CYCLOPENTYL METHYL ETHER

(CAS #5614-37-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

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TABLE OF CONTENTS

GreenScreen® Executive Summary for Cyclopentyl Methyl Ether (CAS #5614-37-9) i
Chemical Name 1
GreenScreen® Summary Rating for Cyclopentyl Methyl Ether 2
Environmental Transformation Products 2
Introduction 2
U.S. EPA Safer Choice Program's Safer Chemical Ingredients List 3
GreenScreen® List Translator Screening Results 3
Hazard Statement and Occupational Control 3
Physicochemical Properties of Cyclopentyl Methyl Ether 4
Toxicokinetics 4
Hazard Classification Summary 5
- Group I Human Health Effects (Group I Human) 5
  - Carcinogenicity (C) Score 5
  - Mutagenicity/Genotoxicity (M) Score 6
  - Reproductive Toxicity (R) Score 8
  - Developmental Toxicity incl. Developmental Neurotoxicity (D) Score 9
  - Endocrine Activity (E) Score 12
- Group II and II* Human Health Effects (Group II and II* Human) 13
  - Acute Mammalian Toxicity (AT) (Group II) Score 13
  - Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score 13
  - Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score 14
  - Neurotoxicity (single dose, N-single) (Group II) Score 17
  - Neurotoxicity (repeated dose, N-repeated) (Group II*) Score 18
  - Skin Sensitization (SnS) (Group II*) Score 18
  - Respiratory Sensitization (SnR) (Group II*) Score 19
  - Skin Irritation/Corrosivity (IrS) (Group II) Score 19
  - Eye Irritation/Corrosivity (IrE) (Group II) Score 20
- Ecotoxicity (Ecotox) 20
  - Acute Aquatic Toxicity (AA) Score 20
  - Chronic Aquatic Toxicity (CA) Score 21
- Environmental Fate (Fate) 21
  - Persistence (P) Score 21
  - Bioaccumulation (B) Score 22
- Physical Hazards (Physical) 22
  - Reactivity (Rx) Score 22
  - Flammability (F) Score 23

Use of New Approach Methodologies (NAMs) in the Assessment, Including Uncertainty Analyses of Input and Output 24
References 26
APPENDIX A: Hazard Classification Acronyms 29
APPENDIX B: Results of Automated GreenScreen® Score Calculation for Cyclopentyl Methyl Ether (CAS #5614-37-9) 30
APPENDIX C: Pharos Output for Cyclopentyl Methyl Ether (CAS #5614-37-9) 31
APPENDIX D: VEGA Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9) 32
APPENDIX E: Toxtree Carcinogencity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9) 50
APPENDIX F: Danish QSAR Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9) 51
APPENDIX G: OncoLogic Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9) 52
APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Cyclopentyl Methyl Ether (CAS #5614-37-9) 53
APPENDIX I: EPI Suite™ Modeling Results for Cyclopentyl methyl ether (CAS #5614-37-9) 54
APPENDIX J: Change in Benchmark Score 58
Licensed GreenScreen® Profilers 59

TABLE OF FIGURES

Figure 1: GreenScreen® Hazard Summary Table for Cyclopentyl Methyl Ether 2

TABLE OF TABLES

Table 1: GHS H Statements for Cyclopentyl methyl ether (CAS #5614-37-9) (ECHA 2023) 3
Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Cyclopentyl methyl ether (CAS #5614-37-9) 4
Table 3: Physical and Chemical Properties of Cyclopentyl methyl ether (CAS #5614-37-9) 4
Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses 24
Table 5: Change in GreenScreen® Benchmark™ for Cyclopentyl Methyl Ether 58

GreenScreen® Executive Summary for Cyclopentyl Methyl Ether (CAS #5614-37-9)

Cyclopentyl methyl ether is water-soluble, liquid, dialkyl ether solvent that is flammable and volatile. Commercially available cyclopentyl methyl ether is often stabilized with butylated hydroxytoluene (BHT), according to published safety data sheets. Cyclopentyl methyl ether has been advertised as a safer alternative to ether solvents such as tetrahydrofuran (THF), diethyl ether, tert-butyl methyl ether (MTBE), and other solvents such as methylene chloride and 1,4-dioxane. Compared to other solvents, cyclopentyl methyl ether has lower peroxide formation, higher hydrophobicity, higher stability under acidic and basic conditions, higher boiling point, lower melting point, lower heat of vaporization, narrower explosion area, and lower solubility of salts. Cyclopentyl methyl ether is also used as a chemical intermediate in organic synthesis.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive toxicity-R and developmental toxicity-D)
- Benchmark 2g
  - High flammability-F

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), cyclopentyl methyl ether meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if cyclopentyl methyl ether were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, respiratory sensitization, persistence, and bioaccumulation, and *in vitro* testing for mutagenicity. 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 cyclopentyl methyl ether's NAMs dataset include lack of or limited experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of validated test methods for respiratory sensitization. Cyclopentyl methyl ether's Type II (extrapolation output) uncertainties include the lack of defined applicability domains in some modeling programs, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, and the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without accounting for non-immunologic mechanisms of respiratory sensitization.

GreenScreen® Hazard Summary Table for Cyclopentyl Methyl Ether

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**	*M*	*M*	DG	**M**	**L**	*L*	*M*	*L*	**L**	*L*	**H**	**H**	**M**	**M**	*M*	**vL**	*L*	**H**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Cyclopentyl methyl ether (CAS #5614-37-9)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Rachel Doerer, M.P.H.
Title: Toxicologist
Organization: ToxServices LLC
Date: January 3, 2023, February 23, 2023

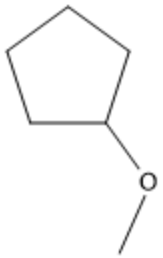
Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: January 25, 2023, March 23, 2023

Expiration Date: March 23, 2028[2]

Chemical Name: Cyclopentyl methyl ether

CAS Number: 5614-37-9

Chemical Structure(s):



Also called:
Methoxycyclopentane; Cyclopentane, methoxy-; CYCLOPENTYL METHYL ETHER; Cyclpentylmethylether; Methyl cyclopentyl ether (PubChem 2023).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A relatively complete dataset was identified for cyclopentyl methyl ether; therefore, a surrogate was not used in this assessment.

Identify Applications/Functional Uses: (Watanabe et al. 2007, Watanabe 2013)
1. Solvent
2. Chemical intermediate

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

[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).
[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive toxicity-R and developmental toxicity-D)
- Benchmark 2g
  - High flammability-F

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), cyclopentyl methyl ether meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if cyclopentyl methyl ether were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Cyclopentyl Methyl Ether

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**	*M*	*M*	DG	**M**	**L**	*L*	*M*	*L*	**L**	*L*	**H**	**H**	**M**	**M**	*M*	**vL**	*L*	**H**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Cyclopentyl methyl ether is expected to partition to soil where it will undergo very limited biodegradation (2%) (see persistence section below). Cyclopentyl methyl ether has no hydrolysable functional groups and has a hydrolysis half-life of >1 year at pH 4, 7, and 9 in a hydrolysis assay (EU Method C.7, OECD Guideline 111) (ECHA 2023). Accordingly, there are no anticipated transformation products of concern.

Introduction

Cyclopentyl methyl ether water-soluble, liquid, dialkyl ether solvent that is flammable and volatile. Commercially available cyclopentyl methyl ether is often stabilized with butylated hydroxytoluene (BHT), according to published safety data sheets. Cyclopentyl methyl ether is also used as a chemical intermediate in organic synthesis (Watanabe 2013).

[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 cyclopentyl methyl ether 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 2023). 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).

Cyclopentyl methyl ether is not on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for cyclopentyl methyl ether can be found in Appendix C.

- Cyclopentyl methyl ether is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Cyclopentyl methyl ether is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group II.
- Cyclopentyl methyl ether is not on any lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for cyclopentyl methyl ether. Hazard statements reported in the ECHA REACH dossier for cyclopentyl methyl ether are reported in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for Cyclopentyl methyl ether (CAS #5614-37-9) (ECHA 2023)

H Statement	H Statement Details
H225	Highly flammable liquid and vapor
H302	Harmful if swallowed
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 Cyclopentyl methyl ether (CAS #5614-37-9)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Vapor respirator; protective gloves; safety glasses; face-shield; protective clothing; protective boots	TCI America 2018	None identified	

Physicochemical Properties of Cyclopentyl Methyl Ether

Cyclopentyl methyl ether is a clear, colorless liquid at standard temperature and pressure. Based on its vapor pressure of 4,270 Pa (32.03 mmHg) and boiling point of 107°C it is a volatile organic compound. Its water solubility of 12.5 g/L indicates it is very soluble in water, and its log K_{ow} of 1.6 suggests it is not likely to be bioaccumulative.

Table 3: Physical and Chemical Properties of Cyclopentyl methyl ether (CAS #5614-37-9)		
Property	**Value**	**Reference**
Molecular formula	$C_6H_{12}O$	PubChem 2023
SMILES Notation	COC1CCCC1	PubChem 2023
Molecular weight	100.16	PubChem 2023
Physical state	Liquid	ECHA 2023
Appearance	Clear, colorless	ECHA 2023
Melting point	-25°C	ECHA 2023
Boiling point	107°C	ECHA 2023
Vapor pressure	4,270 Pa (32.03 mmHg) at 25°C	ECHA 2023
Water solubility	12.5 g/L at 20°C	ECHA 2023
Dissociation constant	N/A	ECHA 2023
Density/specific gravity	0.86 g/cm^3 at 20°C	ECHA 2023
Partition coefficient	Log K_{ow} = 1.6 at 20°C	ECHA 2023

Toxicokinetics

A GLP-compliant OECD Guideline 417 toxicokinetics study was performed in male and female Sprague-Dawley rats, in which animals (number per sex not reported) were given a single oral administration of cyclopentyl methyl ether (99.98% purity) at doses of 20 and 500 mg/kg. The results described below indicate cyclopentyl methyl ether follows nonlinear kinetics following single oral administration (Klimisch Score 1, Reliable without restriction) (Unnamed 2013 study report, 001 Key, ECHA 2023)

- *Absorption:* Rats generally had two absorption peaks following oral administration of a single dose, indicating cyclopentyl methyl ether may be absorbed at multiple sites after entering the digestive tract and/or there was hepato-enteric circulation. Some rats displayed three absorption peaks. The first times of maximum plasma concentration (Tmax) were 0.23±0.20 and 0.69±0.38h for 20 and 500 mg/kg, respectively, and the second Tmax values were 0.67±0.29 and 5.50±1.00h for 20 and 500 mg/kg, respectively. These data suggest absorption of the test substance is delayed with increased dose. Combined with data analysis from administration of a single intravenous injection of cyclopentyl methyl ether at a dose of 5 mg/kg, authors reported the absorption fraction of cyclopentyl methyl ether following oral administration to be 114.28±109.93% and 115.03±86.32% for the 20 and 500 mg/kg dose levels, respectively.
- *Distribution:* Five minutes after administration of a single oral dose, concentrations in the digestive tract were high; 30 minutes after administration, the concentration of the test substance

in the digestive tract decreased while its concentration in other tissues increased in different degrees. Concentration in the digestive tract was still high at 6 hours after administration, followed by tissues rich in lipids (fat, uterus, ovary, brain, testis, epididymis). In female rats administered a single oral dose of 20 mg/kg cyclopentyl methyl ether, the highest concentrations were found in the fat and the ovary; body distribution in the male rat was similar to that of female rats. Cyclopentyl methyl ether had a high affinity for the tissues rich in lipids and decreased relatively slowly in fat, with a slower decrease in males compared to females. The apparent volume of distribution (Vz) was 5.45±3.37 L/kg.

