2-METHYLTETRAHYDROFURAN (2-MeTHF)

(CAS #96-47-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 17, 2023

Expiration Date: April 17, 2028

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GreenScreen® Executive Summary for 2-Methyltetrahydrofuran (2-MeTHF) (CAS #96-47-9)

2-Methyltetrahydrofuran is used as a solvent and reactant in chemical production, solvent for organometallic reagents, and component of gasoline alternatives. It is a clear, colorless liquid that is nonreactive but is flammable. Based on its vapor pressure of 97.3 mm Hg at 25°C and its boiling point of 78°C, it is a volatile organic compound (VOC).

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

- Benchmark 2e
  - Moderate Group I Human Health Hazards (carcinogenicity-C, reproductive toxicity-R, developmental toxicity-D)
- Benchmark 2f
  - Very High Group II Human Health Hazard (eye irritation-IrE)
- 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), 2-methyltetrahydrofuran meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if 2-methyltetrahydrofuran 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 biodegradation, and bioaccumulation; *in vitro* assays for genotoxicity, endocrine activity, and skin irritation; and an *ex vivo* assay for eye irritation. 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 2-methyltetrahydrofuran's NAMs dataset include no or insufficient experimental data for carcinogenicity, respiratory sensitization, endocrine activity, skin irritation, eye irritation, and bioaccumulation, and lack of established test methods for respiratory sensitization. 2-Methyltetrahydrofuran's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of Oncologic to evaluate 2-methyltetrahydrofuran's carcinogenic potential, the inconsistency of experimental results for training set chemicals in the VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in vitro* testing of receptor binding, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the combination of OECD Guideline 431/439 *in vitro* skin irritation tests not allowing for identification of mild skin irritants (GHS Category 3 skin irritants). Some of 2-methyltetrahydrofuran's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for 2-Methyltetrahydrofuran

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	**M**	**M**	DG	*M*		**L**	*M*	**L**	**L**	*L*	*H*	**vH**	**L**	*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 2-Methyltetrahydrofuran (CAS #96-47-9)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: March 28, 2023

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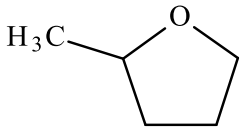
Date: April 17, 2023

Expiration Date: April 17, 2028[2]

Chemical Name: 2-Methyltetrahydrofuran

CAS Number: 96-47-9

Chemical Structure(s):



Also called: 25265-68-3; 202-507-4; 2-Methyltetrahydrofuran; 2-Methyloxolane; Furan, 2-methyl-tetrahydro-; Furan, tetrahydro-2-methyl-; Methyltetrahydrofuran; Tetrahydro-2-methylfuran; Tetrahydrosylvan; 2-Methyl tetrahydrofuran; Furan, tetrahydromethyl-; MTHF; 2-MeTHF; Methyl tetrahydrofuran; (R)-2-methyltetrahydrofuran; 2-Methyl-tetrahydrofuran; 2-Methyl-tetrahydro-furan; Tetrahydrosilvan; 2-Methylfuranidine; MeTHF; UN2536; Methyl-tetrahydrofuran; Me-THF; 2-Methyletrahydrofuran; Methyl tetrahydrofurane; 2-Methyltetrahydrofuran; 2-Methyltetrahydrofurane; 2-Methyl tetrahydrofurane; 2-Methyl-tetrahydrofurane; Tetrahydrofuran, 2-methyl-; (2S)-2-Methyltetrahydrofuran; 2-Methyltetrahydrofuran [MI]; (+/-)-2-Methyltetrahydrofuran; 4-Amino-chroman-8-carboxylicacidmethylesterhydrochloride (PubChem 2023).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Due to the lack of measured carcinogenicity and inhalation developmental toxicity data for 2-methyltetrahydrofuran and conflicting results for similar chemicals in the VEGA carcinogenicity models (VEGA 2021), ToxServices included carcinogenicity data for tetrahydrofuran (CAS #109-99-9) in a weight of evidence approach. 2-Methyltetrahydrofuran and tetrahydrofuran have a high degree of structural similarity, differing only by a methyl group, as demonstrated by a maximum common substructure (MCS) Tanimoto coefficient of 0.8333 (ChemMine 2023).

[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).

Surrogate: Tetrahydrofuran (CAS #109-99-9)

Identify Applications/Functional Uses (Haz-Map 2023)**:**
1. Solvent and reactant in chemical production
2. Solvent for organometallic reagents
3. Component of gasoline alternatives

Known Impurities[3]:
2-Methyltetrahydrofuran may contain low levels of furan (CAS#110-00-9) and 2-methylfuran (CAS #534-22-5) (EFSA 2022). The screen is performed on the theoretical pure substance.

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

- Benchmark 2e
  - Moderate Group I Human Health Hazards (carcinogenicity-C, reproductive toxicity-R, developmental toxicity-D)
- Benchmark 2f
  - Very High Group II Human Health Hazard (eye irritation-IrE)
- Benchmark 2g
  - High Flammability

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), 2-methyltetrahydrofuran meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if 2-methyltetrahydrofuran 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 2-Methyltetrahydrofuran

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

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

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

2-Methyltetrahydrofuran was not readily biodegradable under the conditions of an OECD Guideline 301D/EU Method C.4-E (closed bottle test) ready biodegradability test (ECHA, CAS #96-47-9, 2023). ToxServices attempted to identify potential hydrolysis products of 2-methyltetrahydrofuran using OECD QSAR Toolbox (OECD 2022) but no hydrolysis products were identified under acidic, basic, or neutral conditions. Therefore, ToxServices concludes that 2-methyltetrahydrofuran's Benchmark™ Score is not modified by transformation products.

Introduction

2-Methyltetrahydrofuran functions as a solvent and reactant in chemical production, solvent for organometallic reagents, and component of gasoline alternatives (Haz-Map 2023). It is produced from hemicelluloses (PubChem 2023).

ToxServices assessed 2-methyltetrahydrofuran against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2023a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

2-Methyltetrahydrofuran is not listed on the U.S. EPA's 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 2-methyltetrahydrofuran can be found in Appendix C.

- 2-Methyltetrahydrofuran is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 2-Methyltetrahydrofuran (UN2536) is listed on the U.S. DOT list as a Hazard Class 3 chemical ("Flammable Liquid"), Packing Group II.
- 2-Methyltetrahydrofuran is on the following list for multiple endpoints:

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

  - German FEA - Substances Hazardous to Waters - Class 2 - Hazard to Waters
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements identified for 2-methyltetrahydrofuran based on the REACH dossier authors' self-classifications (ECHA, CAS #96-47-9, 2023) are indicated 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 2-Methyltetrahydrofuran (CAS #96-47-9) (ECHA, CAS #96-47-9, 2023)

H Statement	H Statement Details
H225	Highly flammable liquid and vapour
H302	Harmful if swallowed
H315	Causes skin irritation
H318	Causes serious eye damage

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for 2-Methyltetrahydrofuran (CAS #96-47-9)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, safety eyewear, protective clothing, air-purifying or air-fed respirator	ECHA, CAS #96-47-9, 2023	None identified	N/A

Physicochemical Properties of 2-Methyltetrahydrofuran

2-Methyltetrahydrofuran is a clear, colorless liquid under standard temperature and pressure. It is volatile based on its vapor pressure of 97.3 mm Hg, indicating it exists as a liquid-vapor mixture. It is very soluble in water (140,000 mg/L), but is slightly more soluble in octanol than in water (log K_{ow} = 1.85).

Table 3: Physical and Chemical Properties of 2-Methyltetrahydrofuran (CAS #96-47-9)

Property	Value	Reference
Molecular formula	$C_5H_{10}O$	PubChem 2023
SMILES Notation	CC1CCCO1	PubChem 2023
Molecular weight	86.13 g/mol	PubChem 2023
Physical state	Liquid	ECHA, CAS #96-47-9, 2023
Appearance	Clear, colorless	ECHA, CAS #96-47-9, 2023
Melting point	< - 20°C (OECD Guideline 102) (measured)	ECHA, CAS #96-47-9, 2023
Boiling point	78°C (measured)	ECHA, CAS #96-47-9, 2023
Vapor pressure	97.3 mm Hg at 25°C (measured)	PubChem 2022
Water solubility	140,000 mg/L (measured)	ECHA, CAS #96-47-9, 2023
Dissociation constant	Not relevant	ECHA, CAS #96-47-9, 2023
Density/specific gravity	0.855 at 20°C (measured)	ECHA, CAS #96-47-9, 2023

Table 3: Physical and Chemical Properties of 2-Methyltetrahydrofuran (CAS #96-47-9)		
Property	**Value**	**Reference**
Partition coefficient	Log K_{ow} = 1.85 at 25°C (measured)	EFSA 2022

Toxicokinetics

- *Absorption*
  - 2-Methyltetrahydrofuran (99% non-radiolabeled purity, 93-98% radiochemical purity) was almost completely absorbed (93-100%) from the gastrointestinal tracts of F344 rats and B6C3F1 mice following gavage dosing at 1, 10, or 100 mg/kg in water or intravenously at 1 mg/kg in 0.9% saline (EFSA 2022, ECHA, CAS #96-47-9, 2023).
- *Distribution*
  - In the rats and mice studies mentioned above, 2-methyltetrahydrofuran didn't preferentially accumulate in any specific organs, although the highest amounts of radioactivity was detected in the kidneys and liver following oral and intravenous dosing, respectively (EFSA 2022, ECHA, CAS #96-47-9, 2023).
- *Metabolism*
  - High performance liquid chromatography (HPLC) radio-chromatograms identified two polar compounds in rat urine and three highly polar compounds in mouse urine, with similar profiles following oral and intravenous dosing. The polar metabolites were not identified, but they eluted prior to the parent 2-methyltetrahydrofuran, suggesting they were more polar (EFSA 2022, ECHA, CAS #96-47-9, 2023).
- *Excretion*
  - For all three doses administered, 2-methyltetrahydrofuran was primarily eliminated in the urine from mice, followed by exhaled carbon dioxide (CO_2) and VOC. In rats, the dominant elimination route was exhaled CO_2 followed by urinary excretion. For both species, the degree of elimination via exhaled VOC increased with dose, from 1-5% at lower doses to 15% and 27% in mice and rats, respectively, at the 100 mg/kg dose. Exhalation of the parent compound accounted for the majority of this increase. In mice and rats, fecal excretion was not a significant route of elimination. After 72 hours, only < 8% or 8-22% of radioactivity administered remained in the body of mice and rats, respectively (EFSA 2022, ECHA, CAS #96-47-9, 2023).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

2-Methyltetrahydrofuran was assigned a score of Moderate for carcinogenicity based on ToxServices classifying it as a Category 2 carcinogen under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when they are classified as GHS Category 2 carcinogens or when there is limited or marginal evidence of carcinogenicity in animals (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1998

  - *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a chronic carcinogenicity study, F344 rats (50/sex/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (~99% purity) at 0, 200, 600, or 1,800 ppm for 6 hours/day, 5 days/week, for 105 weeks. Treatment increased the incidence of renal tubular neoplasms in male rats, including two rare carcinomas. Female rats did not exhibit treatment-related increases in tumor incidence. The National Toxicology Program (NTP) concluded that there was some evidence of carcinogenic activity in male rats and no evidence of carcinogenic activity in female rats.
  - *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a chronic carcinogenicity study, B6C3F1 mice (50/sex/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (~99% purity) at 0, 200, 600, or 1,800 ppm for 6 hours/day, 5 days/week, for 105 weeks. Treatment significantly increased the incidences and multiplicity of hepatocellular neoplasms in high concentration female mice. Treatment significantly increased the incidence of non-neoplastic urogenital tract lesions in male mice, but did not increase the incidence of hepatocellular neoplasms in males. The NTP concluded that there was clear evidence of carcinogenic activity in female mice and no evidence of carcinogenic activity in male mice.
- Pharos 2023
  - *Surrogate: Tetrahydrofuran (CAS #109-99-9):* Tetrahydrofuran has a harmonized GHS Category 2 (suspected human carcinogen) classification in the European Union (EU). The International Agency for Research on Cancer (IARC) classified tetrahydrofuran to Group 2B (possibly carcinogenic to humans). United States Environmental Protection Agency (U.S. EPA) classified it as having suggestive evidence of carcinogenic potential. German MAK classified it to Carcinogen Group 4 (non-genotoxic carcinogen with low risk under MAK/BAT levels).
- Toxtree 2018
  - 2-Methyltetrahydrofuran does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity as identified with Toxtree v3.1.0 (Appendix D).
- VEGA 2021
  - ToxServices predicted the carcinogenicity potential of 2-methyltetrahydrofuran using the following six VEGA v1.1.5 models: CAESAR v2.1.9, ISS v.1.0.2, IRFMN/Antares v1.0.0, IRFMN/ISSCAN-CGX v1.0.0, and the IRFMN oral and inhalation classification v1.0.0 models. If an external compound is beyond the defined scope of a given model, it is considered outside that model's Applicability Domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index range from 0 (worst case) to 1 (best case). Generally, AD index values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
  - 2-Methyltetrahydrofuran is outside of the AD for the ISS, IRFMN/Antares, IRFMN/ISSCAN-CGX, and IRFMN oral classification models. Therefore, the results of these models are not incorporated into ToxServices' weight of the evidence evaluation.
  - 2-Methyltetrahydrofuran is within the AD of the CAESAR model (global AD index = 0.959) and the model predicts that it is a carcinogen. The similarity index of 0.919 and accuracy and concordance indices of 1.0 support the use of this model. The similar compounds identified by the model include tetrahydrofuran (CAS #109-99-9), which has a prediction of carcinogen that matches the experimental value. Therefore, ToxServices concludes the prediction for the CAESAR model is acceptable (Appendix E).
  - 2-Methyltetrahydrofuran is also within the AD of the IRFMN inhalation classification (global AD index = 0.959) and the model predicts that it is a carcinogen. The similarity

index of 0.919 and accuracy and concordance indices of 1.0 support the use of this model. The similar compounds identified by the model include tetrahydrofuran (CAS #109-99-9), which has a prediction of non-carcinogen that matches the experimental value. ToxServices notes that the experimental results for the surrogate tetrahydrofuran presented in the IRFMN inhalation classification model training set conflict with the NTP (1998) results discussed above and those presented in the training set for the CAESAR model. Therefore, ToxServices concludes the prediction for the IRFMN inhalation classification model is not acceptable (Appendix E).

