2-ETHYL-2-(HYDROXYMETHYL)-1,3-PROPANEDIOL

(CAS #77-99-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: December 20, 2023

Expiration Date: December 20, 2028

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GreenScreen® Executive Summary for 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS #77-99-6)

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is a non-flammable, non-volatile solid white powder at standard temperature and pressure. It is a saturated polyol most commonly used as a chemical intermediate, but is also used as a conditioning agent, a cross-linking agent, and in the manufacture of varnishes and resins.

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R and developmental toxicity-D)

Data gaps (DG) exist for endocrine activity-E and neurotoxicity (repeated dose)-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 2-ethyl-2-(hydroxymethyl)-1,3-propanediol meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 2-ethyl-2-(hydroxymethyl)-1,3-propanediol were assigned a High score for the data gaps E and Nr*, it would be categorized as a Benchmark 1 Chemical.

The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in 2022 and in this current 2023 update.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation, and *in vitro* testing for genotoxicity and endocrine activity. 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-ethyl-2-(hydroxymethyl)-1,3-propanediol's NAMs dataset include limited, or lack of, experimental data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and persistence, and lack of established test methods for respiratory sensitization. 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol's Type II (extrapolation output) uncertainties include lack of defined applicability domains of some modeling software examining structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and *in vitro* receptor binding activity assays, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol'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-Ethyl-2-(hydroxymethyl)-1,3-propanediol

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

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

GreenScreen® Chemical Assessment for 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS #77-99-6)

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

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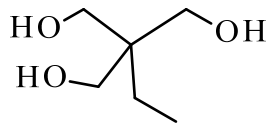
Date: December 20, 2023

Expiration Date: December 20, 2028[2]

Chemical Name: 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol

CAS Number: 77-99-6

Chemical Structure(s):



Also called:
1,1,1-Tris(hydroxymethyl)propane; Trimethylolpropane; 1,1,1-Trimethylolpropane; 1,1,1-Tri(hydroxymethyl)propane; 1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-; 2,2-Bis(hydroxymethyl)-1-butanol; 2-Ethyl-2-(hydroxymethyl)propanediol; EC 201-074-9; EINECS 201-074-9; Ethriol; Ethyltrimethylolmethane; Etriol; Ettriol; Hexaglycerine; Hexaglycerol; Methanol, (propanetriyl)tris-; Propane, 1,1,1-tris(hydroxxymethyl)-; TMP; TMP (alcohol); TMP (VAN); Tri(hydroxymethyl)propane; Trimethylolpropane; Tris(hydroxymethyl)propane; 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol; Propylidynetrimethanol; Propanediol, 2-ethyl-2-(hydroxymethyl)-, 1,3- (PubChem 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).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #s):
A relatively complete dataset was identifed for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol; therefore, no surrogates were used in this assessment.

Identify Applications/Functional Uses: (HSDB 2003)
1. Chemical intermediate
2. Conditioning agent
3. Manufacture of varnishes and resins
4. Crosslinking agent

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

GreenScreen® Summary Rating for 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol[4,5 6,7]: 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental toxicity-D)

Data gaps (DG) exist for endocrine activity-E and neurotoxicity (repeated dose)-Nr*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 2-ethyl-2-(hydroxymethyl)-1,3-propanediol meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 2-ethyl-2-(hydroxymethyl)-1,3-propanediol 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-Ethyl-2-(hydroxymethyl)-1,3-propanediol

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

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

[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.

Environmental Transformation Products

No transformation products were identified for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. It is hydrolytically stable at pH 4, 7 and 9, with a hydrolysis half-life of > 1 year in an OECD Guideline 111 hydrolysis study (ECHA 2023).

Introduction

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is a saturated polyol found in the solid phase at standard temperature and pressure. It is most commonly used as a chemical intermediate, but is also used as a conditioning agent, a cross-linking agent, and in the manufacture of varnishes and resins. The United States Food and Drug Administration (U.S. FDA) recognizes 2-ethyl-2-(hydroxymethyl)-1,3-propanediol as an approved indirect additive under 21 CFR §175.105, §175.300, §175.320, §177.1390, §177.1680, and §177.2420 (U.S. FDA 2023). It is manufactured by aldol condensation of n-butyraldehyde with excess formaldehyde in the presence of a base catalyst such as sodium hydroxide (HSDB 2003).

ToxServices assessed 2-ethyl-2-(hydroxymethyl)-1,3-propanediol against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (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-Ethyl-2-(hydroxymethyl)-1,3-propanediol is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol can be found in Appendix C.

- 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is not listed on the U.S. DOT list.
- 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is on the following lists for multiple endpoints. It is not present on any specified lists for single endpoints.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters
    - Environment Canada – CEPA Domestic Substances List (DSL) – Inherently Toxic to Humans (iTH)

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

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. H Statements reported in the ECHA REACH dossier for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol are reported in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6) (ECHA 2023)

H Statement	H Statement Details
H361fd	Suspected of damaging fertility. Suspected of damaging the unborn child

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Dust respirator; protective gloves; safety glass; protective clothing; protective boots	TCI America 2018	None identified	N/A

Physicochemical Properties of 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol

2-Ethyl-(hydroxymethyl)-1,3-propanediol is a white powder at standard temperature and pressure. It is highly soluble in water but not volatile. Its log K_{ow} of -0.47 to -1.48 suggests it is not likely to bioaccumulate.

Table 3: Physical and Chemical Properties of 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS #77-99-6)

Property	Value	Reference
Molecular formula	$C_6H_{14}O_3$	PubChem 2023
SMILES Notation	CCC(CO)(CO)CO	PubChem 2023
Molecular weight	134.174 g/mol	PubChem 2023
Physical state	Solid	ECHA 2023
Appearance	White powder	ECHA 2023
Melting point	58°C	PubChem 2023, ECHA 2023
Boiling point	289°C 304.2°C	PubChem 2023, ECHA 2023
Vapor pressure	4.49 x 10^{-5} mm Hg at 25°C	PubChem 2023, ECHA 2023
Water solubility	1 x 10^6 mg/L	PubChem 2023
Dissociation constant	pKa = 15	ECHA 2023
Density/specific gravity	1.084 – 1.09 g/cm^3 at 20°C	ECHA 2023
Partition coefficient	Log K_{ow} = -1.48; Log K_{ow} = -0.47	PubChem 2023, ECHA 2023

Toxicokinetics

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is readily absorbed via the gastro-intestinal tract following oral exposure. Rats exposed to up to 10,000 mg/kg of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol showed signs of depression and exhibited increased lacrimation, slow and labored breathing at 1-2 hours

post treatment and exhibited gross pathological findings included changes in lungs, stomach, intestines, and kidneys. Repeated applications of 1% 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in feed (equivalent to 667 mg/kg per study authors) resulted in change to hematology parameters and effects on the liver, spleen, and kidneys. These data are suggestive of absorption via the oral route with systemic availability. Limited evidence of dermal or inhalational absorption has been described in the literature. Although the water solubility, Log K_{ow}, and molecular weight of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol are in the range that favor dermal absorption, no systemic intolerances were reported in dermally-exposed rabbits. Acute inhalational exposure to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol showed some evidence of absorption where animals exposed to 1,800 mg/m^3 had slight disturbance of blood circulation, lung changes, and effects on the liver. Overall, the available data are suggestive of oral and inhalational absorption, but limited dermal absorption following exposure to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (ECHA 2023).

In repeat dose toxicity studies following oral or inhalational exposure to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, histopathological changes were observed primarily in the spleen and the liver, suggesting preferential distribution to those organs. No other data on the distribution of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol was identified in the literature (ECHA 2023).

The polar structure of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol suggests that it will be directly conjugated in a phase-II reaction or will undergo further oxidation in the alcohol moieties of the molecule (ECHA 2023).