- *Metabolism:* As cyclopentyl methyl ether volatilized quickly, the *in vitro* test of liver microsomal metabolism and recombinant enzyme metabolism test could not be conducted, and there are significant deviations in the *in vitro* protein binding test. The binding rates of 50 μg/mL cyclopentyl methyl ether to plasma protein from rat, dog, monkey, and human were 95.7%, 0.6%, 96.1%, and 96.3%, respectively, suggesting strong binding affinity.
- *Elimination:* Following single gavage administration, the amount of excreted test substance in bile, feces, and urine was very low. The authors stated this was due to the volatility of cyclopentyl methyl ether; as the collections of bile, feces and urine were in the open, the test substance in the collected samples volatilized considerably. However, the authors did state elimination decreased with dose increase. No accumulation was detected in rats administered an oral dose of cyclopentyl methyl ether for 7 days.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Cyclopentyl methyl ether was assigned a score of Low for carcinogenicity based on a lack of structural alerts for genotoxic and non-genotoxic carcinogenicity as identified by Toxtree and modeling using both rule-based and statistical-based models in the VEGA platform and Danish QSAR Database indicating a low concern for carcinogenicity. 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 as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- VEGA 2021
  - CAESAR v2.1.9 model predicts cyclopentyl methyl ether to be a non-carcinogen with moderate confidence. The global acceptability domain index (ADI) is 0.657, indicating that the prediction is not reliable (Appendix D)[9]. Therefore, this model was not included in the weight of evidence.
  - ISS v1.0.2 model predicts cyclopentyl methyl ether to be a non-carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix D).
  - IRFMN/Antares v1.0.0 model predicts cyclopentyl methyl ether to be a possible non-carcinogen with moderate confidence. The ADI is 0.635, indicating that the prediction is not reliable (Appendix D). Therefore, this model was not included in the weight of evidence.

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

  - IRFMN/ISSCAN-CGX v1.0.0 model predicts cyclopentyl methyl ether to be a possible non-carcinogen with moderate confidence. The ADI is 0.635, indicating that the prediction is not reliable (Appendix D). Therefore, this model was not included in the weight of evidence.
  - IRFMN oral classification v1.0.0 reports cyclopentyl methyl ether is a non-carcinogen with moderate confidence. The ADI is 0.78, indicating that the prediction is reliable (Appendix D).
  - IRFMN inhalation classification v1.0.0 reports cyclopentyl methyl ether is a non-carcinogen with high confidence. The ADI is 0.929, indicating that the prediction is reliable (Appendix D).
- Toxtree 2018
  - Cyclopentyl methyl ether does not contain a structural alert for genotoxic or nongenotoxic carcinogenicity (Appendix E).
- DTU 2023
  - Danish (Q)SAR Database for the CAS number 5414-37-9 reports that cyclopentyl methyl ether is in the domains of all seven E Ultra FDA RCA cancer models, which all predicted it to be negative for carcinogenicity. It is outside the domain of all seven FDA RCA cancer Leadscope models. Regarding the liver specific cancer in rat or mouse model, cyclopentyl methyl ether is outside of the applicability domain of three of the four models (Leadscope, and SciQSAR models and the overall battery), but is within the domain of the CASE Ultra model and predicted to be negative (DTU 2022, Appendix C).
- U.S. EPA 2021
  - Attempts were made to evaluate the carcinogenic potential of cyclopentyl methyl ether using the most current version of OncoLogic (v9.0); however, OncoLogic indicated that its chemical class is not supported in the current version of software (Appendix G).

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

Cyclopentyl methyl ether was assigned a score of Low for mutagenicity/genotoxicity based on consistently negative results for negative for mutagenicity in bacterial cells and mammalian cells *in vitro*, and negative results for clastogenicity in mammalian cells *in vitro* and *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 high as it is based on high quality data for the target substance.

- 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 2023
  - *In vitro:* Cyclopentyl methyl ether tested negative for mutagenicity in a bacterial reverse mutation assay (OECD Guideline 471, EU Method B.13/14, EPA OPPTS 870.5100, and Japan: Guidelines for Screening Mutagenicity Testing of Chemicals, GLP-compliant). *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP_2 *uvr*A pKM 101 were exposed to cyclopentyl methyl ether (99.6% purity) in DMSO at concentrations of 50, 150, 500, 1,500, and 5,000 µg/plate, with and without metabolic activation (liver homogenate derived from Aroclor 1254 induced rats). The positive controls were sodium azide, 9-aminoacridine, 2-nitrofluorene, 2-(2-furyl)-3-(5-nitro)-2-furyl)acrylamide, 2-aminoanthracene, and benzo(a)pyrene. Results were negative for all strains at all concentrations, with and without activation. Cytotoxicity was not observed and the test substance was fully soluble in DMSO, but the test was conducted up to the limit concentration. Controls performed as expected. The range-finding test was performed using

a standard plate incorporation assay, and the definitive test was performed with pre-incubation (Klimisch Score 1, reliable without restriction) (Unnamed 2001 study report, 001 Key).

- *In vitro:* Cyclopentyl methyl ether tested negative for mutagenicity in an *in vitro* mammalian gene cell mutation test (OECD Guideline 490, GLP-compliant). Mouse lymphoma L5178Y cells were exposed to cyclopentyl methyl ether (99.99% purity) in DMSO at concentrations of 20.48, 51.2, 128, 320, 800, and 2,000 µg/mL, with and without metabolic activation (S9 mix). Positive controls were cyclophosphamide and methylmethanesulfonate. Results were negative for mutagenicity at all concentrations, with and without activation. Cytotoxicity and precipitation were not observed, but the test was conducted up to the limit concentration. Controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Klimisch Score 1, reliable without restriction) (Unnamed 2018 study report, 003 Key).
- *In vitro:* Cyclopentyl methyl ether tested negative for clastogenicity in an *in vitro* chromosome aberration study in mammalian cells (OECD Guideline 473, EU Method B.10, EPA OPPTS 870.5375, and Japan: Guidelines for Screening Mutagenicity Testing of Chemicals, GLP-compliant). Chinese hamster lung fibroblasts (V79) were exposed to cyclopentyl methyl ether (99.8% purity) in DMSO at concentrations of 62.6, 125.2, 250.4, 500.8, and 1,001.6 µg/mL, with and without metabolic activation (liver homogenate derived from Aroclor 1254 induced rats). Positive controls were mitomycin C and cyclophosphamide. In the range-finding test in the absence of metabolic activation, there were increased chromosomal aberrations observed at 250.4 µg/mL, including gap-type aberrations; however there was no dose-response and the results were not reproducible. In the second test, results were negative for the induction of chromosomal aberrations at all concentrations, with and without activation. Cytotoxicity was not observed, the test substance was fully soluble in DMSO, testing was performed up to the recommended limit concentrations, and controls performed as expected. Authors concluded the test substance was not clastogenic under the conditions of the test (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report, 002 Key).
- *In vivo:* Cyclopentyl methyl ether tested negative in an *in vivo* micronucleus assay in mammalian somatic cells (OECD Guideline 474, EU Method B.12, EPA OPPTS 870.5395, GLP-compliant). Male and female CD-1 mice were exposed to a single dose of cyclopentyl methyl ether (99.96% purity) by gavage in corn oil at doses of 0, 500, 1,000, and 2,000 mg/kg (2/sex/dose in preliminary test and 7 males/dose in 500 and 1,000 mg/kg groups and 14 males/dose in control and 2,000 mg/kg groups in micronucleus assay). The positive controls was mitomycin C. Bone marrow samples harvested from the femurs were evaluated for the presence of micronucleated cells. Clinical signs of toxicity at 2,000 mg/kg included underactivity, overactivity, flattened posture, abnormal gait, fast and irregular respiration, and reduced righting reflexes. At 1,000 mg/kg, clinical signs included underactivity, abnormal gait, and fast respiration. All animals survived to scheduled termination. There were no increases in micronucleated erythrocytes and no decreases in the proportion of immature erythrocytes in treated mice compared to controls. Authors concluded the test substance did not induce chromosome aberrations or bone marrow cell toxicity under the conditions of the test (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report).

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

Cyclopentyl methyl ether was assigned a score of Moderate for reproductive toxicity based on reproductive toxicity in the form of reduced testis weight in a two-generation reproductive toxicity study in Sprague-Dawley rats at doses that also resulted in systemic toxicity, and reproductive effects in the form of prolonged gestation length, which also appeared to be secondary to parental systemic toxicity, in a reproductive and developmental toxicity screening test also in Sprague-Dawley rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is marginal evidence of reproductive toxicity in animals and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is low as results were not reproducible in a way that would discern if adverse reproductive effects are secondary to systemic toxicity and details of statistical significance and severity are lacking for both studies.

- 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 2023
    - *Oral:* In a two-generation reproductive toxicity study (OECD Guideline 416, non-GLP), Sprague-Dawley rats (24/sex/dose) were exposed to cyclopentyl methyl ether (99.9% purity) in drinking water emulsified with plant oil and Tween® 80 at 0, 313, 1,250, or 5,000 mg/L. F0 males were exposed from 10 weeks pre-mating until successful mating; F0 females were exposed from 2 weeks pre-mating through mating, pregnancy, and lactation. Among these animals, there were no clinical signs of toxicity reported by study authors, no premature deaths, and no treatment-related effects on histopathology in evaluated tissues/organs. Body weight gain was decreased in male rats at the mid- and high-dose before mating and in high dose female rats before mating (statistical significance and severity not reported). Body weights of pregnant rats were decreased at the high dose on gestation days (GD) 0, 7, 14, and 20 compared to controls (statistical significance and severity not reported). Body weights of maternal rats at GD 0, 4, 7, 14, and 21 and total body weight gain during lactation were reduced compared to controls (statistical significance and severity not reported). Average water consumption was reduced in mid- and high-dose F0 males and females (statistical significance and severity not reported). There were no statistically significant differences in mating success, pregnancy rate, live birth rate, or pup viability at day 4, or on survival after weaning at day 21 for any dose group compared to controls. Among F1 generation offspring, reproductive effects were reported at the top dose of 5,000 mg/L, comprising decreased average litter weights on days 14 and 21, and decreased pup weights on days 7, 14, and 21 (statistical significance and severity were not reported, and it is not clear if these effects were related to the decreased body weight gain and decreased consumption for parental animals prior to mating and/or during gestation). High dose rats also had increased relative testicular weights (statistical significance and severity not reported). Among F2 generation offspring, reproductive effects were reported at the top dose of 5,000 mg/L, comprising decreased average litter weights on days 14 and 21, and decreased average pup body weights on days 14 and 21 (statistical significance and severity not reported, and it is not clear if these effects were related to the decreased body weight gain and decreased consumption for parental animals prior to mating and/or during gestation). Authors assigned a NOAEL for the P0, F1, and F2 generations at 1,250 mg/L, equivalent to 169.18 mg/kg/day for males and 193.45 for females. For parental toxicity, the NOAEL is based on decreased body weight, body weight gain, and absolute and relative testis weights (statistical significance and severity not reported). The NOAEL for the F1 generation is based on mortality of 1 rat at 5,000 mg/L, decreased body weights, body

weight gain, and absolute and relative testis weights at 5,000 mg/L (statistical significance and severity not reported). The NOAEL for F2 rats is based on decreased average litter weights and pup body weights on days 14 and 21 for the high dose group (Klimisch Score 2, reliable with restrictions based on guideline study, non-GLP but in compliance with China National Metrology Accreditation) (Unnamed 2014 study report, 001 Key).

