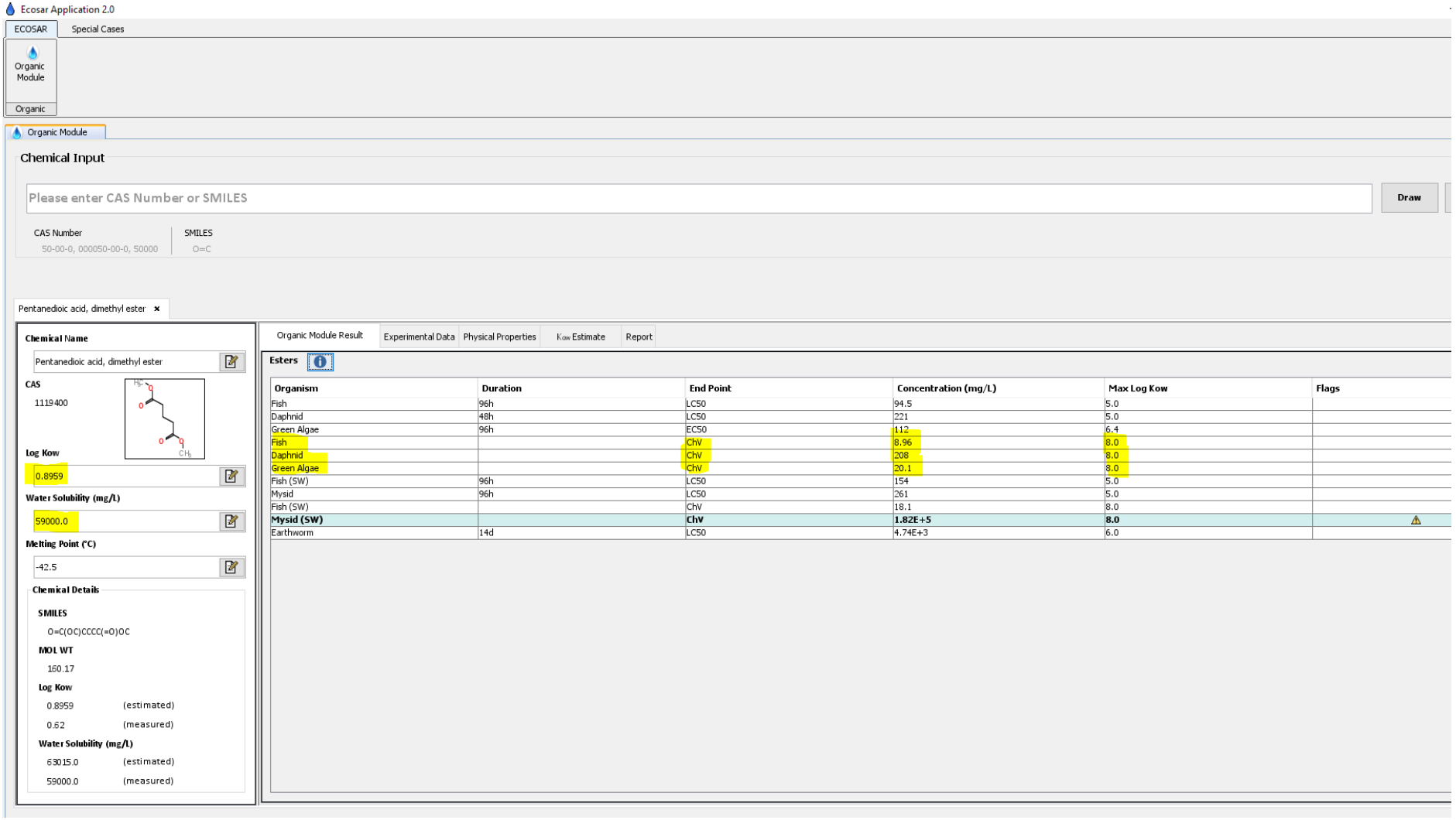




APPENDIX G: OECD Toolbox Respiratory Sensitization Results for DMG (CAS #1119-40-0)



APPENDIX H: ECOSAR Modeling Results for DMG (CAS #1119-40-0)

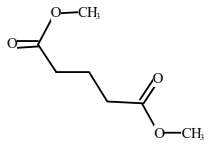


Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	94.5	5.0	
Daphnid	48h	LC50	221	5.0	
Green Algae	96h	EC50	112	6.4	
Fish		ChV	8.96	8.0	
Daphnid		ChV	208	8.0	
Green Algae		ChV	20.1	8.0	
Fish (SW)	96h	LC50	154	5.0	
Mysid	96h	LC50	261	5.0	
Fish (SW)		ChV	18.1	8.0	
Mysid (SW)		**ChV**	**1.82E+5**	**8.0**	⚠
Earthworm	14d	LC50	4.74E+3	6.0	