The low log K_{ow} value is suggestive that 2-ethyl-2-(hydroxymethyl)-1,3-propanediol will not accumulate in fatty tissues following absorption. Based on the molecular structure, size, and water solubility, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is expected to be excreted unchanged in the urine or as the glucuronide/sulfate conjugate (ECHA 2023).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *M*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Moderate for carcinogenicity based on mixed modeling results. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity (CPA 2018b). The confidence in the score is low as it is based on modeling and no measured data were 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.
- VEGA 2023
  - If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
    - CAESAR v2.1.10 model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a carcinogen with moderate confidence. The global ADI is 0.762, indicating that the prediction is reliable (Appendix D).

  - ISS v1.0.3 model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a carcinogen with moderate confidence. The ADI is 0.762, indicating that the prediction is reliable (Appendix D).
  - IRFMN/ISSCAN-CGX v1.0.2 model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a possible non-carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable and is, therefore, disregarded (Appendix D).
  - IRFMN/Antares v1.0.2 model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a possible non-carcinogen with high confidence. The ADI is 0.819, indicating that the prediction is reliable (Appendix D).
  - IRFMN oral classification v1.0.1 predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is a non-carcinogen with high confidence. The ADI is 0.903, indicating that the prediction is reliable (Appendix D).
  - IRFMN inhalation classification v1.0.1 predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is a non-carcinogen with high confidence. The ADI is 0.903, indicating that the prediction is reliable (Appendix D).
- DTU 2023
  - Danish (Q)SAR Database for the CAS number 77-99-6 reports that 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is in the domains of the E Ultra FDA RCA cancer models for the female rat, male mouse, female mouse, mouse, and rodent and it is predicted to be negative by all these models. It is out of the domains of E Ultra FDA RCA cancer models for the male rat and rat. 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is in the domains of the Leadscope FDA RCA cancer models for the male rat, female rat, and male mouse, which predict that it is positive, negative, and positive, respectively, for carcinogenicity. It is out of the domains of Leadscope FDA RCA cancer models for rat, female mouse, mouse, and rodent. Regarding the liver-specific cancer in rat or mouse model, the Case Ultra, Leadscope, and overall battery predictions are negative and the compound is in the applicability domain; 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is outside the applicability domain of the SciQSAR model (Appendix E).
- U.S. EPA 2021
  - Attempts to model the carcinogenic potential of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol using OncoLogic™ (v9.0) were made; however, this chemical does not fit into any of the chemical classes evaluated by OncoLogic™. Therefore, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol cannot be evaluated using OncoLogic™ (Appendix F).
- ToxTree 2018
  - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol contains a structural alert for nongenotoxic carcinogenicity; substituted n-alkylcarboxylic acids (Appendix G).
- Based on the weight of evidence, a score of Moderate was assigned. VEGA models produced mixed results; three of the six models predicted 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a possible non-carcinogen or non-carcinogen with high confidence and reliable results. The remaining two models in VEGA predicted 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be a carcinogen with moderate confidence. The results from Danish (Q)SAR models were also mixed. It was in the domain for five of seven of the E Ultra FDA RCA cancer models, which all predicted it to be negative; however, it was in the domain for three of the seven Leadscope FDA RCA cancer models, two of which predicted it to be positive. Regarding the liver specific cancer in rat or mouse model, it was in the applicability domain for the model battery and the prediction was negative. OncoLogic™ could not be used to predict the carcinogenic potential of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol as it is not included in any of the chemical classes supported by the program.

According to Toxtree, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol does contain an alert for non-genotoxic carcinogenicity (substituted n-alkylcarboxylic acids). While conclusions from ECHA dossier indicate it is not likely to be carcinogenic as it is not mutagenic (see genotoxicity section below) and no (histo)pathological alterations indicative for a potential carcinogenic effect were observed in the available repeated dose toxicity studies (ECHA 2023), there are no long-term carcinogenicity studies to discount the possibility of nongenotoxic carcinogenicity. Therefore, the positive modeling predictions could not be ruled out, and ToxServices assigned a Moderate score for this endpoint.

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for mutagenicity/genotoxicity based on consistently negative results for genotoxicity in *in vitro* studies. 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 experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECB 2000, ECHA 2023
  - *In vitro:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (99.9% purity) was negative for mutagenicity in a GLP-compliant study conducted according to OECD Guideline 471 and assigned a Klimisch score of 1 (reliable without restriction). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP_2 *uvr*A were exposed to the test substance at concentrations of 0, 312.5, 625, 1,250, 2,500, or 5,000 µg/plate with and without rat liver S9 metabolic activation extract. Distilled water functioned as the vehicle for negative control plates. The vehicle, untreated negative, and positive (AF-2, sodium azide, 9-aminoacridine, 2-aminoanthracene) controls were reported as valid. Treatment did not produce cytotoxicity or statistically significant increase the frequency of revertants at any concentration in the presence or absence of metabolic activation, and the investigators concluded that the test material does not induce gene mutations.
  - *In vitro:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (99.51% purity) was negative for mutagenicity in a GLP-compliant Ames test assigned a Klimisch score of 2 (reliable with restrictions). *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to the test substance at concentrations up to 5,000 µg/plate with and without rat liver S9 metabolic activation extract. The vehicle, untreated negative, and positive (sodium azide, nitrofurantoin, 4-nitro-1,2-phenylene diamine, 2-aminoanthracene) controls were reported as valid. Treatment did not produce cytotoxicity or statistically significant increase the frequency of revertants at any concentration in the presence or absence of metabolic activation, and the investigators concluded that the test material does not induce gene mutations.
  - *In vitro:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (99.9% purity) was negative for clastogenicity in a GLP-compliant study conducted according to OECD Guideline 473 and assigned a Klimisch score of 1 (reliable without restriction). Chinese hamster lung cells were cultured in an unidentified medium with test material dissolved in distilled water to reach overall concentrations of 0, 0.34, 0.67, or 1.34 mg/mL. Samples from each concentration were incubated in the presence or absence of rat liver S9 metabolic activation extract then examined for chromosomal aberrations or polyploidy. The vehicle, untreated negative, and positive (mitomycin C, cyclophosphamide) controls were reported as valid.

Treatment did not significantly increase the incidence of chromosome aberrations in the presence or absence of metabolic activation, so the authors declared the compound of interest to be non-clastogenic in this assay.

- ECHA 2023
    - *In vitro:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol (99.6% purity) was negative for mutagenicity in a GLP-compliant study conducted according to OECD Guideline 476 and assigned a Klimisch score of 1 (reliable without restriction). Cells from the Chinese hamster lung fibroblast line V79 were seeded in an unidentified cell culture medium mixed with the test material dissolved in deionized water to achieve total sample concentrations of 43.8, 87.5, 175, 350, 700, or 1,400 µg/mL. Cells in each concentration were plated with and without rat liver S9 metabolic activation extract. Two experiments were conducted—first, all samples were incubated for four hours and then examined for evidence of excess gene mutations. In the second experiment, S9-exposed cells were incubated for four hours while cells without S9 in their medium were exposed for 24 hours before all samples were evaluated for evidence of gene mutations. The vehicle, untreated negative, and positive (7.12 dimethylbenz(a)anthracene, ethylmethane sulfonate) controls were reported as valid. Treatment did not produce reproducible threefold increases in the mutation frequency in the presence or absence of metabolic activation, so the investigators concluded the test material was not mutagenic in this assay.