- *ToxServices notes this study meets GHS Category 2 based on reproductive toxicity (reduced testis weights)(severity and statistical significance not reported) occurring only at doses that also resulted in parental systemic toxicity.*

- *Oral:* In a reproductive and developmental toxicity screening test (OECD Guideline 421, GLP-compliant) Sprague-Dawley rats (10/sex/dose) were exposed to cyclopentyl methyl ether (99.97% purity) by gavage in corn oil at 0, 50, 150, or 450 mg/kg/day. Males were exposed for a minimum of 4 weeks and females were exposed from 15 days before pairing until day 6 after birth of the F1 generation. Among P0 rats, there were no treatment-related changes in organ weights and no adverse effects on histopathology in examined tissues/organs. One high dose male was euthanized on day 18 of treatment due to poor clinical condition characterized by underactive behavior, hunched posture, fast breathing, poor reflexes, and partially closed eyelids. Macroscopic examination revealed dark liver and adrenals, reduced stomach and cecal content, and abnormal orange viscous fluid in the jejunum with colon and rectum devoid of content. Microscopic examination of abnormalities revealed no treatment related lesions. On the first day of treatment, approximately 30 minutes after dosing, three high dose males had an unsteady gait and one of these also was underactive. On day 2 at 30 minutes, only two males had unsteady gait, and on day 3 only one animal was observed as underactive. Underactivity following treatment was no longer observed by treatment day 4. Males at 450 mg/kg/day had reduced body weight gain compared to controls. Males and females at 450 mg/kg/day had reduced food consumption during the two weeks prior to pairing. There was a slight reduction in food consumption in treated females on lactation days 4 to 6 compared to controls, but there was no dose response. There were no effects on estrus cycle, mating performance, or fertility or gestation indices at any dose. High dose females had slightly but statistically significant increased gestation length compared to controls, but it was still within the normal range of 22 to 23.5 days. The authors reported no treatment related pathological findings on epididymides, testes, pituitary, or sperm morphology. F1 offspring displayed no clinical signs of toxicity, and there were no treatment-related effects on mortality, body weight and body weight gain, gross pathology, histopathology, litter size, or sex ratio reported. Authors assigned a NOAEL of 450 mg/kg/day for reproductive toxicity, and a NOAEL of 150 mg/kg/day for systemic toxicity in parental animals based on decreased body weight and food consumption at 450 mg/kg/day (Klimisch Score 1, reliable without restriction) (Unnamed 2012 study report, 002 Supporting).

  - *ToxServices notes this study meets GHS not classified based on observations of reproductive effects (slightly prolonged gestation length) occurring only at doses well above onset of parental systemic toxicity.*

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Cyclopentyl methyl ether was assigned a score of Moderate for developmental toxicity based on developmental effects in two of three developmental toxicity studies in rats at the same doses that resulted in parental systemic toxicity, and ToxServices classifying it as a GHS Category 2 developmental toxicant. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is marginal evidence of developmental toxicity in animal studies and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is low as

developmental effects occurred in the presence of parental toxicity and it is not possible to determine if they are secondary.

- 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 2023
    - *Oral:* In the previously described two-generation reproductive toxicity study (OECD Guideline 416, non-GLP), Sprague-Dawley rats (24/sex/dose) were exposed to cyclopentyl methyl ether (99.9% purity) in drinking water emulsified with plant oil and Tween®-80 at 0, 313, 1,250, or 5,000 mg/L. F0 males were exposed from 10 weeks pre-mating until successful mating; F0 females were exposed from 2 weeks pre-mating through mating, pregnancy, and lactation. Among F0 animals, there were no clinical signs of toxicity reported by study authors, no premature deaths, and no treatment-related effects on histopathology in evaluated tissues/organs. Body weight gain was decreased in male rats at the mid- and high-dose before mating and in high dose female rats before mating (statistical significance and severity not reported). Body weights of pregnant rats were decreased at the high dose on GD 0, 7, 14, and 20 compared to controls (statistical significance and severity not reported). Body weights of maternal rats at GD 0, 4, 7, 14, and 21 and total body weight gain during lactation were reduced compared to controls (statistical significance and severity not reported). Average water consumption was reduced in mid- and high-dose F0 males and females (statistical significance and severity not reported). There were no statistically significant differences in mating success, pregnancy rate, live birth rate, or pup viability at day 4, or on survival after weaning at day 21 for any dose group compared to controls. Authors assigned a NOAEL for the P0, F1 and F2 generations at 1,250 mg/L, equivalent to169.18 mg/kg/day for males and 193.45 for females. For parental toxicity, the NOAEL is based on decreased body weight, body weight gain, and absolute and relative testis weights (statistical significance and severity not reported). The NOAEL for the F1 generation is based on mortality of 1 rat at the high dose and decreased body weights, body weight gain, and absolute and relative testis weights at 5,000 mg/L (statistical significance and severity not reported). The NOAEL for F2 rats is based on decreased average litter weights and pup body weights on days 14 and 21 for the high dose group (statistical significance and severity not reported) (Klimisch Score 2, reliable with restrictions based on guideline study, non-GLP but in compliance with China National Metrology Accreditation) (Unnamed 2014 study report, 001 Key).
        - *ToxServices notes this study meets GHS Category 2 based on developmental effects (decreased body weights, testis weights, average litter weights and/or pup weights) occurring only at doses that also resulted in parental systemic toxicity (statistical significance and severity not reported).*
    - *Oral:* In the previously described reproductive and developmental toxicity screening test (OECD Guideline 421, GLP-compliant) Sprague-Dawley rats (10/sex/dose) were exposed to cyclopentyl methyl ether (99.97% purity) by gavage in corn oil at 0, 50, 150, or 450 mg/kg/day. Males were exposed for a minimum of 4 weeks and females were exposed from 15 days before pairing until day 6 after birth of the F1 generation. Among P0 rats, there were no treatment-related changes in organ weights, and no adverse effects on histopathology in examined tissues/organs. One high dose male was euthanized prior to the end of the study due to poor clinical condition characterized by underactive behavior, hunched posture, fast breathing, poor reflexes and partially closed eyelids. Macroscopic examination revealed dark liver and adrenals, reduced stomach and cecal content, and

abnormal orange viscous fluid in the jejunum with colon and rectum devoid of content. Microscopic examination of abnormalities revealed no treatment related lesions. On the first day of treatment, approximately 30 minutes after dosing, three high dose males had an unsteady gait and one of these also was underactive. On day 2 at 30 minutes, only two males had unsteady gait, and on day 3 only one animal was observed as underactive. Underactivity following treatment was no longer observed by treatment day 4. Males at 450 mg/kg/day had reduced body weight gain compared to controls. Males and females at 450 mg/kg/day had reduced food consumption during the two weeks prior to pairing. There was a slight reduction in food consumption in treated females on lactation days 4 to 6 compared to controls, but there was no dose response. There were no effects on estrus cycle, mating performance, or fertility, or gestation indices at any dose. High dose females had slightly but statistically significant increased gestation length compared to controls, but it was still within the normal range of 22 to 23.5 days. The authors reported no treatment-related pathological findings on epididymides, testes, pituitary or sperm morphology. F1 offspring displayed no clinical signs of toxicity, and there were no treatment-related effects on mortality, body weight and body weight gain, gross pathology, histopathology, litter size, or sex ratio reported. Authors assigned a NOAEL of 450 mg/kg/day for developmental toxicity, and a NOAEL for systemic toxicity in parental animals at 150 mg/kg/day based on decreased body weight and food consumption at 450 mg/kg/day (Klimisch Score 1, reliable without restriction) (Unnamed 2012 study report, 002 Supporting).

- *ToxServices notes this study meets GHS not classified based on lack of developmental effects reported in the study.*

- *Oral:* In a prenatal developmental toxicity study (OECD Guideline 414, non-GLP, but in compliance with China National Metrology Accreditation) Sprague-Dawley rats were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in water emulsified with Tween® 80 at doses of 0, 50, 200, or 800 mg/kg/day on GD 6-15. There were 10 males/dose and 22, 24, 25, and 21 females at 0, 50, 200, and 800 mg/kg/day, respectively. Among test animals, the authors reported no premature deaths or clinical signs of toxicity. There was no effect on water consumption. Pregnant dams exhibited reduced body weight at 800 mg/kg/day from day 9, and reduced body weight gain during pregnancy (statistical significance and severity not reported). There were no effects on early or late resorptions, fetus viability, pregnancy duration, or number of pregnancies. At 800 mg/kg/day, effects included reductions in uterus weight, average fetal body weight, length, and tail length compared to controls (statistical significance and severity not reported). One pup in the 800 mg/kg/day group had gastroschisis (abdominal wall defect where intestines protrude) with no tail and left hind foot valgus. One pup in the 800 mg/kg/day group from another litter had a rib deletion. Some fetuses in the low, mid, and high dose group had hypoplastic supraoccipitals, hypoplastic interparietals, and agenesis of other skull bone but differences were not statistically significant on a litter basis compared to controls. There were no observations of visceral malformations. Total teratogenic rate in the 800 mg/kg/day group was 0.8%, which was not statistically significantly increased compared to controls. Authors assigned a maternal and developmental NOAEL of 200 mg/kg/day based on decreased body weight and weight gain in dams, and reduced fetal body weight, length, and tail length in pups at 800 mg/kg/day (Klimisch Score 2, reliable with restrictions based on guideline study, non-GLP, but in compliance with China National Metrology Accreditation) (Unnamed 2013 study report).
    - *ToxServices notes this study meets GHS Category 2 based on observations of developmental effects occurring only at doses that also resulted in parental systemic toxicity.*

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

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral:* In a subchronic oral toxicity study (OECD Guideline 408, non-GLP) Sprague-Dawley rats (10/sex/dose) were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in water at 0, 32, 125, and 500 mg/kg/day for 90-days. Animals were evaluated based on cage side observations, clinical observations, body weights, food consumption and efficiency, water consumption, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. Males had increased relative testes and adrenal weights at 500 mg/kg/day compared to controls. Authors assigned a NOAEL of 32 mg/kg/day (actual dose received) based on decreased body weight gain, food consumption and food efficiency in high dose males, and numerous hematological, clinical chemistry, and organ weight changes at the mid- and high dose (Klimisch 2, reliable with restrictions based on guideline study, non-GLP, but testing was performed in accordance with China National Metrology Accreditation) (Unnamed 2014 study report, 001 Key).
  - *Oral:* In a 28-day oral study (OECD Guideline 407, EU Method B.7, Ministry of Health and Welfare for Japan – Part II of the Chemical Substance Control Law of 1986, GLP-compliant), male and female Crl:CD (SD)IGS BR rats (10/sex/control and high dose, and 5/sex/low- and mid-dose) were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in corn oil at 0, 15, 150, or 700 mg/kg/day. Animals were evaluated for cage side and clinical observations, body weights, food efficiency, water consumption, hematology, clinical chemistry, urinalysis, neurobehavioral examination, gross pathology, organ weights, and histopathology. Two high dose male rats sacrificed at day 16 had increased relative adrenal weights and decreased absolute and relative spleen weights, along with dark adrenals, and pale spleen. Authors assigned a NOAEL of 150 mg/kg/day (Klimisch 1, reliable without restriction) (Unnamed 2003 study report, 002 Supporting).
  - *Oral:* In a two-generation reproductive toxicity study (OECD Guideline 416, non-GLP), Sprague-Dawley rats (24/sex/dose) were exposed to cyclopentyl methyl ether (99.9% purity) in drinking water emulsified with plant oil and Tween® 80 at 0, 313, 1,250, or 5,000 mg/L. F0 males were exposed from 10 weeks pre-mating until successful mating; F0 females were exposed from 2 weeks pre-mating through mating, pregnancy, and lactation. Authors assigned a NOAEL for the P0, F1 and F2 generations at 1,250 mg/L, equivalent to 169.18 mg/kg/day for males and 193.45 for females. For parental toxicity, the NOAEL is based on decreased body weight, body weight gain, and absolute and relative testis weights at 5,000 mg/L. The NOAEL for the F1 generation is based on mortality of 1 rat at the high dose, decreased body weights and body weight gain, and decreased absolute and relative testis weights at 5,000 mg/L (Klimisch 2, reliable with restrictions based on guideline study, non-GLP but in compliance with China National Metrology Accreditation) (Unnamed 2014 study report, 001 Key).
  - *Inhalation:* In a subchronic inhalation toxicity study (OECD Guideline 413, GLP-compliant), male and female Crj: CD(SD) rats (10/sex/dose, plus an extra 6/sex for control and high dose recovery groups) were exposed to cyclopentyl methyl ether (99.93% purity) at 0, 0.2, 0.4, 0.8, or 4 mg/L (MMAD and GSD not recorded) by whole body inhalation 6 hours/day, 5 days/week for 13 weeks. Effects in males at the end of the recovery period