APPENDIX I: EPI Suite™ Modeling Results for DMG (CAS #1119-40-0)

(Estimated values included in the GreenScreen® are highlighted and bolded)

EPI Suite Results For CAS 1119-40-0



```
SMILES : O=C(OC)CCCC(=O)OC
CHEM   : Pentanedioic acid, dimethyl ester
MOL FOR: C7 H12 O4
MOL WT : 160.17
----------------------------- EPI SUMMARY (v4.11) -------------------------
Physical Property Inputs:
Log Kow (octanol-water):    0.49
Boiling Point (deg C)  :    216.00
Melting Point (deg C)  :    -38.00
Vapor Pressure (mm Hg) :    0.1
Water Solubility (mg/L):    63.1
Henry LC (atm-m3/mole) :    ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  0.90
Log Kow (Exper. database match) =  0.62
Exper. Ref:  HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  166.02  (Adapted Stein & Brown method)
Melting Pt (deg C):  -83.29  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  0.161  (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) :  21.4  (Mean VP of Antoine & Grain methods)
MP  (exp database):  -42.5 deg C
BP  (exp database):  214 deg C
VP  (exp database):  1.80E-01 mm Hg (2.40E+001 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  8.399e+004
log Kow used: 0.49 (user entered)
melt pt used: -38.00 deg C
Water Sol (Exper. database match) =  5.9e+004 mg/L (25 deg C)
Exper. Ref:  CHEM EVAL RES INST JAPAN (2002)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  22475 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
```

```
Bond Method :   7.36E-007  atm-m3/mole  (7.45E-002 Pa-m3/mole)
Group Method:   9.09E-008  atm-m3/mole  (9.21E-003 Pa-m3/mole)
Exper Database: 6.43E-07  atm-m3/mole  (6.52E-002 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  3.340E-004 atm-m3/mole  (3.384E+001 Pa-m3/mole)
VP:   0.1 mm Hg (source: User-Entered)
WS:   63.1 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  0.49  (user entered)
Log Kaw used:  -4.580  (exp database)
Log Koa (KOAWIN v1.10 estimate):  5.070
Log Koa (experimental database):  None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :   1.0197
Biowin2 (Non-Linear Model)     :   0.9999
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   3.1256  (weeks       )
Biowin4 (Primary Survey Model) :   4.0746  (days        )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :   0.9221
Biowin6 (MITI Non-Linear Model):   0.9620
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model):  1.0986
Ready Biodegradability Prediction:   YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled):  13.3 Pa (0.1 mm Hg)
Log Koa (Koawin est  ): 5.070
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  2.25E-007
Octanol/air (Koa) model:  2.88E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  8.13E-006
Mackay model           :  1.8E-005
Octanol/air (Koa) model:  2.31E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant =   2.5605 E-12 cm3/molecule-sec
Half-Life =     4.177 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =    50.127 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1.31E-005 (Junge-Pankow, Mackay avg)
2.31E-006 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc    :  10  L/kg (MCI method)
```

```
Log Koc:  1.000       (MCI method)
Koc    :  11.61  L/kg (Kow method)
Log Koc:  1.065       (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C :  1.327E-001  L/mol-sec
Kb Half-Life at pH 8:      60.458  days
Kb Half-Life at pH 7:       1.655  years
(Total Kb applies only to esters, carbmates, alkyl halides)
```

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) = -2.7555 days (HL = 0.001756 days)
```

Log BCF Arnot-Gobas method (upper trophic) = -0.022 (BCF = 0.9515)

```
Log BAF Arnot-Gobas method (upper trophic) = -0.022 (BAF = 0.9515)
log Kow used: 0.49 (user entered)

Volatilization from Water:
Henry LC:  6.43E-007 atm-m3/mole  (Henry experimental database)
Half-Life from Model River:       1154  hours   (48.07 days)
Half-Life from Model Lake : 1.269E+004  hours   (528.8 days)