- U.S. EPA 2019, 2021
    - ToxServices attempted to evaluate the carcinogenic potential of 2-methyltetrahydrofuran using Oncologic™ v9.0 (U.S. EPA 2021). However, the class of chemicals 2-methyltetrahydrofuran belongs to is not supported by the current version of the software (Appendix F). Additionally, 2-methyltetrahydrofuran does not belong to the organic chemical classes included in Oncologic™ v8.0 (U.S. EPA 2019). Therefore, ToxServices could not use Oncologic™ to determine the carcinogenic potential of 2-methyltetrahydrofuran.
- DTU 2023
    - 2-Methyltetrahydrofuran is inside the applicability domains of all seven E Ultra FDA RCA carcinogenicity models included in the Danish (Q)SAR Models, and is predicted to be negative for carcinogenicity in male rats, female rats, rats, male mice, female mice, mice, and rodents. It is outside of the applicability domains of all seven Leadscope FDA RCA carcinogenicity models included in the Danish (Q)SAR Models. Finally, 2-methyltetrahydrofuran is outside of the applicability domain for the model battery of liver-specific cancer models in mice or rats, but has a negative in domain prediction from the CASE Ultra model (DTU 2022) (Appendix G).
- In summary, the surrogate tetrahydrofuran is classified as a carcinogen by the EU and IARC due to increased incidences of renal tumors in male rats and liver tumors in female mice following chronic inhalation exposures. While 2-methyltetrahydrofuran does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity, and the results of modeling presented in the Danish QSAR modeling database indicate that it has a low carcinogenic potential in rodents, the VEGA CAESAR model predicts that it is carcinogenic in part due to data available for the surrogate tetrahydrofuran. Due to the high degree of structural similarity between 2-methyltetrahydrofuran and tetrahydrofuran and the availability of chronic carcinogenicity data for tetrahydrofuran demonstrating carcinogenic effects in male rats and female mice via the inhalation route, ToxServices classified 2-methyltetrahydrofuran as a Category 2 carcinogen (H351) under GHS criteria (UN 2021). Chemicals are classified as Category 2 carcinogens when there is "limited evidence of carcinogenicity in animal studies."

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

2-Methyltetrahydrofuran was assigned a score of Low for mutagenicity/genotoxicity based on negative mutagenicity and clastogenicity results in a battery of *in vitro* assays and an *in vivo* micronucleus test. 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 reliable measured data on the target chemical.

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

- ECHA, CAS #96-47-9, 2023
    - An *in vitro* mammalian cell gene mutation assay conducted in a manner similar to OECD Guideline 476 (GLP status not specified) was performed with mouse lymphoma L5178Y cells exposed to 2-methyltetrahydrofuran (purity not specified) in water at 1,500-5,000 µg/mL with and without exogenous metabolic activation (liver S9 from Aroclor-induced rats). Treatment did not produce cytotoxicity and the test substance did not precipitate out of solution, but 2-methyltetrahydrofuran was evaluated up to the recommended concentration limit. Treatment did not increase the mutation frequency in the absence of metabolic activation, and a concentration-related increase was not detected in the presence of metabolic activation. The vehicle and positive (ethyltmethanesulphonate or methyltmethanesulphonate, 3-methylcholanthrene or dimethylgenz[a]-anthracene) controls were reported as valid. The authors concluded that 2-methyltetrahydrofuran was not mutagenic under the tested conditions. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Seifried et al. 2006, 001 Key). Note that the numbering of studies may change over time in ECHA dossiers.
    - A bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471 (GLP status not specified) was performed with *Salmonella typhimurium* tester strains TA1535, TA1537, TA98, TA100, and TA102 exposed to 2-methyltetrahydrofuran (purity not specified) in dimethyl sulfoxide (DMSO) at 10-10,000 µg/plate with and without exogenous metabolic activation (rat and hamster liver S9). Treatment did not produce cytotoxicity and the test substance did not precipitate out of solution, but 2-methyltetrahydrofuran was evaluated up to the recommended concentration limit. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive (not specified) controls were reported as valid. The authors concluded that 2-methyltetrahydrofuran was not mutagenic under the tested conditions. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Seifried et al. 2006, 002 Key).
    - A GLP-compliant bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471 was performed with *S. typhimurium* tester strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP_2 exposed to 2-methyltetrahydrofuran (purity not specified) at ≤ 5,490 µg/plate with and without exogenous metabolic activation (not specified). Treatment did not produce cytotoxicity and the test substance did not precipitate out of solution, but 2-methyltetrahydrofuran was evaluated up to the recommended concentration limit. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The positive control ("standard control substances") were reported as confirming the "sensitivity of test system and activity of S9 mix." The authors concluded that 2-methyltetrahydrofuran was not mutagenic under the tested conditions. The REACH dossier reported this study with a reliability score of 4 (not assignable) because only a publication was available for review that did not include full study details (Unnamed study 2011, 003 Supporting). ToxServices included this study in this evaluation because the key pieces of information facilitating hazard classification were reported.
    - An *in vitro* chromosome aberration assay conducted in a manner similar to OECD Guideline 473 (GLP status not specified) was performed with human peripheral lymphocytes exposed to 2-methyltetrahydrofuran (purity not specified) at ≤ 10.7 mM with and without exogenous metabolic activation (not specified). Treatment did not produce cytotoxicity and the test substance did not precipitate out of solution, but 2-methyltetrahydrofuran was evaluated up to the recommended concentration limit. Treatment did not increase the frequency of chromosome aberrations in the presence or absence of metabolic activation. The results for

the positive controls (mitomycin C, 4-nitroquinoline-N-oxide, cyclophosphamide) were not provided. The authors concluded that 2-methyltetrahydrofuran was not clastogenic under the tested conditions. The REACH dossier reported this study with a reliability score of 4 (not assignable) because only a publication was available for review that did not include full study details (Antonucci et al. 2011, 004 Weight of Evidence). ToxServices included this study in this evaluation because the key pieces of information facilitating hazard classification were reported.

  - A GLP-compliant *in vivo* micronucleus assay conducted in a manner similar to OECD Guideline 474 was performed with rats (strain not specified, 5/sex/group) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) at ≤ 26 mg/kg/day daily for three months. At the end of the exposure period, the animals were sacrificed and bone marrow samples were isolated for the micronucleus assessment. Treatment did not increase the frequency of micronuclei or affect the proportion of polychromatic erythrocytes among normochromatic erythrocytes (NCE). The results for the positive control (mitomycin C) were not provided. The authors concluded that 2-methyltetrahydrofuran was not clastogenic under the tested conditions. The REACH dossier reported this study with a reliability score of 4 (not assignable) because only a publication was available for review that did not include full study details (Unnamed study 2011). ToxServices included this study in this evaluation because the key pieces of information facilitating hazard classification were reported.

- EFSA 2022
  - The European Food Safety Authority (EFSA) concluded "[2-methyltetrahydrofuran] does not raise a concern for genotoxicity".

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

2-Methyltetrahydrofuran was assigned a score of Moderate for reproductive toxicity based on ToxServices classifying it as a Category 2 reproductive toxicant under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when they are classified as GHS Category 2 reproductive toxicants or when they produce limited or marginal evidence of reproductive toxicity in animals (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2022, ECHA, CAS #96-47-9, 2023
  - *Oral*: A GLP-compliant, OECD Guideline 443 extended one-generation reproductive toxicity study was performed with Sprague-Dawley rats (20/sex/group) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) in water at 0, 100, 250, or 625 mg/kg/day. The exposure duration was not provided. A total of five cohorts (1A, 1B, 2A, 2B, and 3) of offspring were produced. P generation animals were evaluated for clinical signs of toxicity, body weight, food consumption, estrous cycle, and reproductive performance. Treatment did not adversely affect P generation body weights, food consumption, sperm parameters, estrous cyclicity, mating or fertility indices, duration of gestation, or the number of implantation sites. Females in all groups, including controls, exhibited an increased incidence of dystocia (difficult labor) relative to historical controls. In the high dose group, treatment increased post-implantation loss (20.3% vs. 13.9% for controls) and decreased the live birth index (76.6% vs. 95.5% for controls) and the mean number of live pups on day 1 (9.5 vs. 12.1 for controls). The live birth index for the mid dose group (85.8%) was not statistically significantly different from the concurrent control

group value (95.5%) but was statistically significantly less than the historical control value (98.6%). For cohorts 1A and 1B, females dosed with 250 mg/k/day exhibited decreased fertility indices (68.4% vs. 100% for controls) but did not have decreased live birth indices as detected in the P generation at this dose. Treatment did not adversely affect estrous cyclicity, sexual development, or mating in cohorts 1A and 1B. The authors identified a reproductive toxicity NOAEL of 100 mg/kg/day based on the decreased live birth indices at ≥ 250 mg/kg/day. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2020).

- Based on decreased live birth indices at ≥ 250 mg/kg/day and increased post-implantation loss at 625 mg/kg/day identified in rats as part of an extended one-generation reproductive toxicity study, ToxServices classified 2-methyltetrahydrofuran as a Category 2 (H361f) oral reproductive toxicant under GHS criteria (UN 2021). Chemicals are classified as GHS Category 2 reproductive toxicants when they produce "some evidence of an adverse effect on sexual function or fertility" in animal studies.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M
2-Methyltetrahydrofuran was assigned a score of Moderate for developmental toxicity based on ToxServices classifying it as a Category 2 developmental toxicant under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when they are classified as GHS Category 2 developmental toxicants or produce limited or marginal evidence of developmental toxicity in animals (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2022, ECHA, CAS #96-47-9, 2023
  - *Oral*: A GLP-compliant, OECD Guideline 414/EPA OPPTS 870.3700 prenatal developmental toxicity study was performed with pregnant female Sprague-Dawley rats (24/group) administered gavage doses of 2-methyltetrahydrofuran (99.98% purity) in arachis oil at 0, 100, 300, or 1,000 mg/kg/day on gestation days 3-19. Maternal examinations included clinical signs of toxicity, body weight, food and water consumption, ovaries, and uterine content. Fetal examinations included litter size and weight, fetal body weight, sex ratio, number live offspring, and evaluation of external, skeletal, and visceral malformations. Maternal clinical signs of toxicity include salivation post-dosing and/or ploughing behavior in a small number of high dose dams. Treatment slightly but statistically significantly reduced initial body weight gain in the mid and high dose groups but this metric quickly recovered to control levels. High dose dams exhibited an ~11% reduction in overall body weight gain (statistically significant different from controls), which the authors attributed to a significantly decreased gravid uterine weight. Treatment significantly decreased mean fetal weight (4.5% decrease) in the high dose group. The high dose group also exhibited a slightly lower litter weight and total placental weight, although the mean placental weight did not decrease with treatment. Treatment did not affect the incidence of external, visceral, and skeletal malformations, but did increase the frequency of fetuses exhibiting incomplete nasal ossification relative to the concurrent and historical control values in the high dose group. This skeletal variation was also identified in the mid dose group at a rate higher than the historical control group. The authors concluded that 2-methyltetrahydrofuran treatment did not adversely affect offspring survival or development, although it slightly impacted fetal growth at 1,000 mg/kg/day. Due to what the authors term the "equivocal" fetal growth

impacts, they identified maternal and developmental toxicity NOAELs of 1,000 mg/kg/day, the highest dose tested. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2018, 001 Key). ToxServices considered the altered fetal growth to potentially significantly impact peri- and postnatal growth, and identified maternal and developmental toxicity NOAELs of 300 mg/kg/day based on negative impacts at 1,000 mg/kg/day relative to the concurrent control group. This is in agreement with the conclusions of EFSA (2022).

- *Oral*: A GLP-compliant, OECD Guideline 443 extended one-generation reproductive toxicity study was performed with Sprague-Dawley rats (20/sex/group) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) in water at 0, 100, 250, or 625 mg/kg/day. The exposure duration was not provided. A total of five cohorts (1A, 1B, 2A, 2B, and 3) of offspring were produced. Cohort 2 was used to evaluate developmental neurotoxicity and cohort 3 was used to evaluate developmental immunotoxicity. Cohorts 2 and 3 were dosed with 0, 100, or 250 mg/kg/day. In the high dose F1 generation group, treatment reduced the mean litter size at birth (11.5 vs 12.6 for the control group) and increased the rate of cannibalism or pups found dead (71.4% of litter affected vs. 52.6% for the control group). F1 pups in the 250 mg/kg/day group also exhibited an increased rate of cannibalism or pups found dead (73.9% of litter affected vs. 52.6% for the control group). The authors attributed the increased postnatal offspring deaths at ≥ 250 mg/kg/day to insufficient maternal care due to low qualitative body temperatures and absence of milk in the stomach. High dose pups exhibited an increased mean anogenital distance and normalized mean anogenital distance in F1 animals, but the sexual development of these animals was not negatively impacted. Cohort 2 animals did not exhibit treatment-related impacts on neurobehavioral endpoints (motor activity, functional observation battery, or neuro startle tests) or neuro-histopathological findings. Cohort 3 animals did not exhibit treatment-related immunotoxicity (anti-KLH IgM response). Study authors identified a systemic toxicity NOAEL of 250 mg/kg/day in males based on clinical signs of toxicity and 625 mg/kg/day for females based on lack of effects observed. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2020). ToxServices identified a developmental toxicity NOAEL of 100 mg/kg/day based on increased incidences of cannibalism or pups found dead at ≥ 250 mg/kg/day.