included lower absolute adrenal weight, increased absolute and relative thyroid weight, and increased body weight at 4 mg/L. Effects in females at the end of the recovery period included increased relative weight of the salivary glands, spleen, and adrenals at 4 mg/L. There were no adverse effects for gross pathology for any dosed animals compared to controls. Authors assigned a NOAEC of 0.87 mg/L in males and 0.84 mg/L in females based on salivation and nasal discharge, lower body weight and body weight gain, increased liver and kidney weights, and hyperplasia in the mucosal epithelium of the urinary bladder (Klimisch 1, reliable without restriction) (Unnamed 2004 study report, 001 Key).

- Based on the weight of evidence, a Data Gap was assigned. Numerous repeated dose toxicity studies examined endocrine organs. Effects were reported in the testes, adrenals, spleen and thyroid, but in each study these effects occurred at doses with significant systemic toxicity and none of the studies reported on circulating hormone levels. There is no indication the endocrine system is a primary target, or that other systemic effects are secondary to endocrine activity.

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

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

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

Cyclopentyl methyl ether was assigned a score of Moderate for acute toxicity based on the oral LD_{50} of >200 to <2,000 mg/kg in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when the oral LD_{50} is >300 to 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on high quality data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Source
  - *Oral:* LD_{50} (male and female Sprague-Dawley rats) > 200 and < 2,000 mg/kg (OECD Guideline 423, EU Method B.1 tris, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report).
  - *Dermal:* LD_{50} (male and female Sprague-Dawley rats) > 2,000 mg/kg (OECD Guideline 402, EU Method B.3, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).
  - *Inhalation:* 4-hour LC_{50} (male and female Sprague-Dawley rats) > 21.5 mg/L (OECD Guideline 403, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).

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

Cyclopentyl methyl ether was assigned a score of Low for systemic toxicity (single dose) based on a lack of systemic toxicity in surviving animals in an acute mammalian toxicity studies in rats up to the oral and dermal guidance value of 2,000 mg/kg and the inhalation guidance value of 20 mg/L/4h vapor. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable high-quality data for the target substance.

- 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 2023
  - *Oral:* In an acute oral toxicity study (OECD Guideline 423, EU Method B.1 tris, GLP-compliant) male and female Sprague-Dawley rats were administered cyclopentyl methyl ether (99.8% purity) by gavage in 1% aqueous methylcellulose at doses of 200 mg/kg (3/sex) and 2,000 mg/kg (3 females). Two of three females died at 2,000 mg/kg within 6.5 hours of dosing. No females or males died at 200 mg/kg. Clinical signs included piloerection in all dosed animals. Females at the high dose also demonstrated increased salivation, abnormal gait, lethargy, reduced body temperature, prostration, shallow respiration, lacrimation with prominent eyes, and hunched posture. At the low dose, hunched posture was observed in all males and one female, and abnormal gait in all females and one male. There was no effect on body weight gain for surviving animals. Macroscopic examination of the two female decedents at the high dose revealed congestion characterized by blood vessels injected in the brain, thickened tissues and atrophy of the heart, and congestion and fluid contents in the stomach and alimentary tract. There were no macroscopic findings for surviving animals when examined at day 15 (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report).
  - *Dermal:* In an acute dermal toxicity study (OECD Guideline 402, EU Method B.3, GLP-compliant), male and female Sprague-Dawley rats (5/sex) were exposed to unchanged (no vehicle) cyclopentyl methyl ether (99.99% purity) under occlusion for 24 hours. Low body weight gain was recorded for four females on day 8, and two females on day 15. There were no clinical signs of toxicity, no effects based on gross pathology, no observations of systemic toxicity, and no mortality. Local effects included very slight to well-defined irritation and slight edema in 9 animals at removal of dressing, but effects were resolved by day 5. Dryness and exfoliation were observed in 9 animals and spots and/or scabbing in one animal, which resolved by day 9 (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).
  - *Inhalation:* In an acute inhalation toxicity study (OECD Guideline 403, GLP-compliant), male and female Sprague-Dawley rats (5/sex/concentration) were exposed nose only to cyclopentyl methyl ether vapor (99.99% purity) (MMAD => 1.204 - <=3.775 µm; GSD >1.649 - <= 2.342) up to 21.5 mg/L for 4 hours. All animals survived and there were no signs of toxicity during the exposure period. Clinical signs of lacrimation and red nasal discharge were observed immediately after exposure. All animals gained weight and there were no findings upon macroscopic postmortem examinations (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).

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

Cyclopentyl methyl ether was assigned a score of Low for systemic toxicity (repeated dose) based on oral LOAEL values of 125 mg/kg/day and 700 mg/kg/day in 90-day and 28-day studies in rats, respectively, and an inhalation LOAEC of 2.8 mg/L/6h/day in a 90-day study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when oral LOAEL values are >100 mg/kg/day and inhalation LOAEC values are >1.0 mg/L/6h/day for 90-day studies (CPA 2018b). The confidence in the score is low as the NOAEL/C and LOAEL/C values straddle guidance values and it is unclear if adverse effects would occur below the guidance values.

- 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 2023
    - *Oral:* In a subchronic oral toxicity study (OECD Guideline 408, non-GLP) Sprague-Dawley rats (10/sex/dose) were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in water at 0, 32, 125, and 500 mg/kg/day for 90-days. Animals were evaluated based on cage side observations, clinical observations, body weights, food consumption and efficiency, water consumption, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. Clinical signs included nostril flow fluid and fluffy coat in some high dose animals of both sexes. There were no effects on mortality. High dose male rats had decreased body weight gain, decreased food consumption, and decreased food efficiency. Hematological effects in females included decreased red blood cells (RBC) at the mid- and high-dose, decreased prothrombin time (PT) and hematocrit (HCT) at the high dose, increased white blood cells (WBC) in mid- and high-dose, increased monocytes (MO) and red cell distribution width (RDW) at the high dose, and decreased PT at the high dose. For males, there was increased WBC at the mid-dose only, decreased lymphocytes (LYM) at the high dose, increased MO and PT at the high dose, and decreased platelet count (PLT) at the high dose. For females, clinical chemistry findings included decreased albumin-globulin ratio (A/G) at the mid- and high dose and increased total bilirubin (BIL-T) and alkaline phosphatase (ALP) at the high dose. Males had decreased globulin (GLB) at the high dose and increased A/G at the high dose. No effects on urine parameters were reported. For female rats, the low dose animals had increased relative brain weight, the mid dose animals had increased relative kidney weight, and the high dose had increased relative heart, liver, and kidney weights compared to controls. Males had increased relative brain, liver, testes and adrenal weights at the high dose compared to controls. There were no adverse effects observed with gross pathology or histopathology for non-neoplastic or neoplastic lesions. Authors assigned a NOAEL of 32 mg/kg/day (actual dose received) and LOAEL of 125 mg/kg/day based on decreased body weight gain, food consumption, and food efficiency in high dose males, and numerous hematological, clinical chemistry, and organ weight changes at the mid- and high dose (Klimisch Score 2, reliable with restrictions based on guideline study, non GLP, but testing was performed in accordance with China National Metrology Accreditation) (Unnamed 2014 study report, 001 Key).
        - *Based on dose spacing, it is unclear if adverse effects would occur within the guidance values of >10-100 mg/kg/day for a GHS Category 2 classification for oral 90 day studies.*
    - *Oral:* In a 28-day oral study (OECD Guideline 407, EU Method B.7, Ministry of Health and Welfare for Japan – Part II of the Chemical Substance Control Law of 1986, GLP-compliant), male and female Crl:CD (SD)IGS BR rats (10/sex/control and high dose, and 5/sex/low- and mid-dose) were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in corn oil at 0, 15, 150, or 700 mg/kg/day. Animals were evaluated for cage side and clinical observations, body weights, food efficiency, water consumption, hematology, clinical chemistry, urinalysis, neurobehavioral examination, gross pathology, organ weights, and histopathology. High dose male rats exhibited increased mortality, increased salivation, decreased behavior, piloerection, abnormal gait, body tremors, convulsions, hunched posture, fast respiration and thin appearance. Six of the males were sacrificed early, between day 12 and 15, *in extremis*. High dose males had decreased body weight gains during week 1, and decreased food consumption and actual weight loss during week 2. Hematology performed on the two high dose males sacrificed on day 16 demonstrated increased hematocrit, hemoglobin, RBC, and mean corpuscular volume (MCV), decreased mean corpuscular hemoglobin concentration (MCHC), LYM and eosinophil counts, lower

total WBC, and moderate hypochromasia compared to controls evaluated at day 29. The two high dose male rats sacrificed at day 16 also had increased relative adrenal weights and decreased absolute and relative spleen weights, along with dark adrenals, pale spleen, depressions in stomach and thin appearance. Necrosis of the stomach and lamina propria was reported for 4 of 6 decedent males. High dose females had increased activity in week 4, decreased food utilization in weeks 2 to 4, and decreased body weight gain in weeks 3 and 4. Hematological findings in high dose females at day 29 included increased hematocrit, hemoglobin, and red blood cell counts, and decreased lymphocytes, eosinophil and total white blood cell counts. Clinical chemistry analyses in high dose females revealed increased group mean cholesterol, total protein, and albumin values. Urinalysis in high dose females revealed increased group mean urinary protein and small amounts of ketones in the urine. Mid dose males also had decreased urinary protein and chloride values. As urine-related parameters reported among mid dose males did not correspond with adverse histopathological or microscopic findings, authors assigned a NOAEL of 150 mg/kg/day and a LOAEL of 700 mg/kg/day (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 002 Supporting).