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Moderate for reproductive toxicity based on reduced number of implantations in the F1 generation in an extended one generation reproductive toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animals and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on a reliable, well-conducted guideline study on the target substance.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - *Oral:* In a GLP-compliant OECD Guideline 443 extended one-generation reproductive toxicity with F2 generation study assigned a Klimisch score of 1 (reliable without restriction), male and female Wistar rats (25/sex/dose in F0, 20/sex/dose in F1a, F1b, and F1c, and 10/sex/dose in F1 surplus cohort) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) in drinking water at 0, 740, 2,200, or 6,600 ppm (reported as approximately 0, 70-110, 200-330, and 600-1,000 mg/kg/day, respectively). The F0 generation males were dosed for 11-12 weeks (including 10 weeks pre-mating), the F0 females were dosed for 16-19 weeks (including 10 weeks pre-mating), the F1a animals were dosed for 10-12 weeks, the F1b animals were dosed for 14-19 weeks, and the F1c animals were dosed for 3-5 weeks. An F2 generation was produced from the F1b generation. In the F0 generation, females of the high dose group had decreased body weight and body weight gain. Water consumption was increased in a dose-dependent trend. High dose males had increased lymphocyte counts, white blood cell counts, and red blood cell distribution width; high dose females had increased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Changes to clinical chemistry and urinalysis parameters were all withing historical control ranges. Vacuolation of gray matter in the brain and spinal cord was noted in F0 animals of the mid and high dose groups; mid and

high dose F0 animals also showed vacuolation of skeletal muscle, increased incidence and/or severity of myofiber degeneration/regeneration, and/or mononuclear cell infiltrate. There were no adverse effects to the estrous cycle or sperm motility, mating index, precoital time, number of implantation sites, fertility index, and no histopathological abnormalities in the reproductive organs. Gestation duration was slightly longer in high dose females, and post-implantation survival and litter size was decreased at the high dose. Live birth index, viability index, and weaning index were all unaffected by treatment. In the F1b generation (second parental generation) there were no treatment related mortalities or clinical signs of toxicity. Body weight and food consumption of high dose F1 animals was significantly decreased. Ovary to body weight ratios were increased in high dose females and adrenal gland weights were decreased. There were no significant histopathological abnormalities in reproductive organs, and no adverse effects to mating index, precoital time, and fertility index, however, the number of implantation sites was reduced at the high dose. No effects to gestation index or duration of gestation, no signs of prolonged parturition, and no deficiencies in maternal care were noted. No effects to post-implantation survival, sex ratio, and weaning index, however, litter size and live birth index were reduced at the high dose and postnatal loss was increased also at the high dose. In the F1a generation there were no mortalities or clinical signs of toxicity. Body weight and food consumption was reduced at the high dose. Also at the high dose, retinal gliosis was noted. Hematological findings included increased red blood cell distribution width in high dose males and females, increased MCV in high dose females and increases MCH in mid and high dose females. Bilirubin was decreased in males and females at all dose levels (not significant), urea was increased in mid and high dose animals, and creatine was decreased in high dose females. Urinalysis parameters were unaffected by treatment. In high dose F1a animals, brain weights were decreased and ovary weights were increased; increased liver weights were noted at the mid and high dose groups. There were no effects to sexual maturation, estrous cycle, anogenital distance, or nipple retention of the F1a generation. At the high dose, pups of the F1a generation and the cohort surplus had abnormalities of the skull and/or brain that were attributed to treatment; the F1a generation also had thickened spleens and livers. Histopathological examination revealed ventricular dilation in the brain of the F1 generation; however, there was no evidence of vacuolation of the gray matter, no effects to ovarian follicles, and no changes in sperm motility, concentration and morphology. Finally, in the F2 generation, high dose animals had reduced body weights and brain abnormalities consisting of hydrocephaly, a dome-shaped skull, flaccid brain containing fluid and cavity formation in the cerebrum and agenesis of both eyes or fluid in the skull and flaccid brain, were also noted at the high dose. A dose related decrease in normalized anogenital distance was observed in male pups of all dose levels (not significant) and high dose females. There were no effects to nipple retention. F2 animals also had reduced brain weights and increased spleen weights at the high dose. A single incidence of hydrocephaly and small eye was noted at the low dose, and a single incidence of partly closed eye was noted at the mid dose; however, authors indicated a test item-related effect could not be excluded. A reproductive NOAEL of 6,600 ppm and a developmental NOAEL of 2,200 ppm was reported for the F0 generation based on a lack of adverse changes to reproductive parameters and evidence of developmental toxicity in the form of decreased post-implantation index resulting in decreased litter size, decreased viability and weaning indices, decreased mean combined pup wights and increased spleen weights in male pups. A reproductive NOAEL of 2,200 ppm was identified for the F1 generation based on the reduced number of implantations in the F1b cohort identified at 6,600 ppm. Overall, the authors identified a general toxicity NOAEL of 740 ppm, reproductive toxicity NOAEL of 2,200 ppm, and a developmental

toxicity LOAEL of <740 ppm.
    - Based on effects observed in the extended one-generation reproductive toxicity study described above, the REACH dossier authors self-classified 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to GHS Category 2 for reproductive toxicity.
  - *Oral:* In a GLP-compliant OECD Guideline 421 reproduction/developmental toxicity screening test assigned a Klimisch score of 1 (reliable without restriction), male and female Wistar rats (10/sex/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0, 1,500, 3,000, or 6,000 ppm (reported as approximately 0, 250, 500, and 1,000 mg/kg/day, respectively) in drinking water. Males were exposed for 30 days (from 14 days prior to mating through mating period); females with offspring were exposed for 51-57 days (14 days prior to mating up to 14-16 days after delivery); females that failed to deliver pups were exposed for 42-44 days. In the parental generation, there were no mortalities and no clinical signs of toxicity reported. Males had reduced body weight at the high dose and to a lesser extend at the mid dose. Females of the mid and high dose lost weight in a dose-dependent manner. Length and regularity of the estrous cycles, sperm measures, and fertility index were not affected by treatment. In the F1 generation, there were no mortalities or clinical signs reported in pups and body weights were unaffected by treatment. The viability index was not affected by treatment and there were no gross pathological abnormalities. A reproductive and developmental NOAEL of 6,000 ppm (mean overall test item intake of 579 and 802 mg/kg/day in males and females, respectively) was identified based on the lack of adverse effects to reproductive parameters.
- ECB 2000, ECHA 2023
  - *Oral:* In a GLP-compliant OECD Guideline 422 combined repeated dose toxicity study with the reproduction/developmental toxicity screening test assigned a Klimisch score of 1 (reliable without restrictions), Slc:SD rats (12/sex/dose) were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (99.9% purity) for approximately 45 days, including a mating period. The test material was dissolved in water and administered via oral gavage at doses of 0, 12.5, 50, 200, or 800 mg/kg/day. Animals of the parental generation were observed for weight gain, physical or behavioral abnormalities, reproductive index, copulation index, number of copulated pairs, number of mated pairs, fertility index, and pairing days until copulation. Animals were also euthanized and subjected to necropsy for organ macroscopic evaluation at the end of the study period. Reproductive organs evaluated were not specified. No effects were observed in the exposed animals at any dose, and a reproductive NOAEL of 800 mg/kg/day, the highest dose tested, was reported for this study.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Moderate for developmental toxicity based on marginal evidence of developmental toxicity in the presence of maternal toxicity in an OECD Guideline 414 prenatal developmental toxicity study in rats and limited evidence of developmental toxicity in an extended one generation reproductive toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when marginal evidence of developmental toxicity is available or when they are classified as GHS Category 2 (CPA 2018b). The confidence in the score is High as it's based on effects reported in well-conducted and reported studies, that are not commonly associated with maternal toxicity.