- NTP 1998, ECHA, CAS #109-99-9, 2023
  - *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant female Sprague-Dawley rats (approximately 33/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (99.3-100.2% purity) at 0, 600, 1,800, or 5,000 ppm for 6 hours/day, 7 days/week on gestation days 6-19. The animals were sacrificed on gestation day 20. Based on a conversion factor of 1 ppm / 2.95 mg/m^3 (NIOSH 2019), these concentrations are equivalent to 1,770, 5,310, and 14,750 mg/m^3, respectively, and 1.77, 5.31, and 14.75 mg/L, respectively. Maternal evaluations included clinical signs of toxicity, body weight, ovaries, and uterine content. Fetal evaluations included litter and fetal body weights, sex ratio, and incidence of external, visceral, and skeletal malformations. Treatment reduced maternal body weights at the high concentration, but did not adversely affect the number of implantations, the mean percentage of live pups per litter, the mean percentage of resorptions per litter, or the fetal sex ratio. Tetrahydrofuran exposure significantly reduced fetal body weights in the high concentration group, but did not affect the incidence of malformations or variations. Both the NTP and the REACH dossier authors reported a developmental toxicity NOAEC/LOAEC of 1,800/5,000

ppm (5.31/14.75 mg/L) based on effects on fetal body weight. ToxServices identified a material toxicity NOAEC/LOAEC of 1,800/5,000 ppm (equivalent to 5.31/14.75 mg/L) based on reduced maternal body weights in the high concentration group. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1988, 001 Key).

- *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant female CD-1 mice (approximately 33/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (99.3-100.2% purity) at 0, 600, 1,800, or 5,000 ppm for 6 hours/day, 7 days/week on gestation days 6-17. The animals were sacrificed on gestation day 18. Based on a conversion factor of 1 ppm / 2.95 mg/m^3 (NIOSH 2019), these concentrations are equivalent to 1,770, 5,310, and 14,750 mg/m^3, respectively, and 1.77, 5.31, and 14.75 mg/L, respectively. Maternal evaluations included clinical signs of toxicity, body weight, ovaries, and uterine content. Fetal evaluations included litter and fetal body weights, sex ratio, and incidence of external, visceral, and skeletal malformations. Treatment induced narcosis in approximately 30% of mid concentration dams and in all high concentration dams during and for one hour after exposure. Seven dams in this group died during the first six days of exposure, and the remaining animals in this group were removed from exposure after that timepoint. Treatment reduced mean maternal body and uterine weights in the mid and high concentration groups. Inhalation to tetrahydrofuran vapors decreased the number of live fetuses/litter (control, low concentration, mid concentration: 11.9, 11.1, 9.3) and the percent of live fetuses/litter (control, low, mid: 93.1%, 91.2%, 77.4%) and increased the percent of total resorptions/litter (control, low, mid: 6.9%, 8.4%, 22.6%) and percent of early resorptions (control, low, mid: 4.7%, 6.7%, 14.6%). Treatment did not adversely affect fetal body weights or the fetal sex ratio. There was an increased incidence of reduced sternebral ossification that was correlated to exposure but did not reach statistical significance. NTP (1998) reported that results indicate that tetrahydrofuran may be embryotoxic in mice, but that if the fetus survives development continues normally. The NTP and REACH dossier authors identified maternal toxicity and developmental toxicity NOAECs/LOAECs of 600/1,800 ppm (1.77/5.31 mg/L). The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1988, 002 Key).
- *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a prenatal developmental toxicity study (presumed to be GLP-compliant), pregnant Cr1:CD rats (7/dose, 14/control in part 1, 14-24/dose and 8/control in part 2) were administered whole body inhalation exposures to tetrahydrofuran vapor (> 99.9% purity) at 0, 200, 500, 2,500, or 5,000 ppm (part 1) or 0, 1,000, or 5,000 ppm (part 2) for 6 hours/day on gestation days 6-15. The animals were sacrificed on gestation day 21. The concentrations of 0, 200, 500, 1,000, 2,500, and 5,000 ppm were equivalent to 0, 0.6, 1.6, 3.2, 8.0, and 15.9 mg/L, respectively. Treatment decreased body weights, reduced muscle tone, lethargy, and increased incidences of incoordination at 5,000 ppm, and reduced response to a noise stimulus during exposure at 1,000 and 5,000 ppm. In part 1, a preliminary study, treatment did not induce developmental toxicity. In part 2, the main study, "embryotoxicity expressed as a developmental delay" was detected in the high concentration group as decreased fetal body weights and sternebral ossification. Treatment produced maternal toxicity as reduced noise stimuli response at 1,000, 2,500, and 5,000 ppm and reduced body weights gain and feed consumption at 5,000 ppm. Authors of the REACH dossier reported that tetrahydrofuran was not selectively developmentally toxic, but that slight embryo-fetal toxicity was detected

only at maternally toxic doses. The REACH dossier authors reported a maternal toxicity NOAEC of 500 ppm based on the response to noise stimuli results and a developmental toxicity (embryotoxicity) NOAEC of 2,500 ppm (8 mg/L). The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1980, 003 Supporting).

- Based on the increased incidence of skeletal variations in a prenatal developmental toxicity test in the presence of maternal toxicity and increased incidences of cannibalism or pups found dead during the postnatal period of an extended one-generation reproductive toxicity study in the absence of maternal toxicity, ToxServices classified 2-methyltetrahydrofuran as a Category 2 developmental toxicant (H361d) oral developmental toxicant under GHS criteria (UN 2021). Chemicals are classified as GHS Category 2 reproductive toxicants for developmental toxicity when they produce "some evidence of an adverse effect on […] development" in animal studies. The surrogate tetrahydrofuran reduced ossification and/or fetal body weights in mice and rats and decreased the number and percent of live fetuses/litter and increased the percent of resorptions in mice following inhalation exposures. The developmental effects in all three prenatal developmental toxicity studies were detected at maternally toxic tetrahydrofuran vapor concentrations. Based on the lack of developmental toxicity in the absence of maternal toxicity across multiple studies involving multiple species, ToxServices considered the developmental toxicity produced by the surrogate tetrahydrofuran to be secondary to maternal toxicity.

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

2-Methyltetrahydrofuran was assigned a score of Data Gap for endocrine activity based on insufficient data available 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, CAS #96-47-9, 2023
  - *Oral*: A GLP-compliant, OECD Guideline 443 extended one-generation reproductive toxicity study was performed with Sprague-Dawley rats (20/sex/group) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) in water at 0, 100, 250, or 625 mg/kg/day. The exposure duration was not provided. A total of five cohorts (1A, 1B, 2A, 2B, and 3) of offspring were produced. Parental males and cohort 1A males and females were evaluated for plasma thyroxine (T4) and thyroid-stimulating hormone (TSH) levels. Treatment did not adversely affect plasma T4 or TSH levels in these animals. High dose pups exhibited an increased mean anogenital distance and normalized mean anogenital distance in F1 animals, but the sexual development of these animals was not negatively impacted. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2020).
  - *Inhalation*: A GLP-compliant, OECD Guideline 413 subchronic repeated inhalation exposure toxicity test was performed with Han Wistar rats (10/sex/group) administered nose-only inhalation exposures to 2-methyltetrahydrofuran vapor (99.98% purity) at measured concentrations of 0, 2.07, 4.62, or 9.96 mg/L for 6 hours/day, 5 days/week for 12 weeks and 7 days/week for the 13th week. The highest concentration tested was characterized as the "maximum tolerated dose." The animals were evaluated for serum triiodothyronine (T3), T4, and TSH levels. Treatment did not alter the circulating levels of these thyroid hormones. The REACH dossier reported this study with a reliability score of 1 (reliable with restriction) (Unnamed study 2018).
- NTP 1998, ECHA, CAS #109-99-9, 2023

  - *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant female Sprague-Dawley rats (approximately 33/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (99.3-100.2% purity) at 0, 600, 1,800, or 5,000 ppm for 6 hours/day, 7 days/week on gestation days 6-19. The animals were sacrificed on gestation day 20. Based on a conversion factor of 1 ppm / 2.95 mg/m^3 (NIOSH 2019), these concentrations are equivalent to 1,770, 5,310, and 14,750 mg/m^3, respectively, and 1.77, 5.31, and 14.75 mg/L, respectively. Treatment did not adversely affect the fetal sex ratio. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1988, 001 Key).
  - *Inhalation*: *Surrogate: Tetrahydrofuran (CAS #109-99-9):* In a GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant female CD-1 mice (approximately 33/dose) were administered whole body inhalation exposures to tetrahydrofuran vapor (99.3-100.2% purity) at 0, 600, 1,800, or 5,000 ppm for 6 hours/day, 7 days/week on gestation days 6-17. The animals were sacrificed on gestation day 18. Based on a conversion factor of 1 ppm / 2.95 mg/m^3 (NIOSH 2019), these concentrations are equivalent to 1,770, 5,310, and 14,750 mg/m^3, respectively, and 1.77, 5.31, and 14.75 mg/L, respectively. Treatment did not adversely affect the fetal sex ratio. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1988, 002 Key).
- U.S. EPA 2023b
  - 2-Methyltetrahydrofuran was active in 0/8 estrogen receptor (ER) assays [gene symbols: ESR1 – estrogen receptor α (6 assays); ESR2 – estrogen receptor β (2 assays)], 0/7 androgen receptor (AR) assays (gene symbol: AR), 0/2 steroidogenesis assays (aromatase inhibition), and 0/7 thyroid receptor assays (gene symbols: TRHR – thyrotropin releasing hormone receptor (2 assays); THRA – thyroid hormone receptor α and THRB – thyroid hormone receptor β (2 assays); TSHR – thyroid stimulating hormone receptor (3 assays)]) performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (note: only Tox21 data were considered).
- In summary, 2-methyltetrahydrofuran treatment did not adversely affect serum thyroid hormone levels or sexual development in an OECD Guideline 443 extended one-generation reproductive toxicity study or serum thyroid hormone levels in an OECD Guideline 413 subchronic repeated inhalation exposure toxicity test, both in rats. The surrogate tetrahydrofuran did not adversely affect the fetal sex ratio of rats or mice in inhalation prenatal developmental toxicity tests. Additionally, the compound was negative for interactions with estrogen, androgen, and thyroid receptors and steroidogenesis pathways in Tox21 high throughput screening assays. However, ToxServices identified no data for *in vivo* endocrine hormone signaling for 2-methyltetrahydrofuran for the estrogen and androgen pathways. Therefore, insufficient data are available to draw a conclusion for this endpoint and a Data Gap is assigned.

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*

2-Methyltetrahydrofuran was assigned a score of Moderate for acute toxicity based on ToxServices classifying it as a Category 4 acute oral toxicant under GHS criteria (UN 2021). GreenScreen® criteria

classify chemicals as a Moderate hazard for acute toxicity when they are classified as GHS Category 4 acute toxicants (CPA 2018b). The confidence in the score is low due to the lack of an upper bound estimate for the critical oral LD_{50}.

- 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, CAS #96-47-9, 2023
  - *Oral*: LD_{50} (female Wistar rats) > 300 mg/kg (GLP-compliant, OECD Guideline 420). The single animal dosed with 2,000 mg/kg was sacrificed in moribund condition. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
  - *Oral*: LD_{50} (rats, strain and sex not specified) = 3,800 mg/kg. The REACH dossier reported this study with a reliability score of 4 (not assignable) due to being obtained from a secondary source (Deichmann and Gerarde 1969, 002 Supporting).
  - *Dermal*: LD_{50} (male and female Wistar rats) > 2,000 mg/kg (GLP-compliant, OECD Guideline 402). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
  - *Dermal*: LD_{50} (rabbits, sex and strain not specified) = 4,500 mg/kg. The REACH dossier reported this study with a reliability score of 4 (not assignable) (Deichmann and Gerarde 1969, 002 Supporting, ECHA, CAS #96-47-9, 2023). ToxServices included this study for completeness of information.
  - *Inhalation*: 4-hour LC_{50} (rats, sex and strain not specified) = 22 mg/L. The REACH dossier reported this study with a reliability score of 4 (not assignable) (Deichmann and Gerarde 1969, 001 Supporting).
- GHS criteria (UN 2021) define Category 4 acute oral toxicants as chemicals that produce oral LD_{50}s > 300 and ≤ 2,000 mg/kg. Since the key study presented in the REACH dossier only identified a lower bound (> 300 mg/kg) for the oral LD_{50}, and the only animal tested at 2,000 mg/kg was moribund and sacrificed for humane reasons, ToxServices conservatively classified 2-methyltetrahydrofuran as a GHS Category 4 acute oral toxicant. While an oral LD_{50} of 3,800 mg/kg is presented in the REACH dossier for 2-methyltetrahydrofuran, the study is quite old (1969) and is assigned a reliability score of "not assignable" due to the lack of details regarding the study methods and results. Therefore, ToxServices did not assign the classification for this endpoint based on the oral LD_{50} of 3,800 mg/kg. The surrogate tetrahydrofuran is also classified to Category 4 by Japan and New Zealand for the oral route (Pharos 2023). Regarding the dermal route, 2-methyltetrahydrofuran is not classified as an acute dermal toxicant under GHS criteria based on dermal LD_{50}s ≥ 2,000 mg/kg in rats. GHS criteria define acute dermal toxicants as chemicals that produce dermal LD_{50}s ≤ 2,000 mg/kg. Additionally, concerning the inhalation route, ToxServices did not classify 2-methyltetrahydrofuran as an acute inhalation toxicant under GHS criteria based on a 4-hour LC_{50} of 22 mg/L in rats. GHS criteria classify chemicals as acute inhalation toxicants when LC_{50} values are ≤ 20 mg/L (vapors) or ≤ 5 mg/L (dusts and mists).