- *The guidance values were tripled (i.e., 10-100 mg/kg/day * 3 = 30-300 mg/kg/day) as 28-day studies are approximately 1/3 the duration of 90-day studies. Based on dose spacing, it is unclear if adverse effects would occur within the adjusted guidance values of >30-300 mg/kg/day for a GHS Category 2 classification.*

- *Inhalation:* In a subchronic inhalation toxicity study (OECD Guideline 413, GLP-compliant), male and female Crj: CD(SD) rats (10/sex/dose, plus an extra 6/sex for control and high dose recovery groups) were exposed to cyclopentyl methyl ether (99.93% purity) at 0, 0.2, 0.4, 0.8, or 4 mg/L (MMAD and GSD not recorded) by whole body inhalation 6 hours/day, 5 days/week for 13 weeks. Males and females at 4 mg/L displayed increased salivation and nasal discharge after the daily exposure period, and statistically significant decreased body weights (statistical significance and severity not reported). Females at 4 mg/L also had statistically significant decreased food consumption compared to controls on days 43, 57, and 64, but not during the recovery period (statistical significance and severity not reported). Females at 0.2, 0.4, and 0.8 mg/L sporadically exhibited statistically significant decreased food consumption; however, this effect was not consistent and did not coincide with body weight changes. No adverse ocular effects were observed following ophthalmological examination. Males at 4 mg/L had increased reticulocyte ratio and white blood cell counts, and also higher ALAT (GPT) and potassium compared to controls. Males at 0.8 and 4 mg/L exhibited increased absolute and relative liver weights. Males at 4 mg/L exhibited increased absolute and relative kidney weights and decreased absolute brain weights. Males at 0.4 mg/L and higher exhibited decreased absolute salivary gland weights, and at 0.2 mg/L and higher exhibited decreased relative salivary gland weights. High dose females exhibited increased relative liver, kidney, and heart weights, and decreased absolute brain weights. Effects in males at the end of the recovery period included lower absolute adrenal weights, increased absolute and relative thyroid weights, and increased body weight at 4 mg/L. Effects in females reported at the end of the recovery period included increased relative weights of the salivary glands, spleen, and adrenals at 4 mg/L. Statistical significance and severity were not reported for these effects, and the authors reported no treatment-related effects on gross pathology among tissues/organs examined. Hyaline droplet formation in the proximal tubular epithelium of the kidneys was observed in three males at 4 mg/L. Hyperplasia of the mucosal epithelium in the urinary bladder was observed in three males and two females at 4 mg/L. Authors assigned a NOAEC of 0.87 mg/L in males and 0.84 mg/L in females. Effects at the LOAEC of 4 mg/L included

salivation and nasal discharge, lower body weight and body weight gain, increased liver and kidney weights, hyperplasia in the mucosal epithelium of the urinary bladder. Other effects reported at lower concentrations were not considered toxicologically significant or treatment-related due to a lack of dose-response and/or due to their reversibility after the recovery period (Klimisch Score 1, reliable without restriction) (Unnamed 2004 study report, 001 Key).

- *The vapor NOAEC and LOAEC of 0.8 and 4 mg/L are equivalent to 0.57 mg/L and 2.8 mg/L, respectively, when adjusted to the treatment frequency of 7 days/week (i.e., 0.8 mg/L * 5 days/7 days = 0.57 mg/L). Based on dose spacing, it is unclear if adverse effects would occur within the guidance values of >0.2-1.0 mg/L for a GHS Category 2 classification for vapors for 90-day studies.*

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Cyclopentyl methyl ether was assigned a score of Moderate for neurotoxicity (single dose) based on limited signs of narcotic effects, including hunched posture, lethargy and abnormal gait in an acute oral toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when a GHS Category 3 classification for transient narcotic effects is warranted (CPA 2018b). The confidence in the score is low as reversibility of the effects was not reported, similar effects were observed at lethal doses, and there were other signs also present that are inconsistent with narcotic effects.

- 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 2023
  - *Oral:* In an acute oral toxicity study (OECD Guideline 423, EU Method B.1 tris, GLP-compliant) male and female Sprague-Dawley rats were administered cyclopentyl methyl ether (99.8% purity) by gavage in 1% aqueous methylcellulose at doses of 200 mg/kg (3/sex) and 2,000 mg/kg (3 females). Clinical signs included piloerection in all dosed animals. Females at the high dose also demonstrated increased salivation, abnormal gait, lethargy, reduced body temperature, prostration, shallow respiration, lacrimation with prominent eyes, and hunched posture. At the low dose, hunched posture was observed in all males and one female, and abnormal gait in all females and one male. There were no macroscopic findings for surviving animals when examined at day 15 (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report).
  - *Dermal:* In an acute dermal toxicity study (OECD Guideline 402, EU Method B.3, GLP-compliant), male and female Sprague-Dawley rats (5/sex) were exposed to unchanged (no vehicle) cyclopentyl methyl ether (99.99% purity) under occlusion for 24 hours. There were no clinical signs of toxicity and no effects based on gross pathology (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).
  - *Inhalation:* In an acute inhalation toxicity study (OECD Guideline 403, GLP-compliant), male and female Sprague-Dawley rats (5/sex/concentration) were exposed nose only to cyclopentyl methyl ether vapor (99.99% purity) (MMAD => 1.204 - <=3.775 µm; GSD >1.649 - <= 2.342) up to 21.5 mg/L for 4 hours. There were no signs of toxicity during the exposure period. Clinical signs of lacrimation and red nasal discharge were observed immediately after exposure. There were no findings upon macroscopic postmortem examinations (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report).

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

Cyclopentyl methyl ether was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of adverse neurobehavioral effects in an oral 28-day repeated dose toxicity study in rats exposed at up to 700 mg/kg/day. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when the adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as the details of the neurobehavioral examination are not reported.

- 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 2023
  - *Oral:* In the previously described 28-day oral study (OECD Guideline 407, EU Method B.7, Ministry of Health and Welfare for Japan – Part II of the Chemical Substance Control Law of 1986, GLP-compliant), male and female Crl:CD (SD)IGS BR rats (10/sex/control and high dose, and 5/sex/low- and mid-dose) were exposed to cyclopentyl methyl ether (99.9% purity) by gavage in corn oil at 0, 15, 150, or 700 mg/kg/day. Animals were evaluated for neurobehavioral effects, gross pathology, organ weights, and histopathology. High dose male rats had increased mortality, increased salivation, decreased behavior, piloerection, abnormal gait, body tremors, convulsions, hunched posture, fast respiration and thin appearance. Neurobehavioral examination (parameters examined were not described) revealed higher activity in high dose females, which was no longer elevated at the end of the recovery period. Study authors did not consider the effect to be toxicologically significant (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 002 Supporting). ToxServices identified a NOAEL of 700 mg/kg/day for neurotoxicity based on a lack of neurotoxicity reported in the study.
    - *The guidance values were tripled (i.e., 100 mg/kg/day * 3 = 300 mg/kg/day) as 28-day studies are approximately 1/3 the duration of 90-day studies. The NOAEL of 700 mg/kg day exceeds the adjusted guidance values of 300 mg/kg/day for a GHS Category 2 classification; therefore, cyclopentyl methyl ether was not classified for neurotoxicity under GHS.*

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

Cyclopentyl methyl ether was assigned a score of Low for skin sensitization based on a mouse local lymph node assay (LLNA) study in which the mean stimulation index (SI) was <3 when tested at 100% concentration. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable high-quality data for the target substance.

- 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 2023
  - Cyclopentyl methyl ether (purity 99.9%) was not sensitizing to the skin of CBA mice in a local lymph node assay (LLNA) (OECD Guideline 429, GLP-compliant). Mice (1/dose in preliminary study and 4/dose in main study) were exposed to cyclopentyl methyl ether in acetone and olive oil (4:1 v/v) at 25% (main study only), 50%, and 100%. SI values were 1.2, 1.3, and 2.6 at 25, 50 and 100%, respectively. As the SI did not exceed 3, authors concluded the test substance was not sensitizing under the conditions of the test and do not meet the criteria for GHS classification (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).

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

Cyclopentyl methyl ether was assigned a score of Low for respiratory sensitization based on lack of dermal sensitization potential and ECHA (2017)'s guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (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 2022
  - Cyclopentyl methyl ether does not contain any structural alerts for respiratory sensitization (Appendix H)
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As
- methyl ether was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by cyclopentyl methyl ether, and as cyclopentyl methyl ether does not contain any structural alerts for respiratory sensitization (OECD 2022), cyclopentyl methyl ether is not expected to be a respiratory sensitizer.

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

Cyclopentyl methyl ether was assigned a score of High for skin irritation/corrosivity based on results of an acute dermal irritation assay classifying it to GHS Category 2. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on a reliable high quality data for the target substance.

- 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 2023
  - In an acute dermal irritation study (OECD Guideline 404, EU Method B.4, EPA OPPTS 870.2500, GLP-compliant), three New Zealand White rabbits were exposed to unchanged cyclopentyl methyl ether (99.8% purity) under semi-occlusive conditions for 4 hours, followed by a 14-day observation period. Mean erythema scores across the 24-, 48- and 72-hour readings were 2, 1.3, and 3, and for two animals the erythema did not fully reverse within 14 days. Mean edema scores across the 24-, 48- and 72-hour readings were 1, 2, and 1.7, and for one animal the edema did not fully reverse within 14 days. Authors assigned cyclopentyl methyl ether as a GHS Category 2 dermal irritant (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report, 001 Key).
    - *Based on GHS guidance (UN 2021) a GHS Category 2 classification is warranted when the mean score for erythema or edema is ≥2.3 - ≤4.0 in at least two of three tested animals from gradings at 24-, 48- and 72-hours or when there is inflammation persisting to the end of the observation period in at least two animals. While only*

one of the three animals has a mean erythema score greater than 2.3, the lack of reversibility within 14 days in at least two animals suggests a Category 2 classification is appropriate

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): H
Cyclopentyl methyl ether was assigned a score of High for eye irritation/corrosivity based on results of an acute ocular irritation assay classifying it to GHS Category 2A. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when a GHS Category 2A classification is warranted (CPA 2018b). The confidence in the score is high as it is based on a reliable high-quality study for the target substance.

- 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 2023
  - In an acute eye irritation assay (OECD Guideline 405, EU Method B.5, EPA OPPTS 870.2400, GLP-compliant), three New Zealand White rabbits were exposed to 0.1 mL unchanged cyclopentyl methyl ether (99.8% purity) in the eye. There was no rinsing and animals were observed for 14 days. Mean scores across 24-, 48-, and 72- hours were reported. Conjunctival irritation based on redness was scored at 2, 2, and 1.7 and was fully reversible for all animals within 14 days. Chemosis scores were 0, 0.3, and 0 and was fully reversible within 2 days for the one rabbit with a positive score. Cornea opacity and iris scores were 0 for all animals at 24, 48 and 72 hours. There were no signs of toxicity or ill health for any rabbits during the study. Authors assigned cyclopentyl methyl ether as a GHS Category 2 ocular irritant (Klimisch Score 1, reliable without restriction) (ECHA 2020a).
    - *Based on GHS guidance (UN 2021) a GHS Category 2A classification is warranted when the mean score for corneal opacity and/or iritis is ≥1 and/or the mean score for conjunctival redness and/or edema (chemosis) are ≥2 in at least two of three tested animals from gradings at 24-, 48- and 72-hours and effects are fully reversible within 21 days. Therefore, Category 2A is warranted based on conjunctival redness scores of 2 in two animals.*

<u>Ecotoxicity (Ecotox)</u>

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M
Cyclopentyl methyl ether was assigned a score of Moderate for acute aquatic toxicity based on an EC_{50} of 35 mg/L in daphnia. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity values are >10 to 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable high quality data for the target substance.

- 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 2023
  - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) > 220 mg/L (EU Method C.1, OECD Guideline 203, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).
  - 48-hour mobility EC_{50} (*Daphnia magna*, daphnia) = 35 mg/L (EU Method C.2, OECD Guideline 202, GLP-compliant) Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).

- 72-hour biomass and growth rate EC_{50} (*Pseudokirchneriella subcapitata*, green algae) > 100 mg/L (EU Method C.3, OECD Guideline 201, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).

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

Cyclopentyl methyl ether was assigned a score of Moderate for chronic aquatic toxicity based on the 21-day NOEC of 1.24 mg/L in daphnia and the NOEC of 2.2 mg/L in algae. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are >1 to 10 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable high-quality data for the target substance.