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

- *Oral:* In a GLP-compliant prenatal developmental toxicity study according to OECD Guideline 414 and assigned a Klimisch score of 1(reliable without restriction), New Zealand white rabbits (22/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol at 50, 150, or 450 mg/kg/day in water on gestation days 6 to 28 via gavage. A maternal toxicity and developmental toxicity NOAEL of 450 mg/kg/day, the highest dose tested, was reported due to the lack of toxicologically significant adverse effects.
- *Oral:* In a GLP-compliant prenatal developmental toxicity study according to OECD Guideline 414 and assigned a Klimisch score of 1(reliable without restriction), Wistar rats were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol at 0, 100, 300, or 1,000 mg/kg/day in water on gestation days 6-20 via gavage. Statistically significant decreased body weight was reported in high dose dams, and absolute and corrected body weight gain was significantly decreased in mid dose dams. Offspring of the mid and high dose dams had decreased body weights. In offspring of the high dose dams, malformations including dysplastic, fore- and hid limb bones, malformation of the eyes, and dilation of brain ventricles, was reported. Skeletal deviations, including retarded ossification and wavy ribs, was also reported in offspring of high dose dams. The authors identified a NOAEL and LOAEL of 100 and 300 mg/kg/day, respectively, due to body weight decrease in maternal animals and fetuses and increased skeletal malformations of the ribs and distal appendages in offspring. However, fetal effects may be secondary to maternal toxicity.
- *Oral:* In the GLP-compliant OECD Guideline 443 extended one-generation reproductive toxicity with F2 generation study in male and female Wistar rats described in detail above, a developmental NOAEL of 2,200 ppm was reported for the F0 generation based on evidence of developmental toxicity in the form of decreased post-implantation index resulting in decreased litter size, decreased viability and weaning indices, decreased mean combined pup wights, and an overall developmental toxicity LOAEL of < 740 ppm was established based on macroscopic findings of the brain/skull and/or eye in the F1 and F2 generations.
    - Based on effects observed in the extended one-generation reproductive toxicity study and the developmental toxicity described above, the REACH dossier authors self-classified 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to GHS Category 2 for developmental toxicity.
- *Oral:* In a GLP-compliant OECD Guideline 421 reproduction/developmental toxicity screening test assigned a Klimisch score of 1 (reliable without restriction), male and female Wistar rats (10/sex/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0, 1,500, 3,000, or 6,000 ppm (reported as approximately 0, 250, 500 and 1,000 mg/kg/day, respectively) in drinking water. Males were exposed for 30 days (from 14 days prior to mating through mating period); females with offspring were exposed for 51-57 days (14 days prior to mating up to 14-16 days after delivery); females that failed to deliver pups were exposed for 42-44 days. A developmental NOAEL of 6,000 ppm (mean overall test item intake of 579 and 802 mg/kg/day in males and females, respectively) was identified based on lack of developmental effects in offspring.
- *Oral:* In a GLP-compliant study conducted according to OECD Guideline 422 and assigned a Klimisch score of 1 (reliable without restrictions), Slc:SD rats were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (99.9% purity) at doses of 0, 12.5, 50, 200, or 800 mg/kg/day in water via gavage. Males were exposed for approximately 42 days, including a mating period; females were exposed from day 14 prior to mating up to day 3 of lactation. Animals of the parental generation were observed for implantation index, delivery index, uterine contents, corpora lutea, number of implantations, and number of early resorptions. Animals of the offspring generation were observed for external abnormalities, litter size, number of pups born alive, sex ratio, number of pups alive on day 4, viability index, and

body weight of offspring on day 4. Animals were also euthanized and subjected to necropsy for organ macroscopic evaluation at the end of the study period. No effects were observed in the offspring of exposed animals at any dose. A developmental toxicity NOAEL of 800 mg/kg/day, the highest dose tested, was reported due to the lack of adverse effects.

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Data Gap for endocrine activity based on insufficient experimental data identified for this endpoint. GreenScreen® criteria classify chemicals as a Low hazard for activity when there is experimental data demonstrating a lack of androgenicity, anti-androgenicity, thyroid effects, estrogenicity, and anti-estrogenicity (CPA 2018b).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral:* In the GLP-compliant OECD Guideline 443 extended one-generation reproductive toxicity with F2 generation study in male and female Wistar rats described in detail above, serum levels of thyroid stimulation hormone (TSH) and thyroxine (T4) were unaffected by treatment in the F0 generation, F1 generation, and cohort surplus. In addition, no statistically significant treatment-related effects were observed on anogenital distance or nipple retention.
  - *Oral:* In a GLP-compliant OECD Guideline 421 reproduction/developmental toxicity screening test assigned a Klimisch score of 1 (reliable without restriction), male and female Wistar rats (10/sex/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0, 1,500, 3,000, or 6,000 ppm (reported as approximately 0, 250, 500 and 1,000 mg/kg/day, respectively) in drinking water. Serum T4 levels in treated F0 animals were not affected by treatment. Additionally, there were no histopathological effects to the thyroid.
  - *Oral:* In a non-GLP, non-guideline study assigned a Klimisch score of 2 (reliable with restrictions), groups of male and female rats (10/sex/dose) were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0.03, 0.1, 0.3, or 1% in the diet (reported to correspond to 20, 67, 200, and 667 mg/kg/day, respectively) for 90 days. Organs of endocrine interest examined for macroscopic and microscopic changes included the pancreas, prostate, epididymides, coagulating gland, seminal vesicle, preputial gland, and uterus. No adverse treatment-related effects were observed in these tissues.
  - *Inhalation:* In a non-GLP, non-guideline subacute inhalation toxicity study assigned a Klimisch score of 2 (reliable with restrictions), two male and two female Alderly Park SPF rats were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol for 15 days. Animals were placed in a whole-body exposure chamber and exposed to a saturated vapor of 0.02 mg/L for six hours per day, five days per week for the test period. Animals were euthanized and subjected to necropsy on day 16, and the adrenal glands and thymus were examined for macroscopic and microscopic changes. No adverse endocrine effects were observed at this exposure level.
- U.S. EPA 2023b
  - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was active in 0/6 estrogen receptor (ER) assays, 0/8 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/8 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix H).
- DTU 2023

  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models (Appendix I):
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is predicted to be negative for estrogen receptor α binding (full training set, human *in vitro*) in Battery, CASE Ultra, and SciQSAR. Negative for estrogen receptor α binding (balanced training set, human *in vitro*) in Battery, Leadscope, and SciQSAR. Negative for estrogen receptor α activation (human *in* vitro) in Battery, CASE Ultra, and SciQSAR. Negative for estrogen receptor activation, CERAPP data (*in vitro*), in Leadscope.
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is predicted to be negative for androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by the Battery, CASE Ultra, Leadscope, and SciQSAR models. Also predicted to be negative for androgen receptor binding, inhibition, and activation by Leadscope.
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol is predicted to be negative for thyroperoxidase (TPO) inhibition (QSAR1 and QSAR2, rat *in vitro*) by Leadscope.
    - All other predictions (PPAR inhibition, RAR inhibition, AhR activation, PXR binding/activation, CYP3A4 induction, CAR activation) were within domain and predicted to be negative by Leadscope.
- VEGA 2023
  - If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
    - The VEGA estrogen receptor-mediated effect IRFMN-CERAPP v1.0.1 model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The global ADI is 0.952, indicating that the prediction is reliable (Appendix J).
    - The VEGA estrogen receptor relative binding affinity IRFMN model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The global ADI is 0.900, indicating that the prediction is reliable (Appendix J).
    - The VEGA androgen receptor-mediated effect (IRFMN/COMPARA) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The global ADI is 0.957, indicating that the prediction is reliable (Appendix J).
    - The VEGA thyroid receptor alpha effect (NRMEA v1.0.1) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1 (Appendix J).
      - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
    - The VEGA thyroid receptor beta effect (NRMEA v1.0.1) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1 (Appendix J).
      - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result (Appendix J).
    - The VEGA glucocorticoid receptor (Oberon v1.0.0) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 0.957 (Appendix J).

- The VEGA thyroperoxidase inhibitory activity (Oberon v1.0.1) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 0.948 (Appendix J).
- The VEGA endocrine disruptor activity screening (IRFMN v1.0.0) model predicts 2-ethyl-2-(hydroxymethyl)-1,3-propanediol to be inactive with no confidence rating. The reliability of this prediction is low based on the model's inability to perform an applicability domain check; therefore, this prediction is disregarded (Appendix J).