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

2-Methyltetrahydrofuran was assigned a score of Data Gap for systemic toxicity (single dose) based on insufficient data for systemic toxicity following single oral doses and inhalation exposures.

- 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, CAS #96-47-9, 2023
    - *Oral*: In the GLP-compliant, OECD Guideline 420 acute oral toxicity test that identified an oral LD_{50} > 300 mg/kg in female Wistar rats exposed to 2-methyltetrahydrofuran (purity not specified), the animals were dosed with 300 mg/kg (5 animals) or 2,000 mg/kg (1 animal). A 14-day observation period followed the dosing. Within 30 minutes of dosing, the animal dosed with 2,000 mg/kg exhibited decreased and labored respiration, hypothermia, and pallor of the extremities and was comatose. The study investigators sacrificed this animal for humane reasons. No deaths, clinical signs of toxicity, or gross pathological changes were identified in the 300 mg/kg group. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
    - *Dermal*: In the GLP-compliant, OECD Guideline 402 test that identified a dermal LD_{50} > 2,00 mg/kg in male and female Wistar rats (5/sex/group) exposed to 2-methyltetrahydrofuran (purity not specified), 2,000 mg/kg was the only dose tested. Treatment did not induce clinical signs of toxicity, dermal irritation, or gross pathological alterations. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
    - *Inhalation*: No details regarding clinical signs of toxicity, body weights, or gross pathological findings were provided for the acute inhalation toxicity study that identified a 4-hour LC_{50} of 22 mg/L in rats exposed to 2-methyltetrahydrofuran (purity not specified). The REACH dossier reported this study with a reliability score of 4 (not assignable) (Deichmann and Gerarde 1969, 001 Supporting).
- GHS criteria (UN 2021) define chemicals as specific target organ toxicant following dermal doses or exposures when they produce non-lethal systemic toxicity following single oral or dermal doses ≤ 2,000 mg/kg or single inhalation exposures ≤ 20 mg/L (vapors) or ≤ 5 mg/L (dusts/mists/fumes). Single dermal doses of 2-methyltetrahydrofuran did not produce evidence of systemic toxicity in exposed rats. However, no details on potential systemic toxicity effects were provided for the acute inhalation toxicity test. Additionally, the single animal orally dosed with 2,000 mg/kg was sacrificed in moribund condition and treatment did not produce evidence of systemic toxicity at an oral dose of 300 mg/kg. Therefore, ToxServices concluded that there are insufficient data available to determine if single inhalation exposures of 2-methyltetrahydrofuran produce systemic toxicity and single oral doses of 2-methyltetrahydrofuran > 300 mg/kg and < 2,000 mg/kg induce systemic toxicity. Accordingly, ToxServices assigned a Data Gap for this endpoint.

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

2-Methyltetrahydrofuran was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated oral doses or inhalation exposures under GHS criteria (UN 2021). No data were identified for the dermal route. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data are available and they are not classified under GHS criteria (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #96-47-9, 2023
    - *Oral*: A GLP-compliant, OECD Guideline 408 subchronic repeated oral dose toxicity study was performed with Sprague-Dawley rats (10/sex/group) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) in water at 0, 80, 250, 500, or 1,000 mg/kg/day

for 90 days. Additional groups of 5 animals/sex were dosed with 0 or 1,000 mg/kg/day for 90 days and maintained for an additional month without treatment (recovery group). The animals were evaluated for clinical signs of toxicity, body weight, food and water consumption, ophthalmology, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Treatment did not adversely affect water consumption, ophthalmology, hematology or urinalysis parameters, or gross pathological findings. Three animals, one female at 500 mg/kg/day, one high dose male, and one low dose female, were euthanized due to dosing errors or lack of recovery from anesthesia following blood collection. No other animals died prior to the scheduled sacrifice. The sole treatment-related clinical sign of toxicity was increased salivation in the two highest dose groups. The authors noted that this finding is common for "test articles that have taste aversion." High dose males and females exhibited 15.75 and 13.4% decreased overall body weight gains relative to the concurrent control. High dose animals in the recovery group exhibited reversibility of body weight gain deficits. High dose males and females exhibited increased serum cholesterol levels at weeks 6 and 13, but this effect was not detected by the end of the recovery period. Animals in the 500 and 1,000 mg/kg/day groups exhibited increased absolute and relative liver and kidney weights. Since the recovery group animals did not exhibit differences in organ weights, the authors did not consider the organ weight changes to be of toxicological concern. At the end of the treatment period, high dose males and females exhibited an increased incidence of hepatocellular hypertrophy. The severity was minimal in 8/10 males and 6/10 females, and mild in 1/10 males. No details regarding histopathological findings in the recovery group were provided. The authors identified a systemic toxicity NOAEL of 250 mg/kg/day based on histopathological changes to the liver identified at ≥ 500 mg/kg/day. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2017, 001 Key).

- *Oral*: A subchronic repeated oral dose toxicity study was performed with male and female Sprague-Dawley rats (number not specified) administered gavage doses of 2-methyltetrahydrofuran (purity not specified) in corn oil at ≤ 26 mg/kg/day for "approximately 3 months." The authors identified a NOAEL of 26 mg/kg/day, the highest dose tested, based on the lack of toxicity detected. No additional details were provided. The REACH dossier reported this study with a reliability score of 4 (not assignable) due to insufficient documentation (Antonucci et al. 2011, 002 Supporting). ToxServices included this study for completeness of information.
- *Inhalation*: A GLP-compliant, OECD Guideline 413 subchronic repeated inhalation exposure toxicity test was performed with Han Wistar rats (10/sex/group) administered nose-only inhalation exposures to 2-methyltetrahydrofuran vapor (99.98% purity) at measured concentrations of 0, 2.07, 4.62, or 9.96 mg/L for 6 hours/day, 5 days/week for 12 weeks and 7 days/week for the 13th week. The highest concentration tested was characterized as the "maximum tolerated dose." The animals were evaluated for clinical signs of toxicity, body weight, food and water consumption, ophthalmology, hematology, clinical chemistry, estrous cyclicity, sperm parameters, gross pathology, organ weights, and histopathology. Treatment induced unsteady gait on return to the home cage and excessive salivation in high dose group animals. High concentration males exhibited decreased body weights gains (85% of the control group value). Treatment increased mean serum alanine transaminase (ALT) levels in a concentration-dependent manner, with increases of 120%, 150%, and 160% in the low, mid, and high concentration groups, respectively. Additionally, high concentration females exhibited increased mean (180%) serum alkaline phosphatase (ALP) activity. The increased serum enzyme levels correlated with increased absolute and relative liver weights in high concentration males and females, but these animals did not

exhibit histopathological changes in the liver at necropsy suggesting that these effects were adaptive in nature. A proportion of treated females exhibited irregular estrous cycles with an extension in regular cycle length from four to five days detected for high concentration females. Since treated females continued to cycle, the authors did not consider these impacts to be adverse. Based on the lack of treatment-related histopathological changes or effects on other parameters that the authors considered adverse, the authors identified a systemic toxicity NOAEC of 9.96 mg/L, the highest concentration tested. The REACH dossier reported this study with a reliability score of 1 (reliable with restriction) (Unnamed study 2018).

- GHS criteria (UN 2021) define specific target organ toxicants following repeated doses or exposures as chemicals that produce systemic toxicity at oral doses ≤ 100 mg/kg/day, dermal doses ≤ 200 mg/kg/day, and inhalation exposures ≤ 1.0 mg/L (vapor) or ≤ 0.2 mg/L (dust/mist/fume) in subchronic studies. Since 2-methyltetrahydrofuran produced a systemic toxicity oral NOAEL/LOAEL of 250/500 mg/kg/day in the GLP-compliant, OECD Guideline 408 subchronic study and a 90-day inhalation NOAEC of 9.96 mg/L in rats (the highest concentration tested), ToxServices did not classify it as a specific target organ toxicant following repeated oral dosing or inhalation exposures under GHS criteria.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
2-Methyltetrahydrofuran was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (CPA 2018b). The confidence in the score is low due to limited animal and human data identified.

- 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, CAS #96-47-9, 2023
  - *Oral*: In the GLP-compliant, OECD Guideline 420 acute oral toxicity test that identified an oral LD_{50} > 300 mg/kg in female Wistar rats exposed to 2-methyltetrahydrofuran (purity not specified), the animals were dosed with 300 mg/kg (5 animals) or 2,000 mg/kg (1 animal). A 14-day observation period followed the dosing. Within 30 minutes of dosing, the animal dosed with 2,000 mg/kg exhibited hypothermia and pallor of the extremities and was comatose. The study investigators sacrificed this animal for humane reasons. No deaths, clinical signs of toxicity, or gross pathological changes were identified in the 300 mg/kg group. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
  - *Dermal*: In the GLP-compliant, OECD Guideline 402 test that identified a dermal LD_{50} > 2,00 mg/kg in male and female Wistar rats (5/sex/group) exposed to 2-methyltetrahydrofuran (purity not specified), 2,000 mg/kg was the only dose tested. Treatment did not induce clinical signs of toxicity or gross pathological alterations. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
  - *Inhalation*: No details regarding clinical signs of toxicity, body weights, or gross pathological findings were provided for the acute inhalation toxicity study that identified a 4-hour LC_{50} of 22 mg/L in rats exposed to 2-methyltetrahydrofuran (purity not specified). The

REACH dossier reported this study with a reliability score of 4 (not assignable) (Deichmann and Gerarde 1969, 001 Supporting).

- Haz-Map 2023
  - 2-Methyltetrahydrofuran is associated with acute solvent syndrome.
- In summary, insufficient data are available for the acute toxicity studies to properly evaluate potential single dose neurotoxicity following oral or inhalation exposures. However, 2-methyltetrahydrofuran is associated with acute solvent syndrome as identified in the Haz-Map database. Therefore, ToxServices classified 2-methyltetrahydrofuran as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2021).

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

2-Methyltetrahydrofuran was assigned a score of Low for neurotoxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated exposures for neurotoxicity under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #96-47-9, 2023
  - *Inhalation*: A GLP-compliant, OECD Guideline 413 subchronic repeated inhalation exposure toxicity test was performed with Han Wistar rats (10/sex/group) administered nose-only inhalation exposures to 2-methyltetrahydrofuran vapor (99.98% purity) at measured concentrations of 0, 2.07, 4.62, or 9.96 mg/L for 6 hours/day, 5 days/week for 12 weeks and 7 days/week for the 13th week. The highest concentration tested was characterized as the "maximum tolerated dose." The animals were evaluated for locomotor activity and in a functional observation battery (FOB) examining grip strength, sensory reactivity, approach response, pinna reflex, auditory startle reflex, and tail pinch response. Neuropathological endpoints were not evaluated in this study. Two high concentration females exhibited elevated gait. Treatment increased total low beam scores for males in the mid and high concentration groups (1.3x and 1.4x, respectively), but did not affect high beam activity scores in exposed males. Treatment did not affect or only produced incidental changes to the remaining parameters. As the effects on low beam scores were only detected in males and were not related to deficits in grip strength or high beam scores, the authors concluded that they were non-adverse. The REACH dossier reported this study with a reliability score of 1 (reliable with restriction) (Unnamed study 2018). Based on the lack of treatment-related adverse effects on neurobehavioral endpoints, ToxServices identified a neurotoxicity NOAEC of 9.96 mg/L, the highest concentration tested.
- GHS criteria (UN 2021) define specific target organ toxicants following repeated inhalation exposure as chemicals that produce systemic toxicity at concentrations ≤ 1.0 mg/L (vapors) or ≤ 0.2 mg/L (dust, mists, aerosols) in subchronic studies. Since 2-methyltetrahydrofuran did not produce neurotoxicity in a FOB in a subchronic repeated inhalation toxicity test in rats at up to 9.96 mg/L, ToxServices did not classify it as a specific target organ toxicant following repeated exposures for neurotoxicity under GHS criteria.

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

2-Methyltetrahydrofuran was assigned a score of Low for skin sensitization based on negative results in an OECD Guideline 429 local lymph node assay. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate negative results and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #96-47-9, 2023
  - A GLP-compliant, OECD Guideline 429 local lymph node assay was performed with female CBA/Ca mice (4/group) administered topical applications of 2-methyltetrahydrofuran (purity not specified) in acetone/olive oil (4:1 v/v) at 25%, 50%, or 100% to the dorsal surface of each ear for three consecutive days. Five days after the first dose, the animals were sacrificed and the draining auricular lymph nodes were isolated for the proliferation assay. The stimulation indices (SIs) were 1.1, 1.1, and 1.5 for the 25%, 50%, and 100% treatments, respectively. Results for the positive control (hexyl cinnamic aldehyde) were not provided. Per the OECD 429 Guideline (link), chemicals are classified as sensitizing when they produce SIs ≥ 3. Since the SIs produced by up to undiluted 2-methyltetrahydrofuran were < 3, the authors concluded that 2-methyltetrahydrofuran was not sensitizing to the skin under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).