- 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 2023
  - 28-day growth rate NOEC (*Gobiocypris rarus*, Chinese rare minnows) = 50.7 mg/L (OECD Guideline 215, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2013 study report, 001 Key).
  - 21-day reproduction NOEC and EC_{50} (*D. magna*, daphnia) = 1.24 and 10.8 mg/L, respectively (OECD Guideline 211, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2013 study report, 001 Key).
  - 72-hour biomass and growth rate NOEC (*P. subcapitata*, green algae) = <2.2 and 2.2 mg/L, respectively (EU Method C.3, OECD Guideline 201, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).
    - According to GHS criteria, aquatic toxicity values for aquatic plants based on growth rate are preferred over those based on yield and/or biomass (UN 2021).

Environmental Fate (Fate)

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

Cyclopentyl methyl ether was assigned a score of Moderate for persistence based on a predicted half-life of 30 days in soil, the predicted dominant compartment. GreenScreen® criteria classify chemicals as a Moderate hazard for persistence when soil is the dominant compartment and the half-life is 16 to 60 days (CPA 2018b). The confidence in the score is low as it is based on modeled half-lives.

- 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 2023
  - Cyclopentyl methyl ether (99.6% purity) was not readily biodegradable when tested in the Modified MITI Test (I) (OECD Guideline 301C, GLP-compliant). The initial test substance concentration was 100 mg/L, and testing was performed using activated sludge (non-adapted). Degradation was 2%, measured as oxygen consumption over 28 days. Controls performed as expected. Authors concluded the test substance was not readily biodegradable under the conditions of the test (Klimisch 1, reliable without restriction) (Unnamed 2001 study report, 001 Key).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that cyclopentyl methyl ether is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 58.2% will partition to soil with a half-life of 30 days, 36.5% will partition to water with a

half-life of 15 days, 5.16% will partition to air with a half-life of 16.1 hours, and 0.117% will partition to sediment with a half-life of 135 days (Appendix I).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Cyclopentyl methyl ether was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 1.6 and a predicted BCF of 4.538. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is ≤4 and the BCF is ≤100 (CPA 2018b). The confidence in the score is high as it is based on a measured log K_{ow} with support from modeling.

- 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 2023
  - Cyclopentyl methyl ether has a measured log K_{ow} of 1.6 in a shake flask method (OECD Guideline 107, EU Method A.8, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2002 study report, 001 Key).
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 5.281 using the regression based model based on a measured log K_{ow} of 1.6, and a BCF of 4.538 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix I).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Cyclopentyl methyl ether was assigned a score of Low for reactivity based on ToxServices not classifying it as reactive under GHS based on its structure and negative results in an explosivity test. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the limited 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 2023
  - Cyclopentyl methyl ether (99.9% purity) was not thermally sensitive (EU Method A.14, GLP-compliant). As the substance is a liquid at room temperature, friction testing for mechanical sensitivity is not warranted (Klimisch 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).
  - Cyclopentyl methyl ether is predicted not to possess oxidizing properties on the basis of an assessment of the structure.
- TCI America 2018
  - An SDS for cyclopentyl methyl ether (>99.5% purity) has a instability rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and physical hazard rating of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- Based on the information presented above indicating that cyclopentyl methyl ether is not reactive, ToxServices did not classify cyclopentyl methyl ether as a reactive chemical under GHS criteria (UN 2021).

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

Cyclopentyl methyl ether was assigned a score of High for flammability based on a flash point of <3°C and an initial boiling point of 107°C, classifying it to GHS Category 2 for flammable liquids (flash point < 23°C and boiling point > 35YC) and its classification as a Hazard Class 3 Packaging Group II by the U.S. DOT. GreenScreen® criteria classify chemicals as a High hazard for flammability when a GHS Category 2 classification for flammable liquids is warranted and they are classified as Hazard Class 3 Packaging Group II by the U.S. DOT (CPA 2018b). The confidence in the score is high as it is based on measured data and an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:* U.S. DOT Hazard Class 3 Packaging Group II.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - Cyclopentyl methyl ether has a flash point was < 3°C when tested with a closed cup method (EU Method A.9, GLP-compliant). As the boiling point is 107°C, authors concluded the test substance is a highly flammable liquid and meets the criteria for GHS Category 2 classification (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).
  - Cyclopentyl methyl ether has an auto-ignition temperature of 185.5°C (EU Method A.15, GLP-compliant) (Klimisch Score 1, reliable without restriction) (Unnamed 2003 study report, 001 Key).
  - A pyrophoric study is waived for cyclopentyl methyl ether as it is stable in the air at room temperature for prolonged periods.

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

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

As shown in Table 5, Type I (input data) uncertainties in cyclopentyl methyl ether's NAMs dataset include lack of or limited experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of validated test methods for respiratory sensitization. Cyclopentyl methyl ether's Type II (extrapolation output) uncertainties include the lack of defined applicability domains in some modeling programs, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, and the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without accounting for non-immunologic mechanisms of respiratory sensitization. Some of cyclopentyl methyl ether's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** Only limited *in vivo* data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). **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 system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 490) cannot reliably detect aneugens, and the exogenous metabolic activation system does not entirely mirror *in vivo*

[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).

[11] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

	metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells)[12]. The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[13]. **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	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301C Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[12] https://www.oecd-ilibrary.org/docserver/9789264264908-en.pdf?expires=1622037214&id=id&accname=guest&checksum=F0669770FC98B49A32E3AFBA1A4D86F5
[13] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

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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 Cyclopentyl Methyl Ether (CAS #5614-37-9)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

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	**Cyclopentyl methyl ether**	**5614-37-9**	*L*	**L**	*M*	*M*	DG	**M**	**L**	*L*	*M*	*L*	**L**	*L*	**H**	**H**	**M**	**M**	*M*	**vL**	*L*	**H**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Cyclopentyl methyl ether	2

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

Table 6

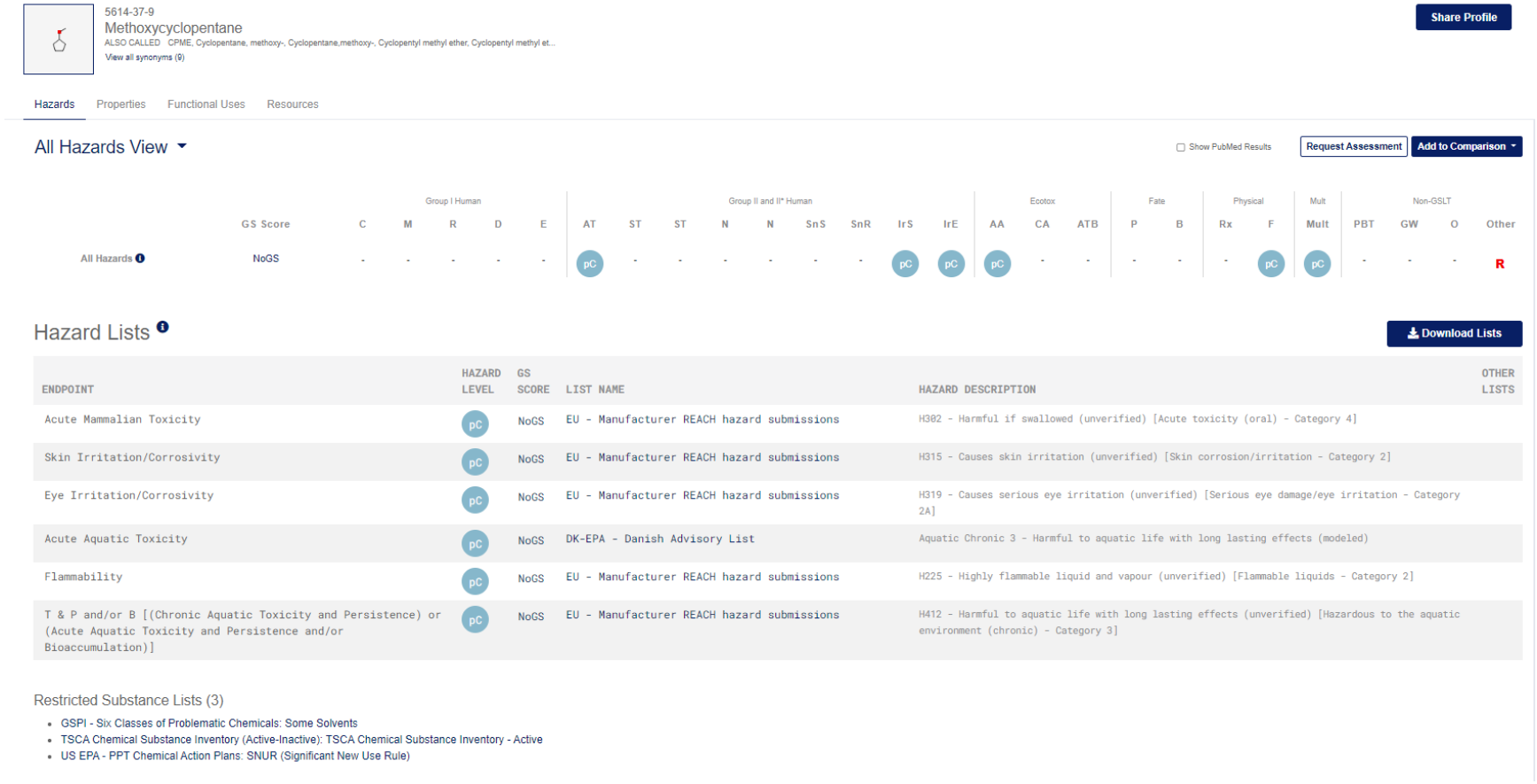
Chemical Name	Final GreenScreen® Benchmark Score
Cyclopentyl methyl ether	2

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 Cyclopentyl Methyl Ether (CAS #5614-37-9)



5614-37-9
Methoxycyclopentane
ALSO CALLED CPME, Cyclopentane, methoxy-, Cyclopentane,methoxy-, Cyclopentyl methyl ether, Cyclopentyl methyl et...
View all synonyms (9)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

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

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) [Acute toxicity (oral) - Category 4]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Acute Aquatic Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Aquatic Chronic 3 - Harmful to aquatic life with long lasting effects (modeled)	
Flammability	pC	NoGS	EU - Manufacturer REACH hazard submissions	H225 - Highly flammable liquid and vapour (unverified) [Flammable liquids - Category 2]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]	

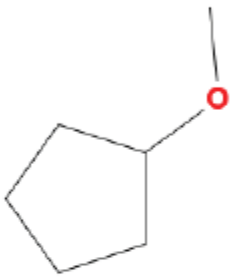
Restricted Substance Lists (3)

- GSPI - Six Classes of Problematic Chemicals: Some Solvents
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active
- US EPA - PPT Chemical Action Plans: SNUR (Significant New Use Rule)

APPENDIX D: VEGA Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9)

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:
- accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

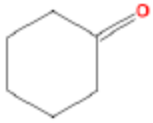
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.125
P(NON-Carcinogen): 0.875
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 109-99-9
Dataset id: 733 (Training set)
SMILES: O1CCCC1
Similarity: 0.869

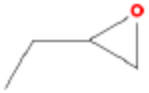
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 108-94-1
Dataset id: 187 (Test set)
SMILES: O=C1CCCCC1
Similarity: 0.859

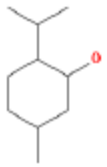
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 106-88-7
Dataset id: 295 (Test set)
SMILES: O1CC1CC
Similarity: 0.851

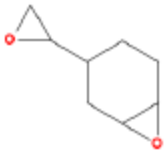
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 89-78-1
Dataset id: 427 (Training set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.81

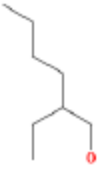
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 106-87-6
Dataset id: 313 (Training set)
SMILES: O1CC1C2CCC3OC3(C2)
Similarity: 0.792

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 104-76-7
Dataset id: 314 (Training set)
SMILES: OCC(CC)CCCC
Similarity: 0.787

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.657
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.864
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.503
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.497
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 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 = 0.749
Explanation: model class assignment is well defined.