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

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

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values > 2,000 mg/kg in animals. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECB 2000, PubChem 2023
  - *Oral:* LD_{50} (rat, sex and strain not specified) = 14,100 mg/kg
  - *Oral:* LD_{50} (mouse, sex and strain not specified) = 13,700 mg/kg
- ECB 2000, ECHA 2023
  - *Oral:* LD_{50} (male and female Wistar rat) > 5,000 mg/kg (GLP and method not specified)
  - *Oral:* LD_{50} (male rat, strain not specified) > 2,500 mg/kg (non-GLP, method not specified)
  - *Inhalation:* 4 hour whole body aerosol LC_{50} (male rat, strain not specified) > 0.85 mg/L (non-GLP, method not specified)
  - *Inhalation:* 4 hour whole body aerosol LC_{50} (rabbit, strain not specified) > 0.29 mg/L (non-GLP, method not specified)
  - *Inhalation:* 4 hour whole body aerosol LC_{50} (rat, strain not specified) > 0.29 mg/L (non-GLP, method not specified)
  - *Inhalation:* 4 hour whole body aerosol LC_{50} (mouse, strain not specified) > 0.29 mg/L (non-GLP, method not specified)
  - *Inhalation:* 4 hour whole body aerosol LC_{50} (guinea pig, strain not specified) > 0.29 mg/L (non-GLP, method not specified)
- ECHA 2023
  - *Oral:* LD_{50} (male rat, strain not specified) = 14,700 mg/kg (non-GLP, method not specified)
  - *Oral:* LD_{50} (male rat, strain not specified) > 5,010 mg/kg (non-GLP, method not specified)
  - *Dermal:* LD_{50} (rabbit, sex and strain not specified) > 10,000 mg/kg (non-GLP, method not specified)
- ECB 2000
  - *Dermal:* LD_{50} (rat, sex and strain not specified) > 500 mg/kg (non-GLP, method not specified)

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for systemic toxicity (single dose) based on a lack of systemic toxicity at oral and dermal doses below 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on experimental data from multiple studies with the target substance.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - *Oral:* In a non-GLP-compliant acute oral toxicity study, male rats (5/dose, strain not specified) were administered the test substance at 1,000, 2,150, 4,640, 10,000, or 21,500 mg/kg via gavage. All animals in the highest-dose group displayed significantly depressed movement as well as a loss of placing, righting, and pain reflexes before dying within 24 hours of the treatment. No other mortality was observed. Necropsies demonstrated pyloric irritation, small intestine and peritoneum distention and edema, and congested kidneys and adrenal glands of those that died. The dose of 1,000 mg/kg was well-tolerated, as none of the animals in this dose group demonstrated behavioral or gross pathological abnormalities. Animals in the three intermediate dose groups demonstrated depressed behavior, slow and labored breathing, ataxia, and lacrimation. No gross pathological changes were reported at 1,000 and 2,150 mg/kg. Doses of 4,600 mg/kg and above induced congestion of blood in the renal medullae.
    - *Oral:* In an acute oral toxicity study, male and female Wistar rats (5/sex/dose) were administered the test substance at 5,000 mg/kg via gavage. There were no mortalities, clinical signs of toxicity, or effects to body weight.
    - *Oral:* In an acute oral toxicity study, male rats (5/dose, strain not specified) were administered the test substance at 1,000 or 5,010 mg/kg via gavage. There were no mortalities, clinical signs of toxicity, no effects to body weight, and no adverse gross pathological effects.
    - *Dermal:* In a non-GLP-compliant acute dermal toxicity study, rabbits (4/dose, sex and strain not specified) were administered the test substance at 1,000, 2,150, 4,640, or 10,000 mg/kg under occlusive conditions for 24 hours. There were no mortalities, no clinical signs of toxicity and no adverse effects to body weight. Hyperemic zones at the cortico-medullary junction was reported in the kidneys of animals administered 2,150 mg/kg and above.
    - *Inhalation:* In a non-GLP-compliant acute inhalation toxicity study, male rats (20/concentration, strain not specified) were exposed to aerosolized 2-ethyl-2-(hydroxymethyl)-1,3-propanediol dissolved in ethanol/lutrol (1:1) via whole body inhalation at nominal concentrations of 2.5 or 5.0 mg/L (corresponded to measured concentrations of 0.59 and 0.85 mg/L, respectively) for 4 hours. No mortality, clinical signs of toxicity, changes to body weight, or gross pathology were observed.

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for systemic toxicity (repeated dose) based on the oral NOAEL and LOAEL of 200 and 800 mg/kg/day in the 45-day oral toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when oral LOAEL values are greater than 100 mg/kg/day for 90 day studies (CPA 2018b). The confidence in the score is high as it is based on reliable and well-reported studies.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral:* In a non-GLP, non-guideline study assigned a Klimisch score of 2 (reliable with restrictions), groups of male and female rats (10/sex/dose) were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0.03, 0.1, 0.3, or 1% in the diet (reported to correspond to 20, 67, 200, and 667 mg/kg/day) for 90 days. Animals were observed for mortality and clinical signs daily, they were weighed once per week, food intake was evaluated for the first four weeks as well as at weeks 11 and 12, blood was drawn for hematology at weeks 5 and 13, urinalysis was conducted at week 13, and animals were euthanized and subjected to necropsy at the end of the exposure period. Blood was collected for serum enzyme levels at the time of euthanasia. Organs of interest were removed and examined for macroscopic changes, and the organs from one male and one female animal each from the highest-dose and control groups were also subjected to microscopic histopathological examination. Organs of interest included lung, salivary glands, gastrointestinal tract, trachea, skeletal muscle, aorta, extraorbital lacrimal gland, axillary and mesenteric lymph nodes, pancreas, skin, urinary bladder, sternum with marrow, prostate, epididymides, coagulating gland, seminal vesicle, preputial gland, uterus, spinal cord, and femoral nerve. Significant adverse effects were observed primarily at the highest dose level, and included slight decreases in hemoglobin levels, red blood cell counts, serum SGPT (alanine aminotransferase) and SAP (serum alkaline phosphatase) activity levels; slight increases were observed in relative weights of kidney, liver, and spleen; microscopic abnormalities were observed in liver (increased number of small lymphocytes and normoblasts, slightly enlarged Kupfer cells) and spleen)increased number of small lymphocytes and normoblastin enlarged sinuses, hyperplasia of phagocytically active teticuloendothelial cells). The second-highest dose induced only decreased SGPT and SAP activity. Authors declared a NOAEL and LOAEL of 0.1% (67 mg/kg/day) and 0.3% (200 mg/kg/day), respectively.
    - *As the LOAEL of 200 mg/kg/day is higher than the GHS cutoff of 100 mg/kg/day for subchronic oral studies (UN 2023) and the NOAEL of 67 mg/kg/day is lower than 100 mg/kg/day for GHS Category 2 classification, there is insufficient information to classify 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in this study.*
  - *Oral:* In a GLP-compliant OECD Guideline 422 combined repeated dose toxicity study with the reproduction/developmental toxicity screening test assigned a Klimisch score of 1 (reliable without restrictions), Slc:SD rats (12/sex/dose) were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (99.9% purity) at doses of 0, 12.5, 50, 200, or 800 mg/kg/day via oral gavage for approximately 45 days. The test material was dissolved in water and administered in a bolus of unspecified volume. Animals were mated and reproductive and developmental parameters were analyzed (described in the R and D sections of this screen). Animals were observed for clinical signs throughout the study, then euthanized and subjected to necropsy as well as macroscopic and microscopic histopathological evaluation of organs. Adverse effects were observed primarily in the highest dose group, and included absolute and relative liver weight increase and histopathological alterations to the kidney tubules. The authors identified a NOAEL and LOAEL of 200 and 800 mg/kg/day, respectively.
    - *Due to the 45-day duration of this study, GHS oral guidance values were doubled (i.e., 100 mg/kg/day * 2 = 200 mg/kg/day) as 45 days is approximately ½ the duration of 90 days studies. Thus, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is not*

classifiable under GHS in this study.