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

2-Methyltetrahydrofuran was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when 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
  - 2-Methyltetrahydrofuran does not contain any structural alerts for respiratory sensitization as identified using OECD QSAR Toolbox v4.5 SP1 (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 2-methyltetrahydrofuran was not sensitizing to the skin in an LLNA (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by 2-methyltetrahydrofuran, and as 2-methyltetrahydrofuran does not contain any structural alerts for respiratory sensitization (OECD 2022), 2-methyltetrahydrofuran is not expected to be a respiratory sensitizer.

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

2-Methyltetrahydrofuran was assigned a score of High for skin irritation/corrosivity based on ToxServices classifying it as a Category 2 skin irritant under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are classified as GHS Category 2 skin irritants (CPA 2018b). The confidence in the score is low as the available data are insufficient to differentiate between GHS Categories 2 and 3.

- 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, CAS #96-47-9, 2023
  - A GLP-compliant, OECD Guideline 431 *in vitro* skin corrosion test was performed with the EpiSkin™ model exposed to 0.05 mL (50 µL) undiluted 2-methyltetrahydrofuran (purity not specified) for 3, 60, or 240 minutes in duplicate. The MTT assay was used to evaluate tissue viability. The relative mean viability was 107.3% after 3 minutes, 57.3% after 60 minutes and 79.1% after 240 minutes. Results for the positive control (glacial acetic acid) were not reported. Per the OECD 431 Guideline (link), chemicals are classified as non-corrosive if the viability is ≥ 35% after the 240 minute exposure. Since the viability for the 240-minute exposure to 2-methyltetrahydrofuran was 79.1%, the authors concluded that 2-methyltetrahydrofuran was not corrosive under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2012, 001 Key).
  - A GLP-compliant, OECD Guideline 439 *in vitro* skin irritation test was performed with EpiSkin™ model exposed to an unspecified volume of undiluted 2-methyltetrahydrofuran (purity not specified) for 15 minutes in triplicate. Following the exposure period, the tissues were maintained without treatment for 42 hours, after which the MTT viability assay was performed. The treatment produced a mean viability of 40.4% of the negative control, compared to 6.7% for the positive control (5% w/v sodium dodecyl sulphate) treatment. Per the OECD 439 Guideline (link), chemicals are classified as non-irritating if the viability is > 50%. Since the viability for the 2-methyltetrahydrofuran treatment was 40.5%, the authors concluded that 2-methyltetrahydrofuran was irritating/corrosive under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2012, 002 Key).
- Per OECD Guideline 439, if "the test chemical is found to be non-corrosive [via OECD Guideline 430, 431 or 435], and shows tissue viability after exposure and post-treatment incubation is less than or equal (≤) to 50%, the test chemical is considered to be irritant to skin in accordance with UN GHS Category 2." However, the test guidance also states that the OECD Guideline 439 does not differentiate between Category 2 and Category 3. Since 2-methyltetrahydrofuran was non-corrosive in an OECD Guideline 431 *in vitro* skin corrosion test and was positive for irritation/corrosion in an OECD Guideline 439 in vitro skin irritation test, ToxServices classified 2-methyltetrahydrofuran as a Category 2 skin irritant under GHS criteria (UN 2021) and OECD testing guidelines.

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

2-Methyltetrahydrofuran was assigned a score of Very High for eye irritation/corrosivity based on ToxServices classifying it as a Category 1 ocular irritant under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when they are classified as GHS Category 1 eye irritants (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for the target chemical.

- Authoritative and Screening Lists

    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - GHS - New Zealand - Eye irritation category 2.
            - Based on mild irritation detected in rabbits (CCID 2023).
- ECHA, CAS #96-47-9, 2023
    - A GLP-compliant, OECD Guideline 437 bovine corneal opacity and permeability test was performed with cow eyes (3 corneas/group) exposed to 0.75 mL undiluted 2-methyltetrahydrofuran (purity not specified) for 10 minutes. The tissues were incubated for 120 minutes following the treatment period. Treated corneas were cloudy after the exposure and incubation periods. The *in vitro* irritation scores (IVISs) were 2.8 for the negative control (0.9% w/v sodium chloride solution), 32.2 for the positive control (ethanol), and 63 for 2-methyltetrahydrofuran. Per the OECD 437 Guideline (link), chemicals are classified as corrosive to ocular tissues (GHS Category 1) when the IVISs are > 55 and non-irritating when the IVISs are ≤ 3. Based on the IVIS of 63, the authors concluded that 2-methyltetrahydrofuran is corrosive to ocular tissue. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013).
- Based on the corrosive effects identified in the *ex vivo* OECD Guideline 437 test, ToxServices classified 2-methyltetrahydrofuran as a Category 1 ocular irritant under GHS criteria (UN 2021).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
2-Methyltetrahydrofuran was assigned a score of Low for acute aquatic toxicity based on acute aquatic toxicity values > 100 mg/L for all three trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are > 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for the target chemical for all three trophic levels.

- 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, CAS #96-47-9, 2023
    - 96-hour $_{LC50}$ (*Oncorhynchus mykiss*, rainbow trout) > 100 mg/L (measured) (GLP-compliant, OECD Guideline 203/EU Method C.1). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2012, 001 Key).
    - 48-hour LC_{50} (*Daphnia magna*) > 139 mg/L (measured) (GLP-compliant, OECD Guideline 202/EU Method C.2). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2007, 001 Key).
    - 72-hour growth rate and biomass EC_{50} (*Desmodesmus subspicatus*, algae) > 104 mg/L(measured) (GLP-compliant, OECD Guideline 201). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2007, 001 Key).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
2-Methyltetrahydrofuran was assigned a score of Moderate for chronic aquatic toxicity based on an estimated chronic aquatic toxicity value of 9.28 mg/L for fish. 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 low as it is based on modeling and the modeling results for crustacea and algae differ significantly from measured values for those trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
    - *Other:*
        - GHS - New Zealand - Hazardous to the aquatic environment - chronic category 3.
            - Based on predicted chronic aquatic toxicity values (CCID 2023).
- ECHA, CAS #96-47-9, 2023
    - 21-day reproduction and mortality NOEC (*D. magna*) ≥ 120 mg/L (measured) (GLP-compliant, OECD Guideline 211). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2010, 001 Key).
    - 72-hour NOEC growth rate and biomass values (*D. subspicatus*, algae) ≥ 104 mg/L (measured) (GLP-compliant, OECD Guideline 201). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2007, 001 Key).
- U.S. EPA 2017a
    - 2-Methyltetrahydrofuran belongs to the Neutral Organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 9.28 mg/L in fish, 5.07 mg/L in daphnia, and 9.65 mg/L in green algae (Appendix I).

Environmental Fate (Fate)

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

2-Methyltetrahydrofuran was assigned a score of Moderate for persistence based on an estimated half-life of 30 days in soil, its dominant environmental compartment. GreenScreen® criteria classify chemicals as a Moderate hazard for persistence when soil is the dominant environmental compartment and the half-life in soil is 16-60 days (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.
- ECHA, CAS #96-47-9, 2023
    - A GLP-compliant, OECD Guideline 301D/EU Method C.4-E (closed bottle test) ready biodegradability test was performed with wastewater treatment plant secondary effluent exposed to 2-methyltetrahydrofuran (purity not specified) at 5.18 mg/L (ThOD/L) for 28 days. At the end of the exposure period, the test substance degraded 2%. The reference substance (sodium benzoate) performed as expected. The authors concluded that 2-methyltetrahydrofuran was not biodegradable under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2007, 001 Key).
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that 2-methyltetrahydrofuran is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 59.8% will partition to soil with a half-life of 720 hours (30 days), 37.6% will partition to water with a half-life of 360 hours (15 days), and 2.52% will partition to air with a half-life of 11.7 hours (0.49 days) (Appendix J).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
2-Methyltetrahydrofuran was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 1.85 and estimated BCFs of 7.213-7.72. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are ≤ 4 and BCF values are ≤ 100 (CPA 2018b). The confidence in the score is high as it is based in part on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2022
  - 2-Methyltetrahydrofuran has a measured log K_{ow} of 1.85 at 25°C.
- U.S. EPA 2017b
  - BCFBAF predicts a BCF of 7.72 L/kg wet-wt for 2-methyltetrahydrofuran using the regression-based model based on a measured log K_{ow} of 1.85, and a BCF of 7.213 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix J).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
2-Methyltetrahydrofuran was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score is low as it is not based on measured data or authoritative listings.

- 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, CAS #96-47-9, 2023
  - 2-Methyltetraydrofuran does not contain functional groups that are associated with oxidizing or explosive properties.
- ToxServices used screening procedures for explosivity to estimate the reactivity properties of 2-methyltetrahydrofuran. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, 2-methyltetrahydrofuran is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix K).
  - Based on the structure of its components or moieties, 2-methyltetrahydrofuran is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of 2-methyltetrahydrofuran has one oxygen, which is bonded only to carbon, classification is not warranted.
- Based on the above information, ToxServices did not classify 2-methyltetrahydrofuran as a reactive chemical under GHS criteria (UN 2021).

Flammability (F) Score (vH, H, M, or L): H
2-Methyltetrahydrofuran was assigned a score of High for flammability based on ToxServices classifying it as a Category 2 flammable liquid under GHS criteria, and on its DOT classification to Class 3 Group 2 (UN 2021). GreenScreen® criteria classify chemicals as a High hazard for flammability

when they are classified as GHS Category 2 flammable liquids, and when they are DOT Class 3 Group 2 (CPA 2018b). The confidence in the score was high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:*
        - DOT Hazard Class 3, Packing Group II.
    - *Screening:*
        - GHS - New Zealand - Flammable liquids category 2.
            - Based on a flash point of -12°C and a boiling point of 78°C (CCID 2023).
- ECHA, CAS #96-47-9, 2023
    - 2-Methyltetraydrofuran has a boiling point of 78°C at 1,013 hPa as reported in a handbook. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions) (Haynes 2010, 001 Key).
    - 2-Methyltetraydrofuran (purity not specified) has a flash point of -10°C as identified in a GLP-compliant, EU Method A.9/ISO 3679 equilibrium method closed cup test. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 2013, 001 Key).
    - 2-Methyltetraydrofuran (100% purity) has a flash point of -11°C as identified in a closed cup test. The REACH dossier reported this study with a reliability score of 4 (not assignable) (Unnamed study 2012, 002 Supporting).
- Based on a boiling point of 78°C and flash points of -11 to -10°C, ToxServices classified 2-methyltetraydrofuran as a GHS Category 2 flammable liquid. GHS criteria (UN 2021) define Category 2 flammable liquids as chemicals with flash points < 23°C and initial boiling points > 35°C.

Use of New Approach Methodologies (NAMs)[9] 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 biodegradation, and bioaccumulation; *in vitro* assays for genotoxicity, endocrine activity, and skin irritation; and an *ex vivo* assay for eye irritation. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

As shown in Table 4, Type I (input data) uncertainties in 2-methyltetrahydrofuran's NAMs dataset include no or insufficient experimental data for carcinogenicity, respiratory sensitization, endocrine activity, skin irritation, eye irritation, and bioaccumulation, and lack of established test methods for respiratory sensitization. 2-Methyltetrahydrofuran's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of Oncologic to evaluate 2-methyltetrahydrofuran's carcinogenic potential, the inconsistency of experimental results for training set chemicals in the VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in vitro* testing of receptor binding, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the combination of OECD Guideline 431/439 *in vitro* skin irritation tests not allowing for identification of mild skin irritants (GHS Category 3 skin irritants). Some of 2-methyltetrahydrofuran'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 for the oral and dermal routes. **Endocrine activity:** No *in vivo* data are available on non-thyroid circulating hormones. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Skin irritation:** No *in vivo* data are available. **Eye irritation:** No *in vivo* data are available.

[9] 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).

	Bioaccumulation: No experimental partition coefficient or BCF values are available.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). Oncologic could not evaluate carcinogenic potential of this chemical (U.S. EPA 2021). Of the two models in VEGA that produced reliable (i.e., Global AD index >0.7) predictions via the inhalation route, the experimental results for the most similar chemical tetrahydrofuran are contradictory. **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[10]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[11] 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[12]. **Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays of receptor binding activity is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Skin irritation**: The OECD Guideline 431 test is only used to identify corrosive substances (GHS Category 1)[13]; and OECD Guideline 439 test only used to identify irritating substances (GHS Category 2), and does not allow the classification as a mild skin irritant (GHS Category 3)[14]. **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.