Removal In Wastewater Treatment:
Total removal:               1.89  percent
Total biodegradation:        0.09  percent
Total sludge adsorption:     1.77  percent
Total to Air:                0.04  percent
(using 10000 hr Bio P,A,S)
```

Level III Fugacity Model: (MCI Method)

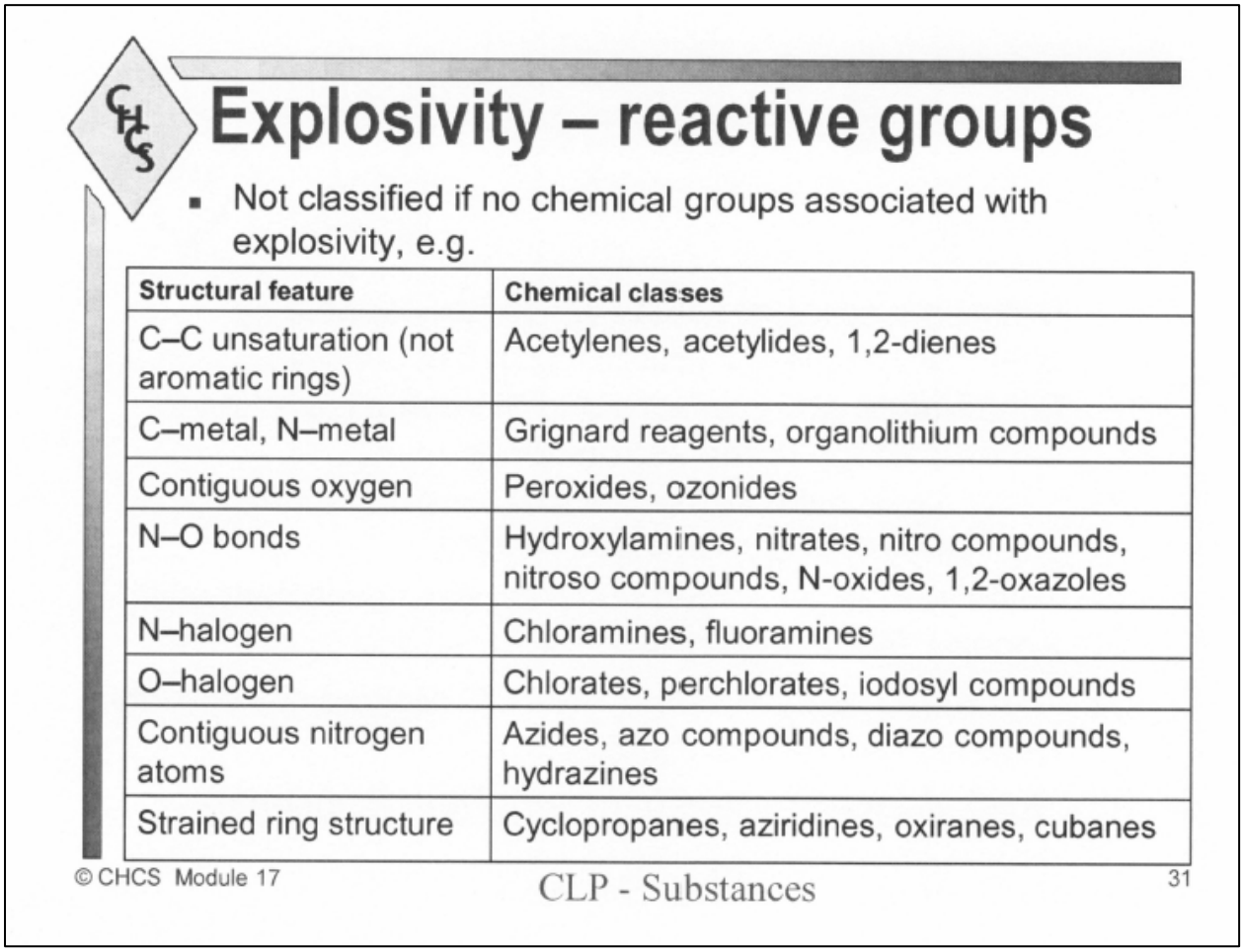
Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	**3.52**	**77.8**	**1000**
Water	**36.8**	**360**	**1000**
Soil	**59.6**	**720**	**1000**
Sediment	**0.0828**	**3.24e+003**	**0**

```
Persistence Time: 432 hr

Level III Fugacity Model: (MCI Method with Water percents)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       3.52            77.8         1000
Water     36.8            360          1000
water     (36.8)
biota     (5.68e-006)
suspended sediment (0.000552)
Soil      59.6            720          1000
Sediment  0.0828          3.24e+003    0
Persistence Time: 432 hr

Level III Fugacity Model: (EQC Default)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       3.9             77.8         1000
Water     43.3            360          1000
water     (43.3)
biota     (6.69e-006)
```