- *Oral:* In a non-GLP-compliant, non-guideline study assigned a Klimisch score of 2 (reliable with restrictions), male and female Wistar rats (10/sex/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0.33, 1, or 3% in the diet (reported as corresponding to 220, 667, and 2,000 mg/kg/day, respectively) for 28 days. At the high dose, food efficiency was slightly decreased, water intake was increased (males only), and relative liver and kidney weights were increased. Histopathological examination revealed minimal tubular nephrosis, slight accentuation of the glomerular tuft, and slight deposits of a proteinaceous material in Bowman's space in the kidneys. At the mid and high dose, slightly enlarged hepatocytes containing homogeneous cytoplasm and slight to moderate pericholangitis was reported. The authors identified a NOAEL and LOAEL of 0.33% (220 mg/kg/day) and 1% (667 mg/kg/day), respectively, for this study.
  - *Due to the 28-day duration of this study, GHS oral guidance values were tripled (i.e., 100 mg/kg/day * 3 = 300 mg/kg/day) as 28 days is approximately 1/3 the duration of 90 days studies. Thus, there is insufficient information to classify 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in this study.*
- *Oral:* In a non-GLP-compliant, non-guideline study assigned a Klimisch score of 2 (reliable with restrictions), male and female Wistar rats (10/sex/dose) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) at 0.3, 1, 2, or 4% in the diet for 28 days. Body weight was decreased at the high dose. Hemoglobin content was decreased at 2% and 4%, and white blood cells were increased at 4%. The kidney, liver, and spleen weights were increased at 1% and above, heart weight was increased at 2% and above, and the thymus was increased at 4%. Gross and histopathological examinations revealed treatment related abnormalities (not specified) in the spleen, liver, and kidneys at 1% and above; the heart and thymus showed no pathological or histopathological changes. The authors identified a NOAEL and LOAEL of 0.3% and 1%, respectively (equivalent to 276 and 920 mg/kg/day, respectively, for males and 309 and 1,030 mg/kg/day, respectively, for females[9]) for this study.
  - *Due to the 28-day duration of this study, GHS oral guidance values were tripled (i.e., 100 mg/kg/day * 3 = 300 mg/kg/day) as 28 days is approximately 1/3 the duration of 90 days studies. Thus, there is insufficient information to classify 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in this study.*
- *Oral:* In a GLP-compliant OECD Guideline 443 extended one-generation reproductive toxicity with F2 generation study assigned a Klimisch score of 1 (reliable without restriction), male and female Wistar rats (25/sex/dose in F0, 20/sex/dose in F1a, F1b, and F1c, and 10/sex/dose in F1 surplus cohort) were administered 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) in drinking water at 0, 740, 2,200, or 6,600 ppm (reported as approximately 0, 70-110, 200-330, and 600-1,000 mg/kg/day, respectively). The F0 generation males were dosed for 11-12 weeks (including 10 weeks pre-mating), the F0 females were dosed for 16-19 weeks (including 10 weeks pre-mating), the F1a animals were dosed for 10-12 weeks, the F1b animals were dosed for 14-19 weeks, and the F1c animals were dosed for 3-5 weeks. An F2 generation was produced from the F1b generation. In the F0 generation, females of the high dose group had decreased body weight and body weight gain. Water consumption was increased in a dose-dependent trend. High dose males had increased lymphocyte counts, white blood cell counts, and red blood cell

[9] Using the food factor values for Wistar rats, subchronic study (TERA Undated): 0.3% = 3,000 ppm = 3,000 mg/kg feed *0.092 kg feed/kg bw/day = 276 mg/kg/day (males); 0.3% = 3,000 ppm = 3,000 mg/kg feed *0.103 kg feed/kg bw/day = 309 mg/kg/day (females).

distribution width; high dose females had increased MCV and MCH. Changes to clinical chemistry and urinalysis parameters were all withing historical control ranges. Vacuolation of gray matter in the brain and spinal cord was noted in F0 animals of the mid and high dose group; mid and high dose F0 animals also showed vacuolation of skeletal muscle, increased incidence and/or severity of myofiber degeneration/regeneration, and/or mononuclear cell infiltrate. In the F1b generation (second parental generation) there were no treatment related mortalities or clinical signs of toxicity. Body weight and food consumption of high dose F1 animals was significantly decreased. In the F1a generation there were no mortalities or clinical signs of toxicity. Body weight and food consumption was reduced at the high dose. Also at the high dose, retinal gliosis was noted. Hematological findings included increased red blood cell distribution width in high dose males and females, increased MCV in high dose females and increases MCH in mid and high dose females. Bilirubin was decreased in males and females at all dose levels (not significant), urea was increased in mid and high dose animals, and creatine was decreased in high dose females. Urinalysis parameters were unaffected by treatment. In high dose F1a animals, brain weights were decreased and ovary weights were increased; increased liver weights were noted at the mid and high dose groups. The F1a generation also had thickened spleens and livers. Histopathological examination revealed ventricular dilation in the brain of the F1 generation; however, there was no evidence of vacuolation of the gray matter. F2 animals also had reduced brain weights and increased spleen weights at the high dose. Overall, the authors identified a general toxicity NOAEL of 740 ppm (70-100 mg/kg/day), the LOAEL is therefore 2,200 ppm (200-330 mg/kg/day).

- *As the LOAEL of 200 mg/kg/day is higher than the GHS oral cutoff of 100 mg/kg/day for subchronic studies (UN 2023) and the NOAEL of 70 mg/kg/day is lower than 100 mg/kg/day for GHS category 2 classification, there is insufficient information to classify 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in this study.*

- *Inhalation:* In a non-GLP, non-guideline subacute inhalation toxicity study assigned a Klimisch score of 2 (reliable with restrictions), two male and two female Alderly Park SPF rats were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol for 15 days. Animals were placed in a whole-body exposure chamber and exposed to a saturated vapor of 0.02 mg/L for six hours per day, five days per week for the test period. Animals were weighed and examined for clinical signs daily throughout the study, and urine was collected on the last day for biochemical testing. Animals were euthanized and subjected to necropsy on day 16, and the lungs, liver, kidneys, spleen, adrenal glands, heart, jejunum, ileum, and thymus were examined for macroscopic and microscopic changes. No adverse effects were observed at this exposure level; therefore, the NOAEC is > 0.02 mg/L based on the results of this study.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Moderate for neurotoxicity (single dose) based on limited evidence of transient narcotic effects in acute toxicity studies that warrant classification to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when a GHS Category 3 classification for transient narcotic effects is warranted (CPA 2018b). The confidence in the score is low as reversibility of effects were not reported, and similar effects were only observed in one oral study but not in two oral studies in rats at higher doses, or in one dermal and one inhalation studies.