[10] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[11] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[12] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[13] https://www.oecd-ilibrary.org/docserver/9789264264618-en.pdf?expires=1614097188&id=id&accname=guest&checksum=5C0F2BF5F910961BDDD2D30A71941A7D
[14] https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1614097324&id=id&accname=guest&checksum=D664A7EDCDE297919BE9A478941EBEC6

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/Oncologic/ /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	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays
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	Y	*In vitro* data: OECD Guideline 431 and 439 assays.
Eye irritation	Y	*Ex vivo* data: OECD Guideline 437 assay
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301D Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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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 2-Methyltetrahydrofuran (CAS #96-47-9)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	2-Methyltetrahydrofuran	96-47-9	M	L	M	M	DG	*M*		L	*M*	L	L	*L*	*H*	vH	L	*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	Yes	Yes
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
2-Methyltetrahydrofuran	2

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

Table 6

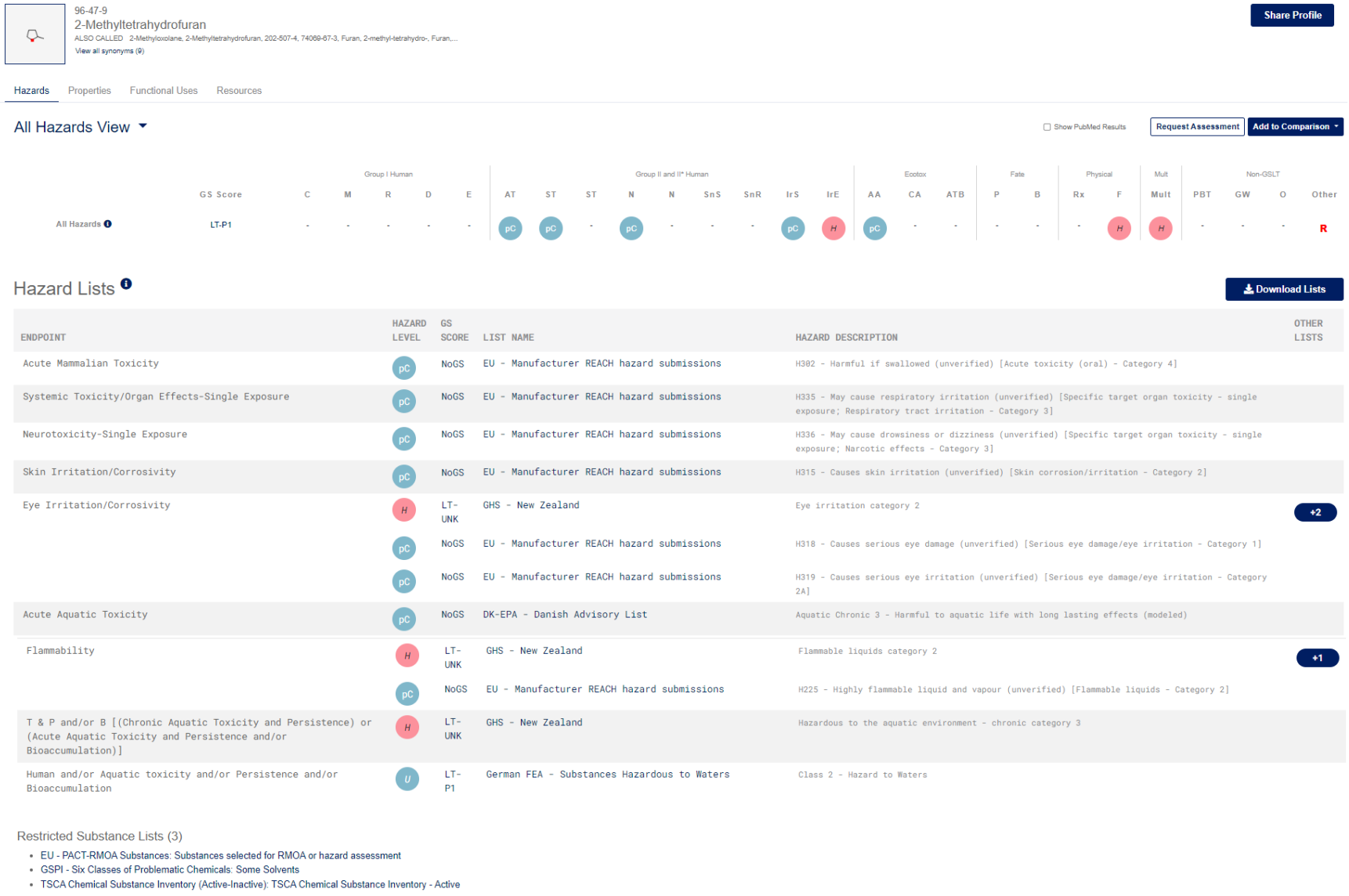
Chemical Name	Final GreenScreen® Benchmark Score
2-Methyltetrahydrofuran	2

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 2-Methyltetrahydrofuran (CAS #96-47-9)



96-47-9
2-Methyltetrahydrofuran
ALSO CALLED 2-Methyloxolane, 2-Methyltetrahydrofuran, 202-507-4, 74069-67-3, Furan, 2-methyl-tetrahydro-, Furan,...
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	LT-P1	-	-	-	-	-	pC	pC	-	pC	-	-	-	pC	H	pC	-	-	-	-	-	H	H	-	-	-	R

Hazard Lists

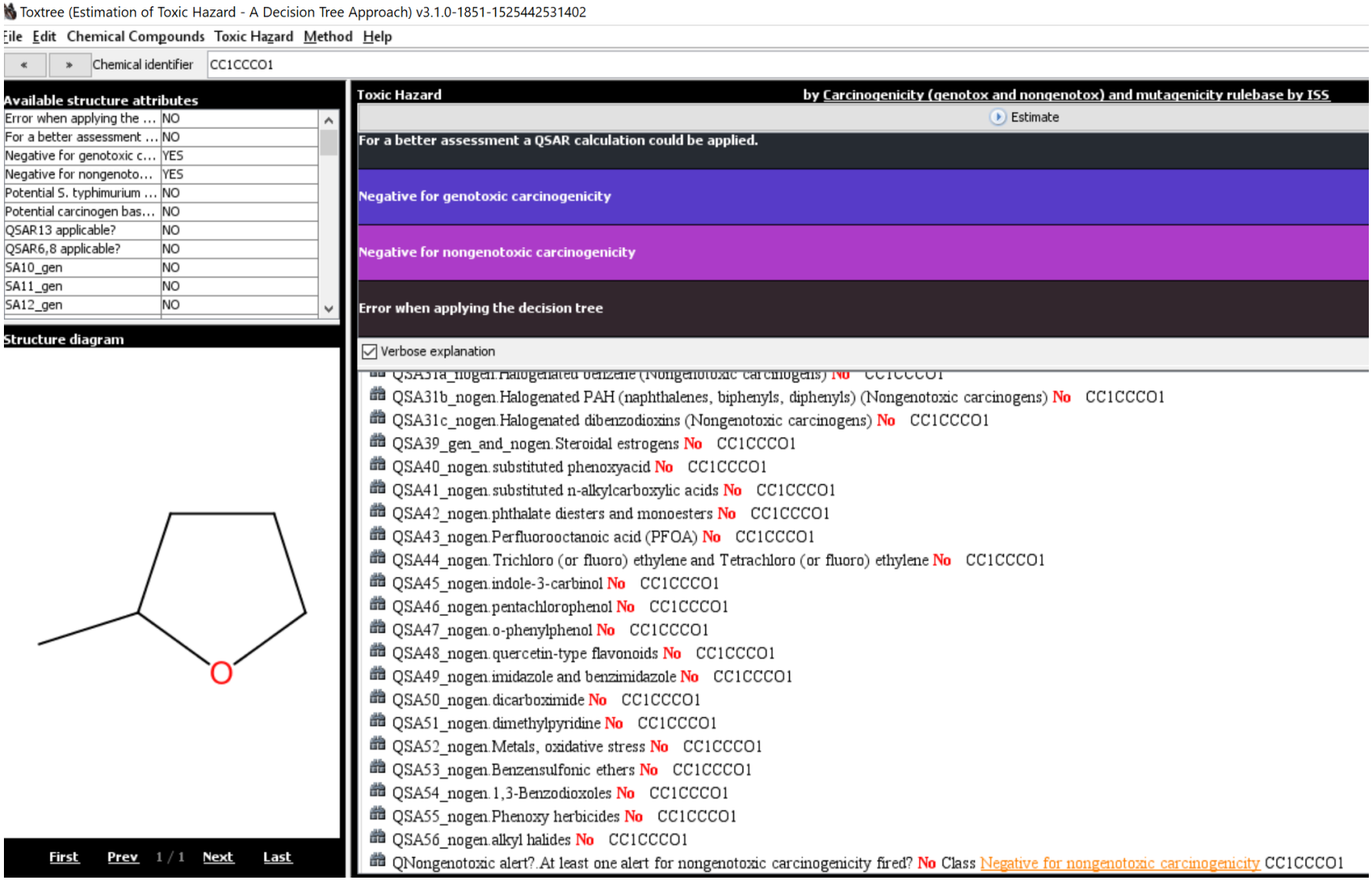
Download Lists

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]	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	
Neurotoxicity-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H336 - May cause drowsiness or dizziness (unverified) [Specific target organ toxicity - single exposure; Narcotic effects - Category 3]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	+2
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified) [Serious eye damage/eye irritation - Category 1]	
	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	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	+1
	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)]	H	LT-UNK	GHS - New Zealand	Hazardous to the aquatic environment - chronic category 3	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	

Restricted Substance Lists (3)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- GSPI - Six Classes of Problematic Chemicals: Some Solvents
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

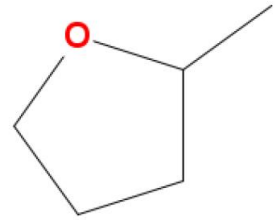
APPENDIX D: Toxtree Carcinogenicity Results for 2-Methyltetrahydrofuran (CAS #96-47-9)



APPENDIX E: VEGA Carcinogenicity Results for 2-Methyltetrahydrofuran (CAS #96-47-9)

1. Prediction Summary

Prediction for compound Molecule 0

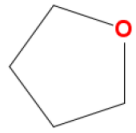


Prediction: Reliability:

Prediction is 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: O1CCCC1C
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.865
P(NON-Carcinogen): 0.135
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

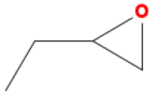
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 109-99-9
Dataset id: 733 (Training set)
SMILES: O1CCCC1
Similarity: 0.934

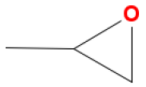
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 106-88-7
Dataset id: 295 (Test set)
SMILES: O1CC1CC
Similarity: 0.906

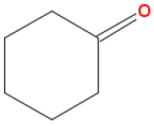
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 75-56-9
Dataset id: 678 (Training set)
SMILES: O1CC1C
Similarity: 0.845

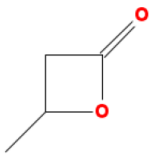
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 108-94-1
Dataset id: 187 (Test set)
SMILES: O=C1CCCCC1
Similarity: 0.813

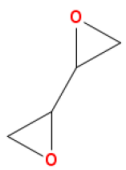
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 3068-88-0
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.8

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 298-18-0
Dataset id: 236 (Test set)
SMILES: O1CC1C2OC2
Similarity: 0.799

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.959
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.919
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.

Model class assignment reliability
Pos/Non-Pos difference = 0.73
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:

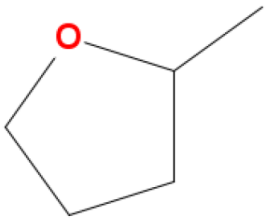
The feature has a good assessment, model is reliable regarding this aspect.

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

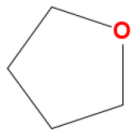


Prediction: Reliability:

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: O1CCCC1C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

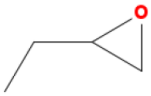
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 109-99-9
Dataset id: 611 (Training set)
SMILES: O1CCCC1
Similarity: 0.934

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

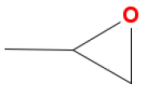


Compound #2

CAS: 106-88-7
Dataset id: 263 (Training set)
SMILES: O1CC1CC
Similarity: 0.906

Experimental value: Carcinogen
Predicted value: Carcinogen

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

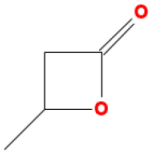


Compound #3

CAS: 75-56-9
Dataset id: 63 (Training set)
SMILES: O1CC1C
Similarity: 0.845

Experimental value: Carcinogen
Predicted value: Carcinogen

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

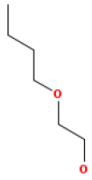


Compound #4

CAS: 3068-88-0
Dataset id: 15 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.8

Experimental value: Carcinogen
Predicted value: Carcinogen

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

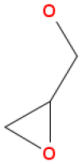


Compound #5

CAS: 111-76-2
Dataset id: 596 (Training set)
SMILES: OCCOCCCC
Similarity: 0.784

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

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



Compound #6

CAS: 556-52-5
Dataset id: 655 (Training set)
SMILES: OCC1OC1
Similarity: 0.765

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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 = 0.919
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.492
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.