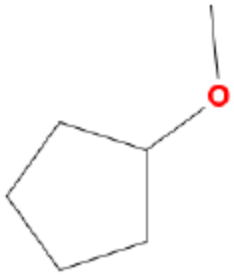
Neural map neurons concordance
Neurons concordance = 1
Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

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 may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

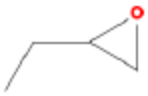
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 109-99-9
Dataset id: 611 (Training set)
SMILES: O1CCCC1
Similarity: 0.869

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

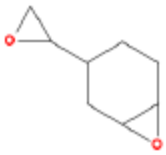


Compound #2

CAS: 106-88-7
Dataset id: 263 (Training set)
SMILES: O1CC1CC
Similarity: 0.851

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA7 Epoxides and aziridines

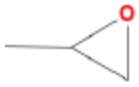


Compound #3

CAS: 106-87-6
Dataset id: 608 (Training set)
SMILES: O1CC1C2CCC3OC3(C2)
Similarity: 0.792

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA7 Epoxides and aziridines

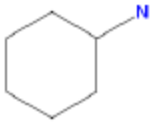


Compound #4

CAS: 75-56-9
Dataset id: 63 (Training set)
SMILES: O1CC1C
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen

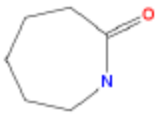
Alerts (not found in the target): SA7 Epoxides and aziridines



Compound #5

CAS: 108-91-8
Dataset id: 834 (Training set)
SMILES: NC1CCCCC1
Similarity: 0.771

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



Compound #6

CAS: 105-60-2
Dataset id: 78 (Training set)
SMILES: O=C1NCCCCC1
Similarity: 0.755

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.86 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.494 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

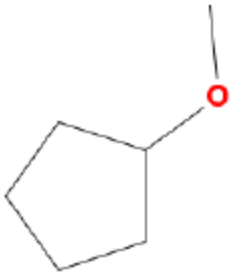
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

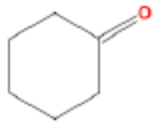
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: N.A.
Dataset id: 737 (Training set)
SMILES: O1CCCC1
Similarity: 0.869

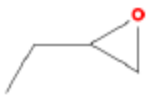
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 187 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.859

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

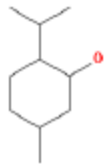


Compound #3

CAS: N.A.
Dataset id: 295 (Training set)
SMILES: O1CC1CC
Similarity: 0.851

Experimental value: Carcinogen
Predicted value: Carcinogen

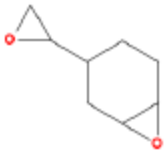
Alerts (not found in the target): Carcinogenity alert no. 105



Compound #4

CAS: N.A.
Dataset id: 427 (Training set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.81

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

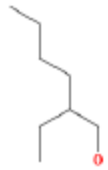


Compound #5

CAS: N.A.
Dataset id: 313 (Training set)
SMILES: O1CC1C2CCC3OC3(C2)
Similarity: 0.792

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 105



Compound #6

CAS: N.A.
Dataset id: 314 (Training set)
SMILES: OCC(CC)CCCC
Similarity: 0.787

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.635 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.859 Explanation: strongly similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.662 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
✗	**Concordance for similar molecules** Concordance index = 0.333 Explanation: 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:

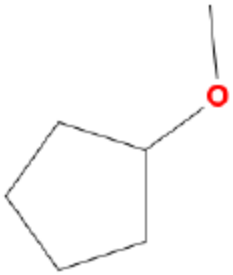
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

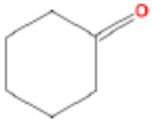
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 109-99-9
Dataset id: 508 (Training set)
SMILES: O1CCCC1
Similarity: 0.869

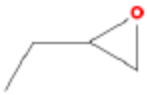
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: 108-94-1
Dataset id: 934 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.859

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

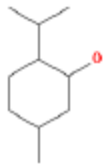


Compound #3

CAS: 106-88-7
Dataset id: 216 (Training set)
SMILES: O1CC1CC
Similarity: 0.851

Experimental value: Carcinogen
Predicted value: Carcinogen

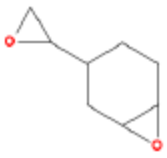
Alerts (not found in the target): Carcinogenity alert no. 23



Compound #4

CAS: 15356-70-4
Dataset id: 654 (Training set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.81

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

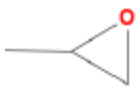


Compound #5

CAS: 106-87-6
Dataset id: 685 (Training set)
SMILES: O1CC1C2CCC3OC3(C2)
Similarity: 0.792

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 29



Compound #6

CAS: 75-56-9
Dataset id: 53 (Training set)
SMILES: O1CC1C
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 23

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.635 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.859 Explanation: strongly similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.662 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
✖	**Concordance for similar molecules** Concordance index = 0.333 Explanation: 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:

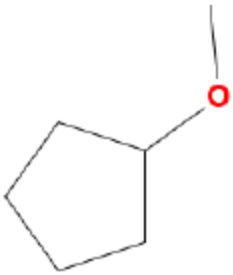
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not adequate

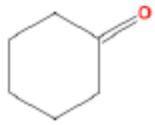
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 109-99-9
Dataset id: 691 (Test set)
SMILES: O1CCCC1
Similarity: 0.869

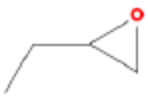
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 108-94-1
Dataset id: 416 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.859

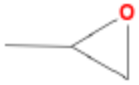
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 106-88-7
Dataset id: 495 (Training set)
SMILES: O1CC1CC
Similarity: 0.851

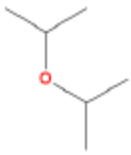
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 75-56-9
Dataset id: 268 (Training set)
SMILES: O1CC1C
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 108-20-3
Dataset id: 459 (Training set)
SMILES: O(C(C)C)C(C)C
Similarity: 0.784

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

Compound #6

CAS: 110-82-7
Dataset id: 415 (Training set)
SMILES: C1CCCCC1
Similarity: 0.771

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.78 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.864 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✗	**Accuracy of prediction for similar molecules** Accuracy index = 0.497 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✓	**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:

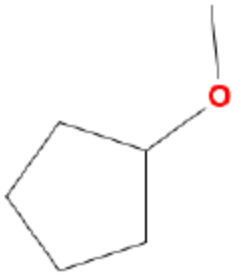
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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.

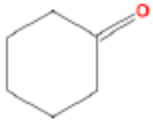
Compound: Molecule 0
Compound SMILES: O(C)C1CCCC1
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 109-99-9
Dataset id: 686 (Training set)
SMILES: O1CCCC1
Similarity: 0.869

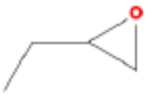
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 108-94-1
Dataset id: 379 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.859

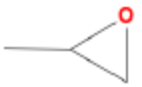
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 106-88-7
Dataset id: 467 (Training set)
SMILES: O1CC1CC
Similarity: 0.851

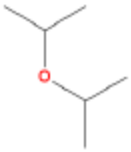
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 75-56-9
Dataset id: 228 (Training set)
SMILES: O1CC1C
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 108-20-3
Dataset id: 426 (Training set)
SMILES: O(C(C)C)C(C)C
Similarity: 0.784

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

Compound #6

CAS: 110-82-7
Dataset id: 377 (Training set)
SMILES: C1CCCCC1
Similarity: 0.771

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.929
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.864
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.

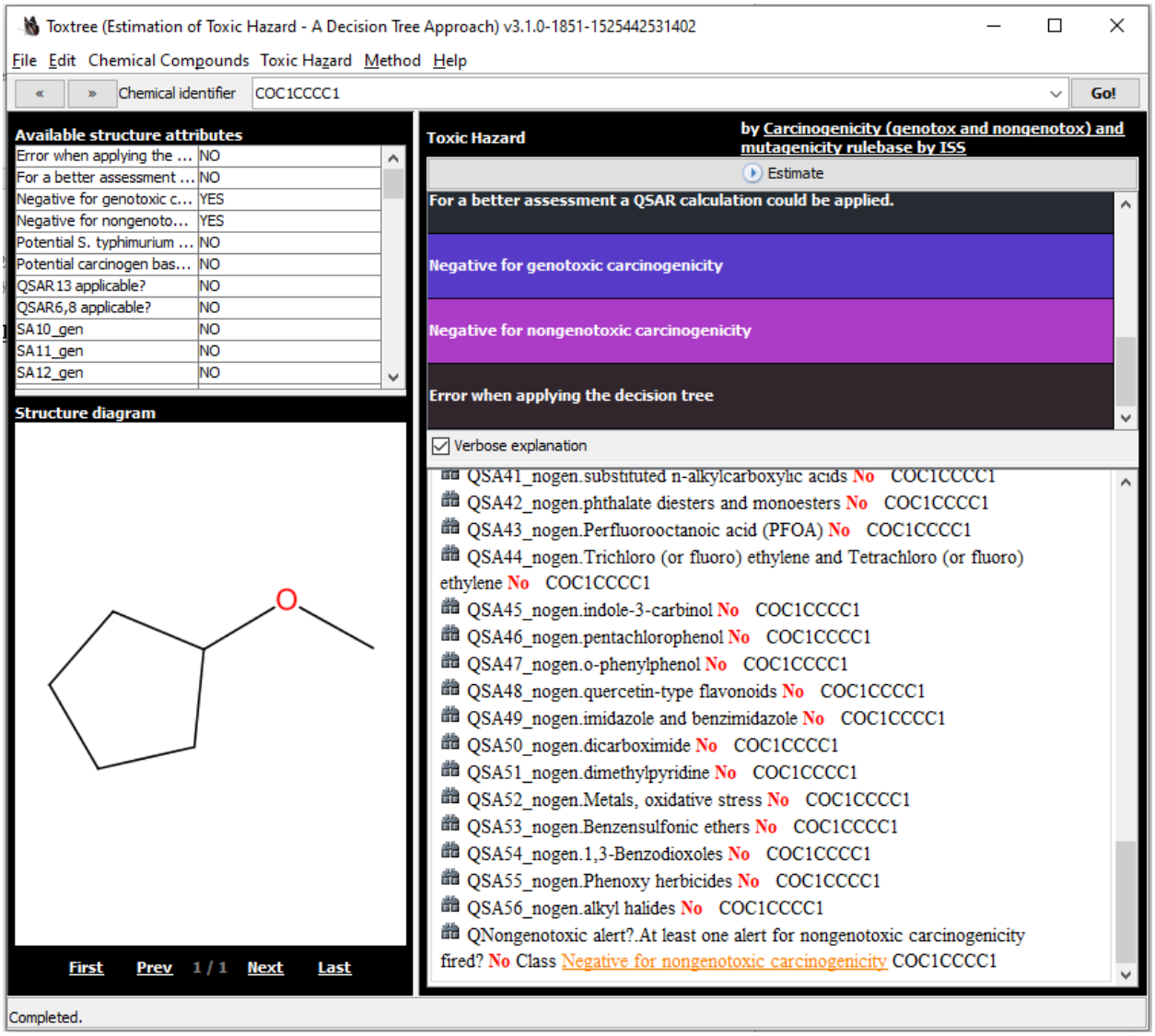
Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