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

- ECHA 2023
    - *Oral:* In a non-GLP-compliant acute oral toxicity study, male rats (5/dose, strain not specified) were administered the test substance at 1,000, 2,150, 4,640, 10,000, or 21,500 mg/kg via gavage. All animals in the highest-dose group displayed significantly depressed movement as well as a loss of placing, righting, and pain reflexes before dying within 24 hours of the treatment. No other mortality was observed. Necropsies demonstrated pyloric irritation, small intestine and peritoneum distention and edema, and congested kidneys and adrenal glands. 1,000 mg/kg was well-tolerated, as none of the animals in this dose group demonstrated behavioral or gross pathological abnormalities. Animals in the three intermediate dose groups demonstrated depressed behavior, slow and labored breathing, ataxia, and lacrimation. Doses above 2,150 mg/kg induced congestion of blood in the renal medullae.
    - *Oral:* In an acute oral toxicity study, male and female Wistar rats (5/sex/dose) were administered the test substance at 5,000 mg/kg via gavage. There were no mortalities, clinical signs of toxicity, or effects to body weight.
    - *Oral:* In an acute oral toxicity study, male rats (5/dose, strain not specified) were administered the test substance at 1,000 or 5,010 mg/kg via gavage. There were no mortalities, clinical signs of toxicity, no effects to body weight, and no adverse gross pathological effects.
    - *Dermal:* In a non-GLP-compliant acute dermal toxicity study, rabbits (4/dose, sex and strain not specified) were administered the test substance at 1,000, 2,150, 4,640, or 10,000 mg/kg under occlusive conditions for 24 hours. There were no mortalities, no clinical signs of toxicity and no adverse effects to body weight. Hyperemic zones at the cortico-medullary junction was reported in the kidneys of animals administered 2,150 mg/kg and above.
    - *Inhalation:* In a non-GLP-compliant acute inhalation toxicity study, male rats (20/concentration, strain not specified) were exposed to aerosolized 2-ethyl-2-(hydroxymethyl)-1,3-propanediol dissolved in ethanol/lutrol (1:1) via whole body inhalation at nominal concentrations of 2.5 and 5.0 mg/L (corresponding to measured concentrations of 0.59 and 0.85 mg/L, respectively) for 4 hours. No mortality, clinical signs of toxicity, changes to body weight, or gross pathology were observed.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified for this endpoint.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for skin sensitization based on negative results for sensitization in a mouse local lymph node assay. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental 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 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not a dermal sensitizer in a GLP-compliant mouse local lymph node assay (LLNA) conducted according to OECD Guideline 429. Female NMRI mice (6/dose) were exposed to the test material at 0, 2, 10, or 50% in dimethylformamide at the dorsal surface of each ear on three consecutive days. Ears and lymph nodes were evaluated for cell proliferation by comparing the weight and cell count data between treated and negative control animals. The positive control treatment, alpha hexyl cinnamic aldehyde at 3%, 10,%, and 30% in acetone/olive oil (4:1) demonstrated a significant increase in ear swelling as well as lymph node cell counts. Stimulation indices (SIs) at 2, 10, and 50% were 1.09, 1.01, and 1.03, respectively. As an SI of 3 was not reached, authors concluded 2-ethyl-2-(hydroxymethyl)-1,3-propanediol was not sensitizing to the skin in this study.
- ECB 2000
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not a dermal sensitizer in a human repeat insult patch test (HRIPT) with 200 volunteers. No further details were provided.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for respiratory sensitization based on lack of dermal sensitization potential following ECHA (2017)'s guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol does not contain any structural alerts for respiratory sensitization (Appendix K).
- 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-ethyl-2-(hydroxymethyl)-1,3-propanediol was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, and as 2-ethyl-2-(hydroxymethyl)-1,3-propanediol does not contain any structural alerts for respiratory sensitization (OECD 2022), 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for skin irritation/corrosivity based on a lack of skin irritation in acute dermal irritation studies in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target substance.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - *In vivo*: 2-Ethyl-2-(hydoxymethyl)-1,3-propanediol was not irritating to the skin in a non-guideline, non-GLP study assigned a Klimisch score of 2 (reliable with restrictions). Two New Zealand white rabbits were exposed to 500 mg 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (purity not reported) moistened into a paste with water, gently spread over the surface of one ear, and covered with a semi-occlusive dressing for 24 hours. The unexposed ear of each animal served as a negative control. At the end of the exposure period, the test material was washed away with water and soap, and the animals were observed for a post-exposure recovery time of seven days. Erythema and edema were evaluated at days 0, 2, and 7 of the recovery period. Scores of zero were recorded for both metrics and both animals at every time point, and the investigators concluded that the test material was not a skin irritant in this study.
    - *In vivo*: 2-Ethyl-2-(hydoxymethyl)-1,3-propanediol was not irritating to the skin in a study conducted similar to OECD Guideline 404 and assigned a Klimisch score of 2 (reliable with restrictions). Vienna white rabbits (2/exposure duration) received 1 g test material applied to a shaved patch on the flank and covered in an occlusive dressing. A second shaved patch without test material but also covered by the dressing served as a negative control site for each animal. Two animals were observed at 1, 5, and 15 minutes after application while another two animals were observed at 20 hours post-application for adverse effects. Test material was removed with water and a mild detergent in all cases. Animals were observed for eight days after the dressing and test material were removed, and were scored for irritation and corrosion along a 0-4 scale. All animals were assigned a score of 0 – no irritation – at 20 hours post-exposure. One animal in the short-exposure treatment condition displayed slight, reversible erythema upon removal of the test material. The study's authors concluded that the compound of interest was not irritating under the conditions of this study.
    - *In vivo*: In an *in vivo* study (non-GLP, method not specified) with a Klimisch score of 2 (reliable with restrictions) rabbits were exposed to 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (100% purity) at doses of 1,000, 2,150, 4,640, or 10,000 mg/kg. Test material was moistened into a paste with water and applied to the shaved abdominal skin surface of four animals. Animals were wrapped in an occlusive gauze dressing for 24 hours, the test material was removed by rinsing with water at the end of the exposure period, and skin was examined for irritation or corrosion for seven days. Slight redness was observed immediately after the exposure period at all doses, but all effects had resolved by day 7 post-exposure.
        - No scoring system was invoked to describe the irritation effects, but the compound appears to have been non-irritating or mildly irritating in this study.
    - Two additional studies have been performed to evaluate skin irritation effects of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, but these studies were each assigned a Klimisch score of 4 (not assignable) due to deficiencies in reporting. Both studies also concluded that the compound of interest is not irritating; therefore, they are not described here in detail.
- ECB 2000
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not irritating to the skin in a human repeat insult patch test (HRIPT) with 200 volunteers. No further details were provided.
- Based on the weight of evidence, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is not likely to present a significant hazard of skin irritation. Though data from the studies described above are not

consistent with the score reporting necessary to classify a compound under GHS criteria (UN 2023), sufficient information is available to note that this hazard is not an endpoint of concern.

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for eye irritation/corrosivity based on lack of eye irritation in acute ocular irritation studies in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *In vivo:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not irritating to the eye in a non-GLP-compliant acute ocular irritation assay (guideline not specified) in which on eye of New Zealand white rabbits (n=2) was instilled with 50 mg unchanged 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. The other eye of each animal served as a negative control. Animals were observed for seven days following exposure, and no irritant effects were observed.
  - *In vivo:* 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not irritating to the eye in a non-GLP study similar to OECD Guideline 405. The study was assigned a Klimisch score of 2 (reliable with restrictions). Prior to application, the test material was heated until it melted into a liquid, which investigators reported at 37-40°C. A droplet of liquid test material was instilled into the conjunctival sac of one eye of two Vienna white rabbits while the other eye received a droplet of saline for a negative control. The test material was not washed or rinsed in any way. Each animal was evaluated for effects to the corneas, irises, conjunctivae, and for chemosis at multiple undisclosed time points within the first day after exposure and on each weekday for the following five days. One of the two rabbits demonstrated slight chemosis in the exposed eye ten minutes after application. Overall, scores of 0 were recorded for all endpoints and no effects persisted to the 24 hour examination. The investigators concluded that the compound of interest was not irritating or corrosive to the eyes in this study.
    - The melting point of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol has been observed at 58°C elsewhere (ECHA 2023, PubChem 2023), so the effects of temperature on the subjects' eyes cannot be ruled out as the cause of the observed chemosis. In addition, the overall score of 0 for chemosis did not warrant GHS categorization (UN 2023).
  - Two additional studies have been performed to evaluate eye irritation effects of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, but these studies were each assigned a Klimisch score of 4 (not assignable) due to deficiencies in reporting. Both studies also concluded that the compound of interest is not irritating; therefore, they are not described here in detail.