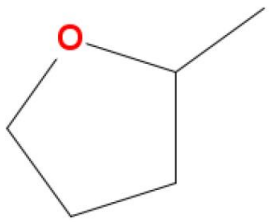
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

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

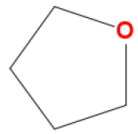


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result 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 optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O1CCCC1C
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

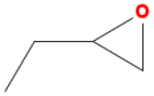
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 737 (Training set)
SMILES: O1CCCC1
Similarity: 0.934

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

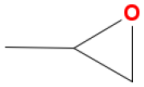


Compound #2

CAS: N.A.
Dataset id: 295 (Training set)
SMILES: O1CC1CC
Similarity: 0.906

Experimental value: Carcinogen
Predicted value: Carcinogen

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

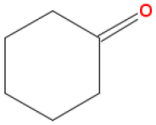


Compound #3

CAS: N.A.
Dataset id: 688 (Training set)
SMILES: O1CC1C
Similarity: 0.845

Experimental value: Carcinogen
Predicted value: Carcinogen

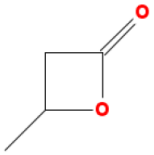
Alerts (not found in the target): Carcinogenity alert no. 105



Compound #4

CAS: N.A.
Dataset id: 187 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.813

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



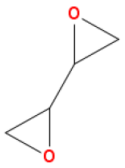
Compound #5

CAS: N.A.
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.8

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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



Compound #6

CAS: N.A.
Dataset id: 236 (Training set)
SMILES: O1CC1C2OC2
Similarity: 0.799

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

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

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 = 0.888
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.65
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

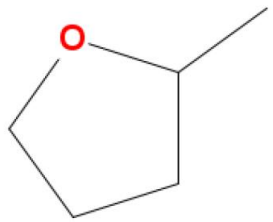
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

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

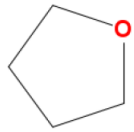


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result 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 optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O1CCCC1C
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

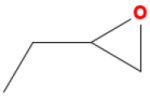
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 109-99-9
Dataset id: 508 (Training set)
SMILES: O1CCCC1
Similarity: 0.934

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

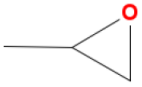


Compound #2

CAS: 106-88-7
Dataset id: 216 (Training set)
SMILES: O1CC1CC
Similarity: 0.906

Experimental value: Carcinogen
Predicted value: Carcinogen

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

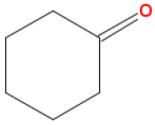


Compound #3

CAS: 75-56-9
Dataset id: 53 (Training set)
SMILES: O1CC1C
Similarity: 0.845

Experimental value: Carcinogen
Predicted value: Carcinogen

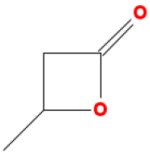
Alerts (not found in the target): Carcinogenity alert no. 23



Compound #4

CAS: 108-94-1
Dataset id: 934 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.813

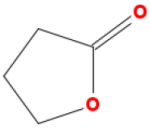
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 3068-88-0
Dataset id: 11 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.8

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: 96-48-0
Dataset id: 931 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.798

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.888
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.65
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

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

Symbols explanation:

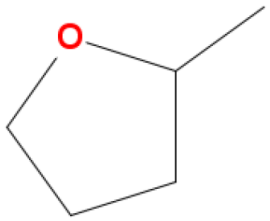
The feature has a good assessment, model is reliable regarding this aspect.

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

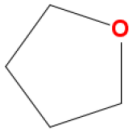
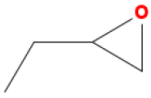
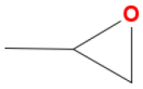
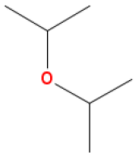
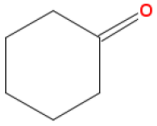
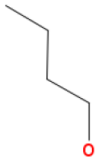


Prediction: Reliability:

Prediction is 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: O1CCCC1C
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

	Compound #1 CAS: 109-99-9 Dataset id: 691 (Test set) SMILES: O1CCCC1 Similarity: 0.934 Experimental value: NON-Carcinogen Predicted value: Carcinogen
	Compound #2 CAS: 106-88-7 Dataset id: 495 (Training set) SMILES: O1CC1CC Similarity: 0.906 Experimental value: NON-Carcinogen Predicted value: Carcinogen
	Compound #3 CAS: 75-56-9 Dataset id: 268 (Training set) SMILES: O1CC1C Similarity: 0.845 Experimental value: Carcinogen Predicted value: Carcinogen
	Compound #4 CAS: 108-20-3 Dataset id: 459 (Training set) SMILES: O(C(C)C)C(C)C Similarity: 0.827 Experimental value: NON-Carcinogen Predicted value: NON-Carcinogen
	Compound #5 CAS: 108-94-1 Dataset id: 416 (Training set) SMILES: O=C1CCCCC1 Similarity: 0.813 Experimental value: NON-Carcinogen Predicted value: NON-Carcinogen
	Compound #6 CAS: 71-36-3 Dataset id: 362 (Training set) SMILES: OCCCC Similarity: 0.806 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 = 0.919 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0 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.
✔	**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:

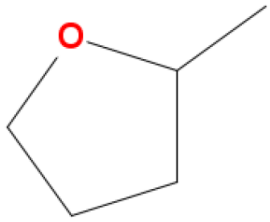
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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

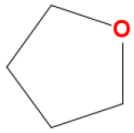


Prediction: Reliability:

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: O1CCCC1C
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

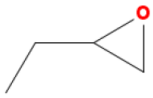
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 109-99-9
Dataset id: 686 (Training set)
SMILES: O1CCCC1
Similarity: 0.934

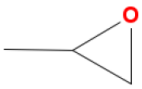
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 106-88-7
Dataset id: 467 (Training set)
SMILES: O1CC1CC
Similarity: 0.906

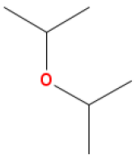
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 75-56-9
Dataset id: 228 (Training set)
SMILES: O1CC1C
Similarity: 0.845

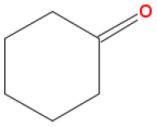
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 108-20-3
Dataset id: 426 (Training set)
SMILES: O(C(C)C)C(C)C
Similarity: 0.827

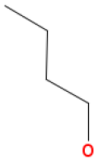
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 108-94-1
Dataset id: 379 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.813

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



Compound #6

CAS: 71-36-3
Dataset id: 314 (Training set)
SMILES: OCCCC
Similarity: 0.806

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.959
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.919
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.

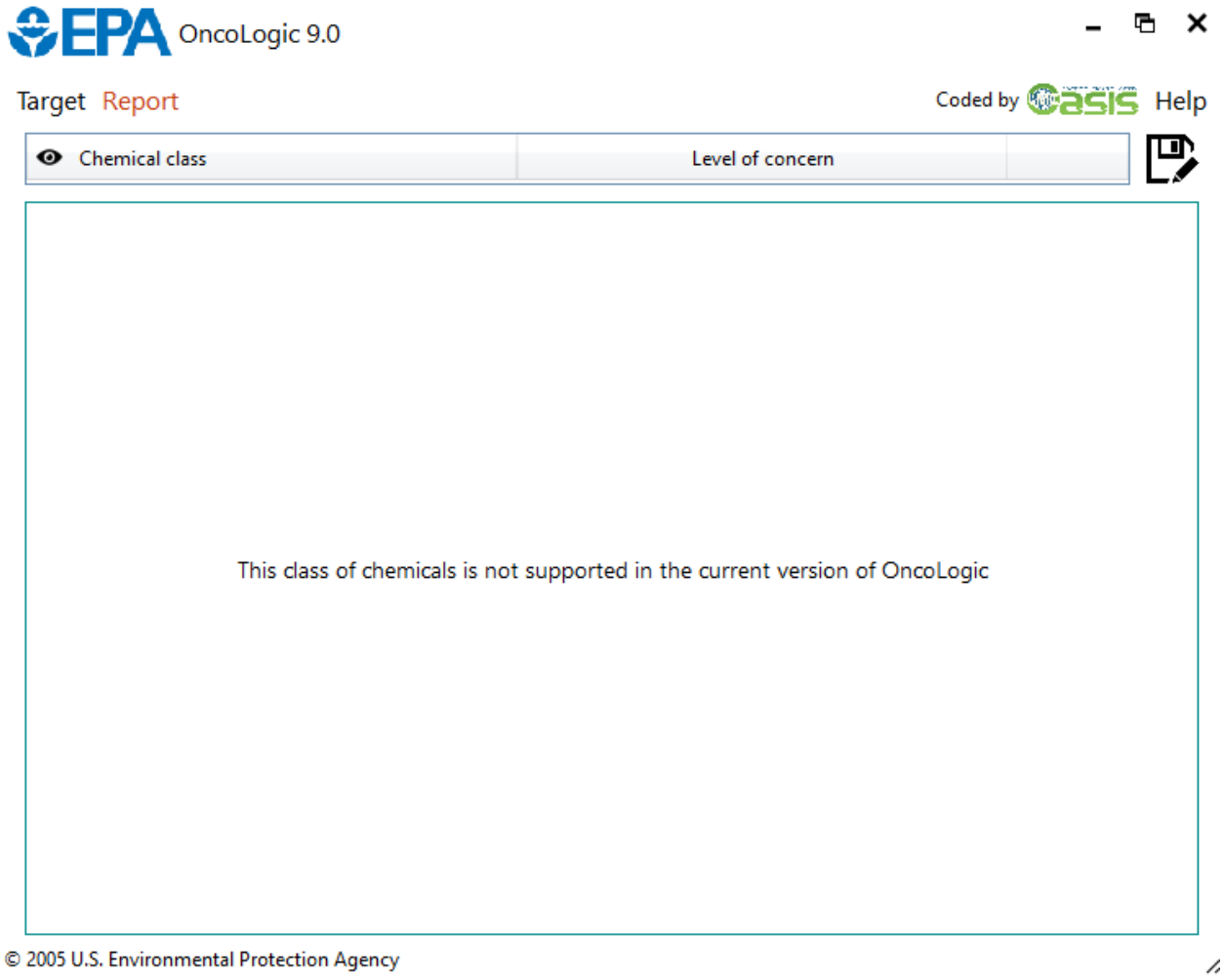
Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

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 F: Oncologic Carcinogenicity Results for 2-Methyltetrahydrofuran (CAS #96-47-9)



APPENDIX G: Danish QSAR Carcinogenicity Results for 2-Methyltetrahydrofuran (CAS #96-47-9)

	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	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

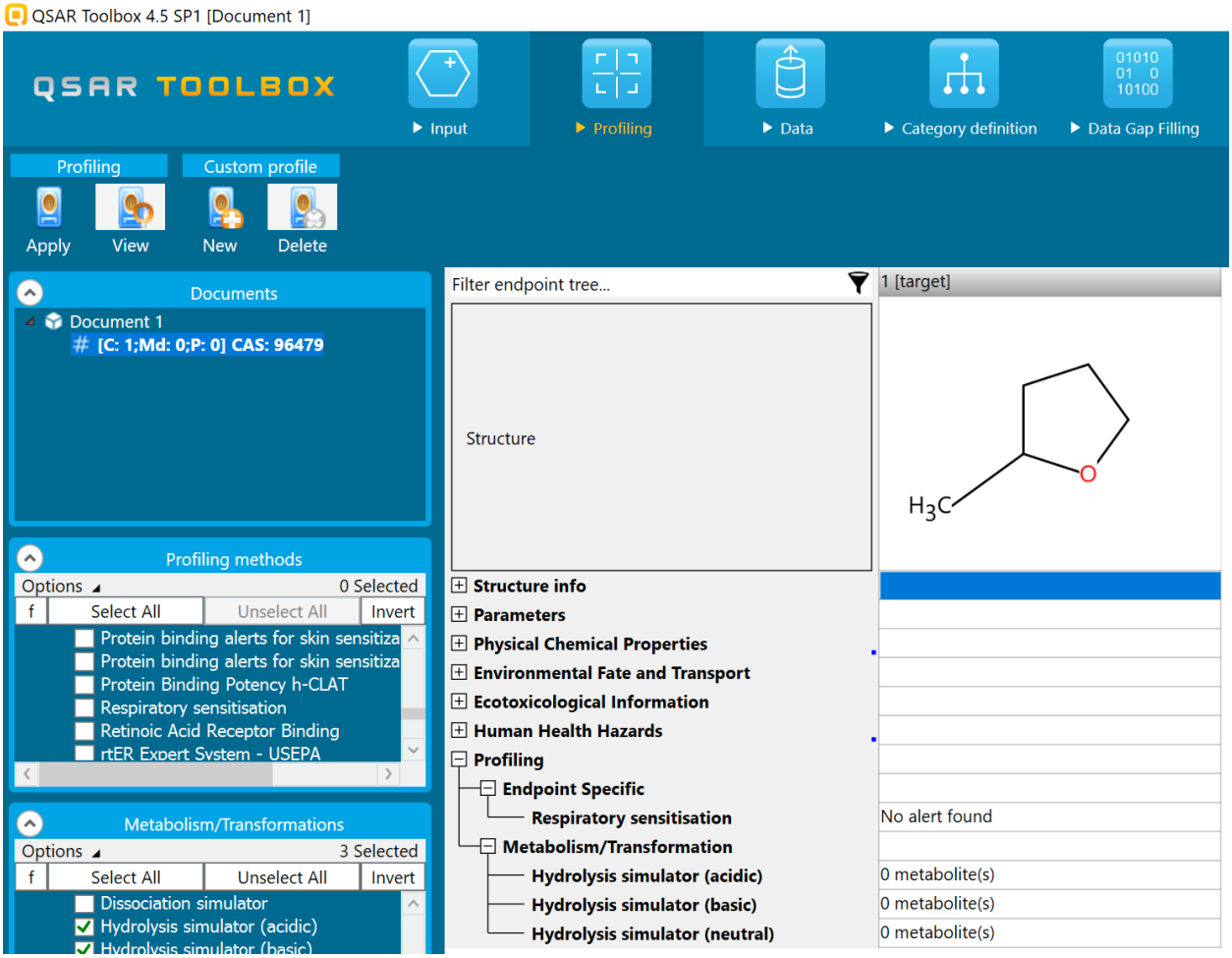
OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

APPENDIX H: OECD Toolbox Respiratory Sensitization Results for 2-Methyltetrahydrofuran (CAS #96-47-9)