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: Toxtree Carcinogencity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9)



APPENDIX F: Danish QSAR Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9)

Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:
- parent only
Oncologic Primary Classification, alerts in:
- parent only

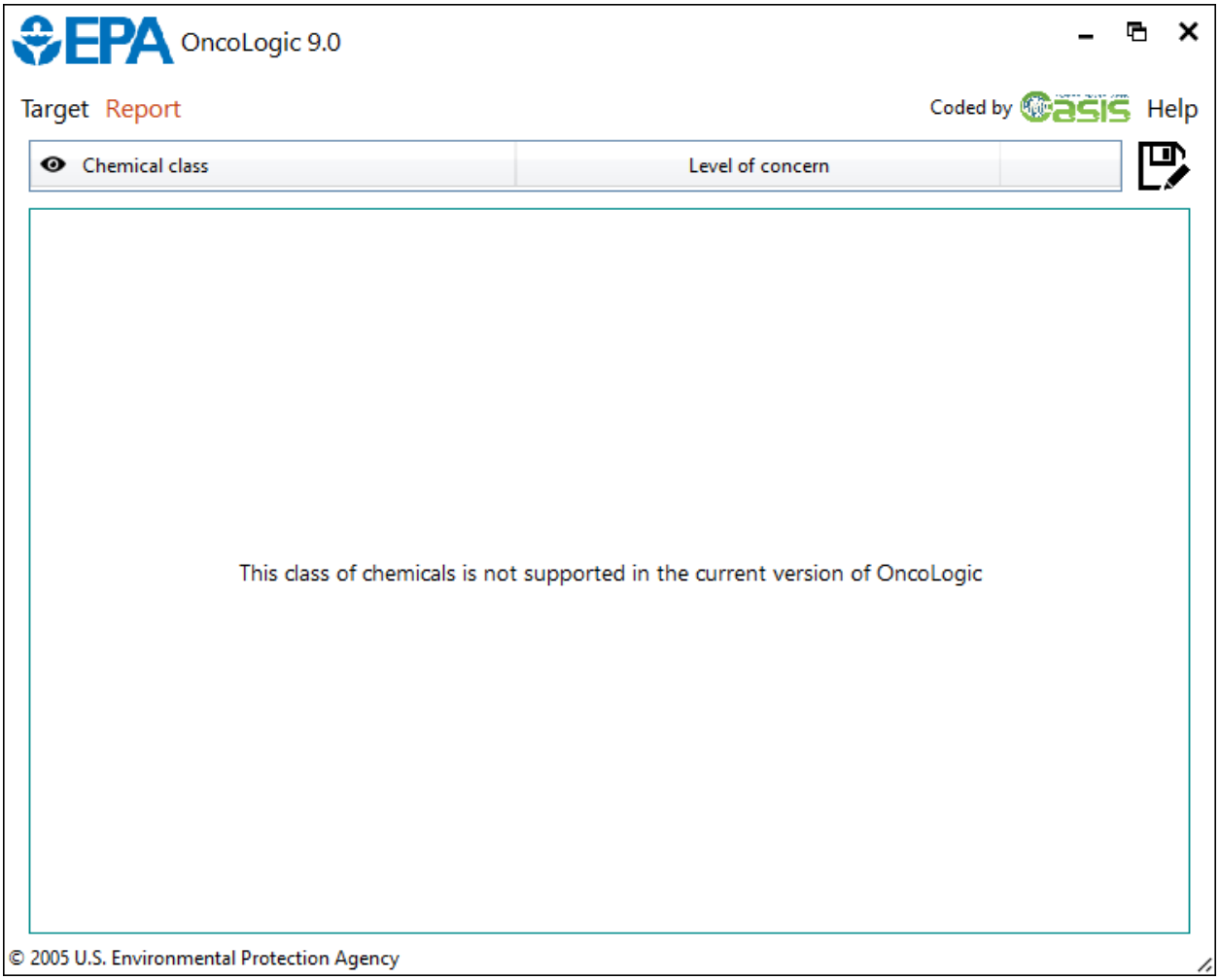
OECD QSAR Toolbox v.4.2 profilers

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

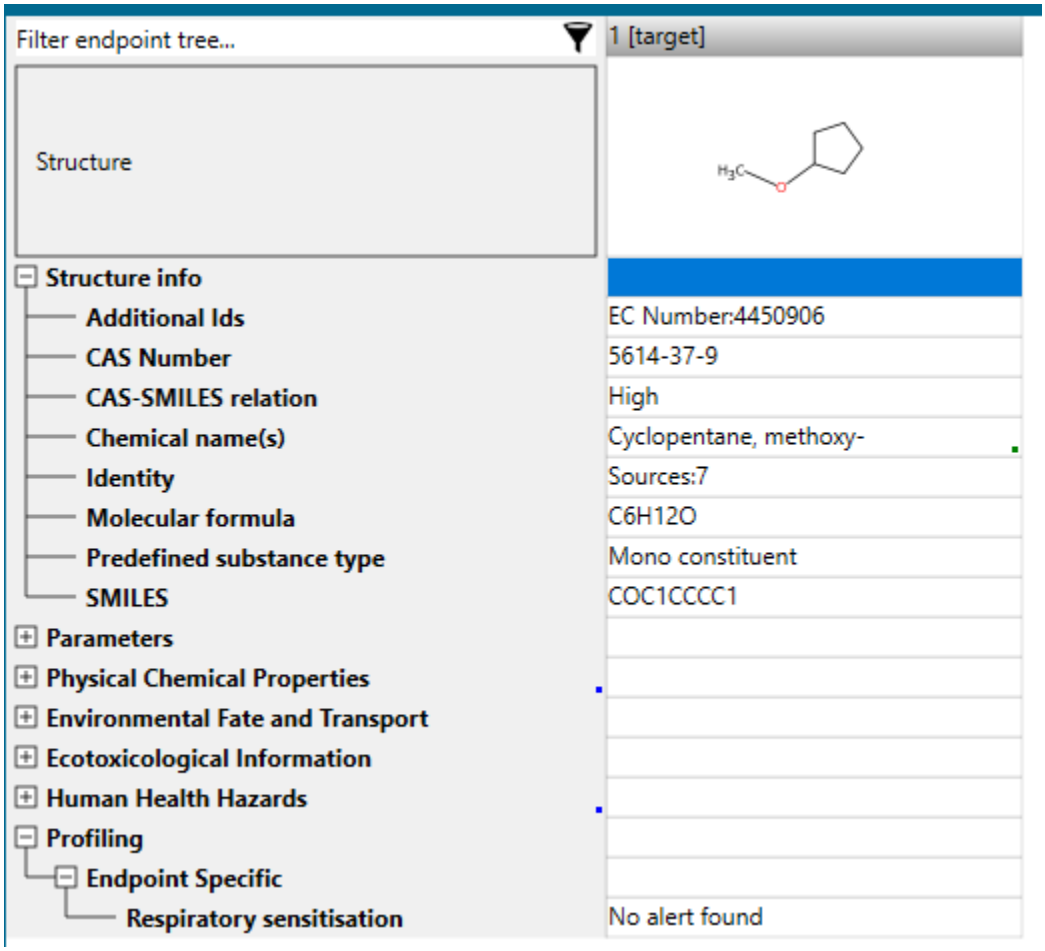
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_OUT	NEG_IN	NEG_OUT	INC_OUT

DTU-developed models

APPENDIX G: OncoLogic Carcinogenicity Results for Cyclopentyl Methyl Ether (CAS #5614-37-9)



APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Cyclopentyl Methyl Ether (CAS #5614-37-9)



Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:4450906
CAS Number	5614-37-9
CAS-SMILES relation	High
Chemical name(s)	Cyclopentane, methoxy-
Identity	Sources:7
Molecular formula	C6H12O
Predefined substance type	Mono constituent
SMILES	COC1CCCC1
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Endpoint Specific	
Respiratory sensitisation	No alert found

APPENDIX I: EPI Suite™ Modeling Results for Cyclopentyl methyl ether (CAS #5614-37-9)

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

CAS Number:
SMILES : C1(OC)CCCC1
CHEM :
MOL FOR: C6 H12 O1
MOL WT : 100.16
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 1.60
Boiling Point (deg C) : 107.00
Melting Point (deg C) : -25.00
Vapor Pressure (mm Hg) : 32.03
Water Solubility (mg/L): 12500
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.85

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 105.57 (Adapted Stein & Brown method)
Melting Pt (deg C): -67.34 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 32.4 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 4.31E+003 (Mean VP of Antoine & Grain methods)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 6969
log Kow used: 1.60 (user entered)
melt pt used: -25.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 22459 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.18E-003 atm-m3/mole (1.20E+002 Pa-m3/mole)
Group Method: 3.62E-004 atm-m3/mole (3.67E+001 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: 3.377E-004 atm-m3/mole (3.422E+001 Pa-m3/mole)
VP: 32 mm Hg (source: User-Entered)
WS: 1.25E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.60 (user entered)
Log Kaw used: -1.317 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 2.917
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.3525
Biowin2 (Non-Linear Model) : 0.1367
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.9692 (weeks)
Biowin4 (Primary Survey Model) : 3.6935 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4901
Biowin6 (MITI Non-Linear Model): 0.6164
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.0587
Ready Biodegradability Prediction: NO

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 4.27E+003 Pa (32 mm Hg)
Log Koa (Koawin est): 2.917
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 7.03E-010
Octanol/air (Koa) model: 2.03E-010
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 2.54E-008
Mackay model : 5.62E-008
Octanol/air (Koa) model: 1.62E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 15.9053 E-12 cm3/molecule-sec
Half-Life = 0.672 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 8.070 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
4.08E-008 (Junge-Pankow, Mackay avg)
1.62E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 32.9 L/kg (MCI method)
Log Koc: 1.517 (MCI method)
Koc : 52.42 L/kg (Kow method)

Log Koc: 1.720 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.723 (BCF = 5.281 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.6827 days (HL = 0.2076 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.657 (BCF = 4.538)
Log BAF Arnot-Gobas method (upper trophic) = 0.657 (BAF = 4.538)
log Kow used: 1.60 (user entered)

Volatilization from Water:
Henry LC: 0.000338 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 2.756 hours
Half-Life from Model Lake : 114 hours (4.749 days)

Removal In Wastewater Treatment:
Total removal: 15.17 percent
Total biodegradation: 0.08 percent
Total sludge adsorption: 1.70 percent
Total to Air: 13.39 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**5.16**	**16.1**	**1000**
Water	**36.5**	**360**	**1000**
Soil	**58.2**	**720**	**1000**
Sediment	**0.117**	**3.24e+003**	**0**

Persistence Time: 229 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	5.16	16.1	1000
Water	36.5	360	1000
water	(36.5)		
biota	(7.26e-005)		
suspended sediment	(0.0018)		
Soil	58.2	720	1000
Sediment	0.117	3.24e+003	0

Persistence Time: 229 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.32	16.1	1000

Water 43.2 360 1000
water (43.2)
biota (8.61e-005)
suspended sediment (0.00106)
Soil 50.3 720 1000
Sediment 0.109 3.24e+003 0
Persistence Time: 196 hr

APPENDIX J: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for cyclopentyl methyl ether. The original GreenScreen® assessment was performed in 2023 under version 1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score.

Table 5: Change in GreenScreen® Benchmark™ for Cyclopentyl Methyl Ether

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
January 25, 2023	BM-2	v. 1.4	New assessment

Licensed GreenScreen® Profilers

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