```
suspended sediment (8.23e-005)
Soil      52.7            720          1000
Sediment  0.0816          3.24e+003    0
Persistence Time: 398 hr
```

APPENDIX J: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

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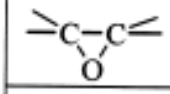
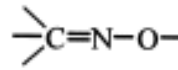
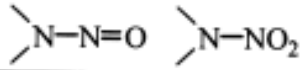
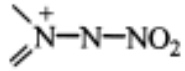
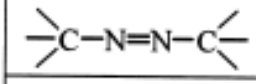
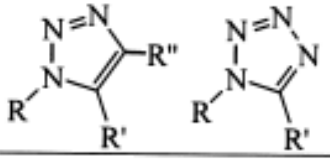
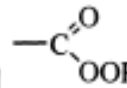
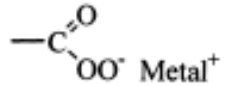
Explosivity – Full List

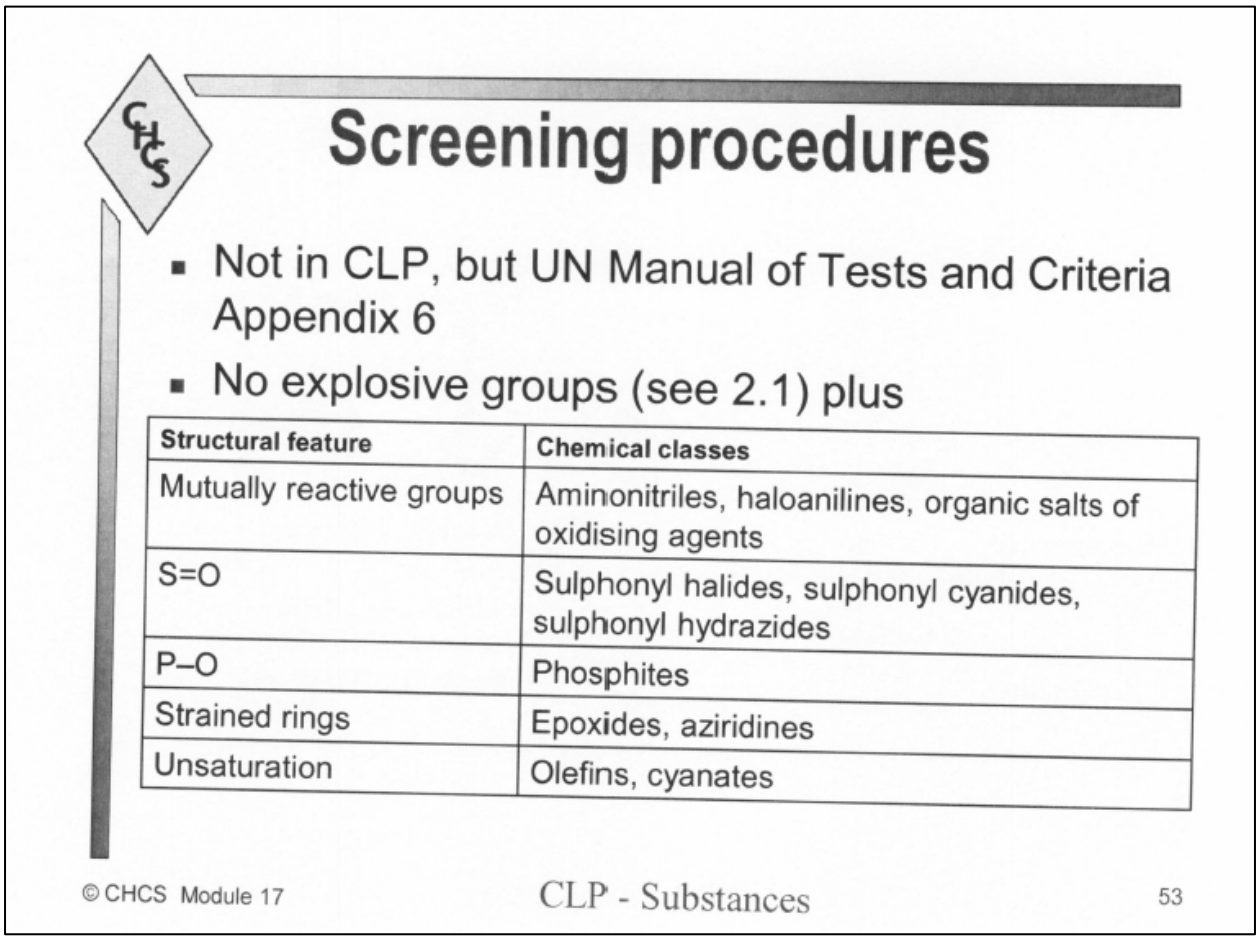
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



Licensed GreenScreen® Profilers

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