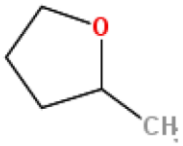
APPENDIX I: ECOSAR Modeling Results for 2-Methyltetrahydrofuran (CAS #96-47-9)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
96479	Furan, tetrahydro-2-methyl-	O(C(CC1)C)C1

Structure



Details	
Mol Wt	86.13
Selected LogKow	1.85
Selected Water Solubility (mg/L)	139000
Selected Melting Point (°C)	-20
Estimated LogKow	1.35
Estimated Water Solubility (mg/L)	3816.94
Measured LogKow	
Measured Water Solubility (mg/L)	139000
Measured Melting Point (°C)	

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	96.49	5	
Daphnid	48h	LC50	54.04	5	
Green Algae	96h	EC50	38.01	6.4	
Fish		ChV	9.28	8	
Daphnid		ChV	5.07	8	
Green Algae		ChV	9.65	8	
Fish (SW)	96h	LC50	121.37	5	

1/ 2

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid	96h	LC50	99.85	5	
Fish (SW)		ChV	12.02	8	
Mysid (SW)		ChV	9.02	8	
Earthworm	14d	LC50	155.22	6	

APPENDIX J: EPI Suite™ Modeling Results for 2-Methyltetrahydrofuran (CAS #96-47-9)

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

CAS Number: 96-47-9
SMILES : O(C(CC1)C)C1
CHEM : Furan, tetrahydro-2-methyl-
MOL FOR: C5 H10 O1
MOL WT : 86.13
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 1.85
Boiling Point (deg C) : 78.00
Melting Point (deg C) : -20.00
Vapor Pressure (mm Hg) : 97.3
Water Solubility (mg/L): 1.4E+005
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.35

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 86.99 (Adapted Stein & Brown method)
Melting Pt (deg C): -76.22 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 104 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.39E+004 (Mean VP of Antoine & Grain methods)
BP (exp database): 78 deg C
VP (exp database): 9.73E+01 mm Hg (1.30E+004 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 3817
log Kow used: 1.85 (user entered)
melt pt used: -20.00 deg C
Water Sol (Exper. database match) = 1.39e+005 mg/L (25 deg C)
Exper. Ref: RIDDICK,JA ET AL. (1986)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 41371 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.12E-004 atm-m3/mole (1.13E+001 Pa-m3/mole)
Group Method: 2.45E-004 atm-m3/mole (2.48E+001 Pa-m3/mole)
Exper Database: 9.30E-05 atm-m3/mole (9.42E+000 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: 7.876E-005 atm-m3/mole (7.981E+000 Pa-m3/mole)
VP: 97.3 mm Hg (source: User-Entered)
WS: 1.4E+005 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.85 (user entered)
Log Kaw used: -2.420 (exp database)
Log Koa (KOAWIN v1.10 estimate): 4.270
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.3592
Biowin2 (Non-Linear Model) : 0.1619
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0002 (weeks)
Biowin4 (Primary Survey Model) : 3.7137 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4981
Biowin6 (MITI Non-Linear Model): 0.6448
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.1787
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): 1.3E+004 Pa (97.3 mm Hg)
Log Koa (Koawin est): 4.270
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.31E-010
Octanol/air (Koa) model: 4.57E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 8.35E-009
Mackay model : 1.85E-008
Octanol/air (Koa) model: 3.66E-007

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 17.4457 E-12 cm3/molecule-sec
Half-Life = 0.613 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 7.357 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1.34E-008 (Junge-Pankow, Mackay avg)
3.66E-007 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 17.25 L/kg (MCI method)
Log Koc: 1.237 (MCI method)
Koc : 72.08 L/kg (Kow method)
Log Koc: 1.858 (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 = 0.888 (BCF = 7.72 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.6661 days (HL = 0.2157 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.858 (BCF = 7.213)
Log BAF Arnot-Gobas method (upper trophic) = 0.858 (BAF = 7.213)
log Kow used: 1.85 (user entered)

Volatilization from Water:
Henry LC: 9.3E-005 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 6.79 hours
Half-Life from Model Lake : 151.9 hours (6.329 days)

Removal In Wastewater Treatment:
Total removal: 6.62 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.96 percent
Total to Air: 4.57 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**2.52**	**11.7**	**1000**
Water	**37.6**	**360**	**1000**
Soil	**59.8**	**720**	**1000**
Sediment	**0.0961**	**3.24e+003**	**0**

Persistence Time: 292 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.52	11.7	1000
Water	37.6	360	1000
water	(37.6)		
biota	(0.000133)		
suspended sediment	(0.000973)		
Soil	59.8	720	1000
Sediment	0.0961	3.24e+003	0

Persistence Time: 292 hr

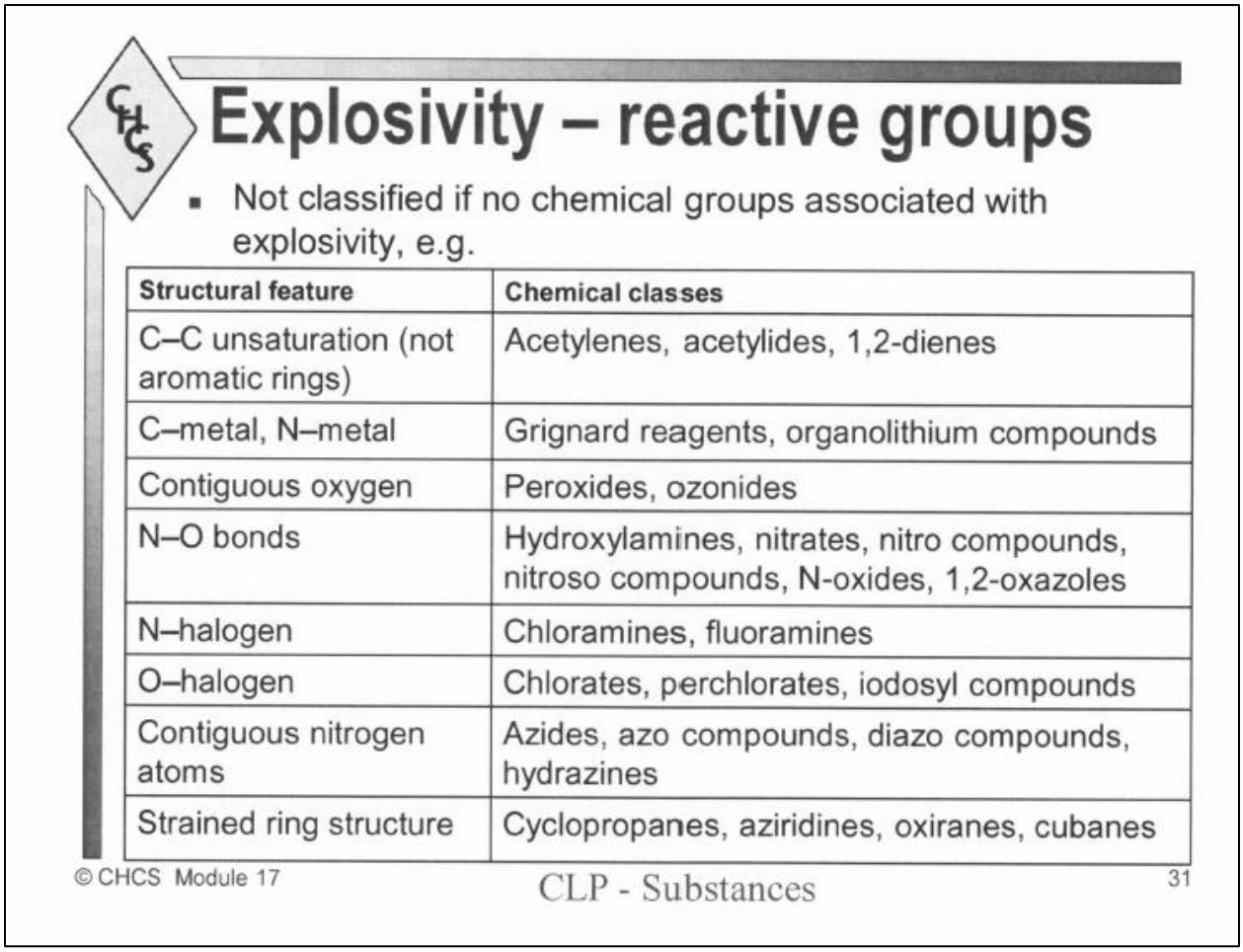
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.23	11.7	1000
Water	33.7	360	1000
water	(33.7)		
biota	(0.000119)		
suspended sediment	(0.00147)		
Soil	64	720	1000
Sediment	0.103	3.24e+003	0

Persistence Time: 317 hr

APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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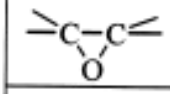
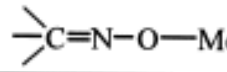
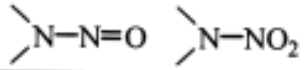
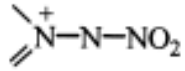
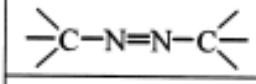
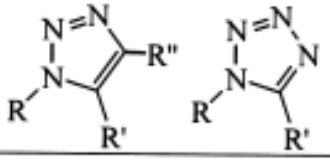
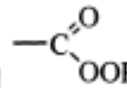
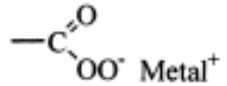
Explosivity – Full List

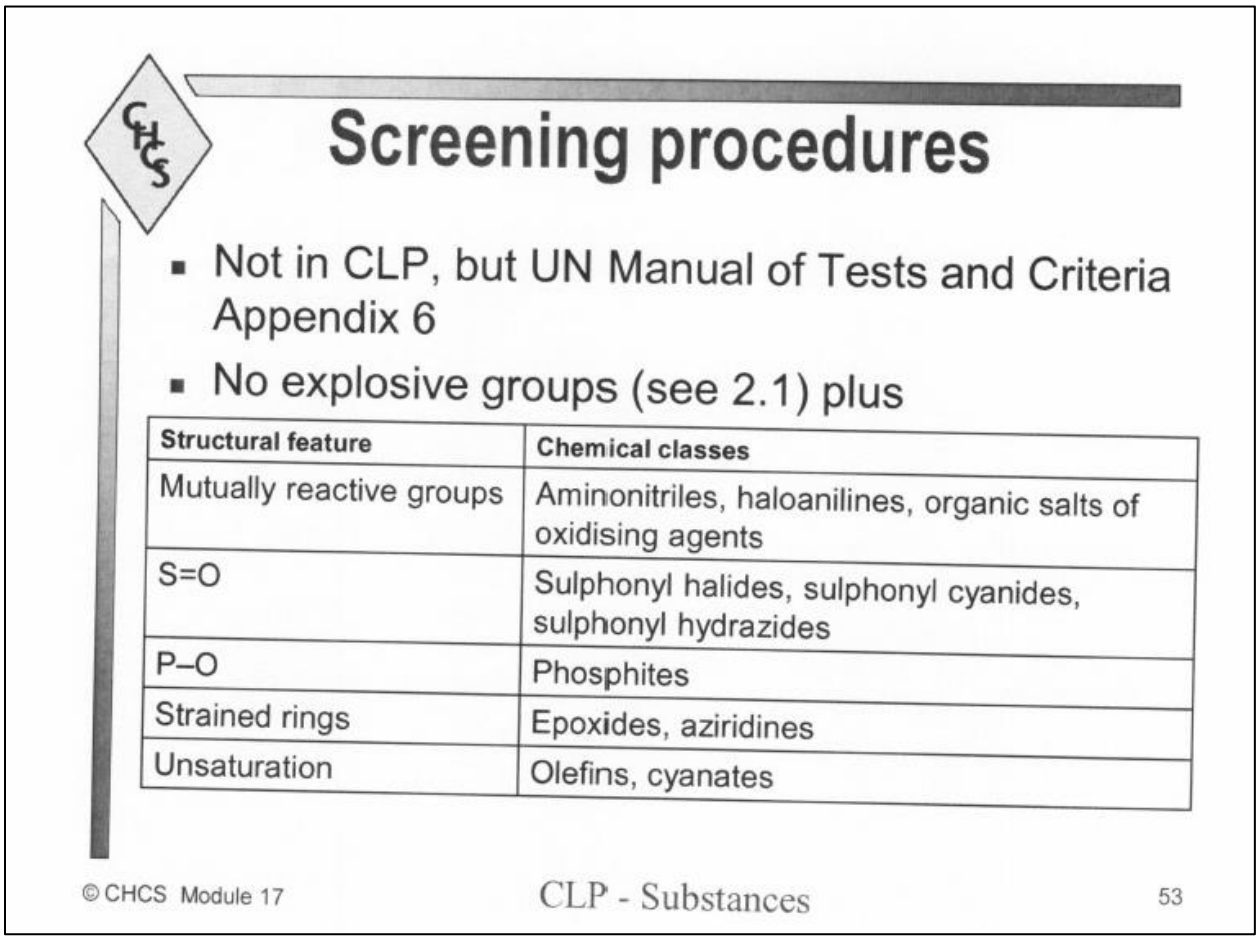
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



APPENDIX L: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for 2-methyltetrahydrofuran. This is a new GreenScreen® assessment.

Table 5: Change in GreenScreen® Benchmark™ for 2-Methyltetrahydrofuran

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
March 28, 2023	BM-2	v 1.4	New assessment

Licensed GreenScreen® Profilers

2-Methyltetrahydrofuran GreenScreen® Evaluation Prepared by:

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2-Methyltetrahydrofuran GreenScreen® Evaluation QC'd by:

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