<u>Ecotoxicity (Ecotox)</u>

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values > 100 mg/L in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than

100 mg/L in all three trophic levels (CPA 2018b). The confidence in the score is high as it is based on measured data 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.
- ECB 2000, ECHA 2023
  - Nominal 96-hour LC_{50} (*Alburnus alburnus*, bleak) > 10,000 mg/L
  - Nominal 48-hour mobility EC_{50} (*Daphnia magna*, daphnia) = 13,000 mg/L
  - Measured 48-hour mobility EC_0 (*D. magna*, daphnia) > 102 mg/L (GLP-compliant, similar to EU Method C.2)
- ECHA 2023
  - 96-hour LC_{50} (*Oryzias latipes*, Japanese rice fish) > 1,000 mg/L (nominal or measured not specified)
  - 72-hour biomass EC_{50} (*Raphidocelis subcapitata*, green algae) > 1,000 mg/L (nominal or measured not specified)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for chronic aquatic toxicity based on measured and predicted chronic aquatic toxicity values of > 10 mg/L in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L in all three trophic levels (CPA 2018b). The confidence in the score is low as experimental data are not available for all 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 2023
  - 21-day NOEC (*D. magna*, daphnia) >1,000 mg/L (nominal or measured not specified)
- U.S. EPA 2017a
  - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol belongs to the neutral organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 374 mg/L in fish, 137 mg/L in daphnia, and 151 mg/L in green algae (Appendix L).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *M*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Moderate for persistence based on a predicted half-life of 30 days in soil, its dominant compartment. GreenScreen® criteria classify chemicals as a Moderate hazard for persistence when soil is the dominant compartment and the half-life is between 16 to 60 days (CPA 2018b). The confidence in the score is low as it is based on modeling supported by experimental data indicating it is not readily or rapidly biodegradable, but inherently degradable.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECB 2000, ECHA 2023
  - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not readily biodegradable in a GLP-compliant OECD Guideline 301E modified OECD screening test. In this assay, industrial, non-adapted, activated sludge was exposed to test substance (99.4% purity) at 19 mg DOC/L

for 28 days. Only 6% degradation occurred within 28 days.
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was inherently biodegradable in a GLP-compliant OECD Guideline 302B Zahn-Wellens Test. In this assay, aerobic, activated sludge (adaption not specified) was exposed to test substance (99.52% purity) at 100 mg DOC/L for 28 days. The test substance degraded 0% in 1 day, 70% in 7 days, 98% in 14 days, 98% in 21 days, and 100% in 28 days.
- ECHA 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not readily biodegradable in an OECD Guideline 301C modified MITI test. In this assay, aerobic activated sludge (adaptation not specified) was exposed to test substance (purity not reported) at 100 mg active ingredient/L for 14 days. After 14 days, 1.7%, 4%, and 3% biodegradation occurred based on O_2 consumption, TOC removal, and test material analysis, respectively.
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not readily biodegradable in an OECD Guideline 301C modified MITI test. In this assay, aerobic activated sludge (adaptation not specified) was exposed to test substance (99% purity) at 100 mg test material/L for 14 days. Based on O_2 consumption, 2.5% biodegraded after 7 days and 4% biodegraded after 14 days.
- ECB 2000
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was inherently biodegradable in a GLP complaint Biodegradation Test following Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn–Wellens test." After 28 days the test substance degraded by 100%. No other details were provided.
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that 2-ethyl-2-(hydroxymethyl)-1,3-propanediol is expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 62.8% will partition to soil with a half-life of 30 days, 37.2% will partition to water with a half-life of 15 days, and 0.0703% will partition to sediment with a half-life of 135 days (Appendix M).

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Very Low for bioaccumulation based on measured log K_{ow} values of -1.48 and -0.47 and a measured BCF of < 17 in the carp. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is less than 4 and the BCF is less than 100 (CPA 2018b). The confidence in the score is high as it is based on measured data for the target substance.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- PubChem 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol has a measured log K_{ow} of -1.48.
- ECHA 2023
    - In a GLP-compliant study conducted according to OECD Guideline 305C and assigned a Klimisch score of 2 (reliable with restrictions), bioaccumulation of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in fish (*Cyprinus carpio*) was evaluated. Two concentrations of test material, 0.5 and 5 mg/L, were prepared in separate fish habitats, each with treated water flowing through at 200-800 mL/minute. 15-20 carp were placed in each vessel, and the fish were observed for six weeks. Water was tested twice every week to confirm test material concentrations. At the end of the exposure period, fish were euthanized, prepared, and analyzed for uptake of test material into the tissues. The

investigators calculated a BCF of < 17 for both concentrations and concluded that bioconcentration probability in this carp species is low.
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol has a measured log K_{ow} of -0.47.
- U.S. EPA 2017b
    - BCFBAF predicts a BCF of 3.162 L/kg wet-wt using the regression based model based on a measured log K_{ow} of -1.48, and a BCF of 0.8936 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix M).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for reactivity based on its stability/physical hazard score of 0 from HMIS and NFPA. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the lack of 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.
- TCI America 2018
    - A safety data sheet for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol reports it has a stability/physical hazard score of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives") and NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water (e.g., helium)").
- ECHA 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol does not contain chemical groups associated with oxidizing or explosive properties.

Flammability (F) Score (vH, H, M, or L): L
2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was assigned a score of Low for flammability based on it not being flammable in a flammability solids assay and its flammability hazard rating of 1 from HMIS and NFPA. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data.
- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol was not flammable in a UN N.1 flammability assay.
- TCI America 2018
    - A safety data sheet for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol reports it has a flammability hazard score of 1 from HMIS ("Materials that must be preheated before ignition will occur. Includes liquids, solids, semi-solids having a flash point above 93°C") and NFPA ("Materials that require considerable preheating, under all ambient temperatures, before ignition and combustion can occur. Includes some finely divided suspended solids that do not require heating before ignition can occur. Flash point at or above 93.3°C").

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

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

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

As shown in Table 4, Type I (input data) uncertainties in 2-ethyl-2-(hydroxymethyl)-1,3-propanediol's NAMs dataset include limited, or lack of, experimental data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and persistence, and lack of established test methods for respiratory sensitization. 2-Ethyl-2-(hydroxymethyl)-1,3-propanediol's Type II (extrapolation output) uncertainties include lack of defined applicability domains of some modeling software examining structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and *in vitro* receptor binding activity assays, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of 2-ethyl-2-(hydroxymethyl)-1,3-propanediol's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** No *in vivo* data for estrogen, androgen, and steroid signaling pathways are available. **Skin sensitization:** Available HRIPT experimental data have very limited reported details. **Skin irritation**: Available HRIPT experimental data have very limited reported details. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Persistence:** No experimental data are available on environmental partitioning and half-lives of ultimate degradation in each compartment.

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

Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). Danish (Q)SAR database contain predictions for a limited number of chemicals that does not include the target chemical (DTU 2023). Of the five models in VEGA that produced reliable (i.e., Global AD index >0.7) predictions, the concordance index of the IRFMN-Antares model is 0.667 and CAESAR model is 0.498, which is below the desirable score of 0.7, and the read-across chemicals used in these models have additional functional groups than the target compound, limiting the confidence of the prediction from these models. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[12] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[13]. **Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays and *in silico* modeling of receptor binding is unknown due to lack of consideration of metabolism and other toxicokinetic factors. EDSP Tox 21 assays do not cover all critical endocrine pathways. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/ Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay

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

Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays *In silico* modeling: Danish QSAR/VEGA
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301/302 Biodegradation tests
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-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
									S	R *	S	R *	*	*								
Table 2: Chemical Details																						
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-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol**	**77-99-6**	*M*	**L**	**M**	**M**	DG	**L**	**L**	**L**	*M*	DG	**L**	*L*	**L**	**L**	**L**	*L*	*M*	**vL**	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol	2

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

Table 6

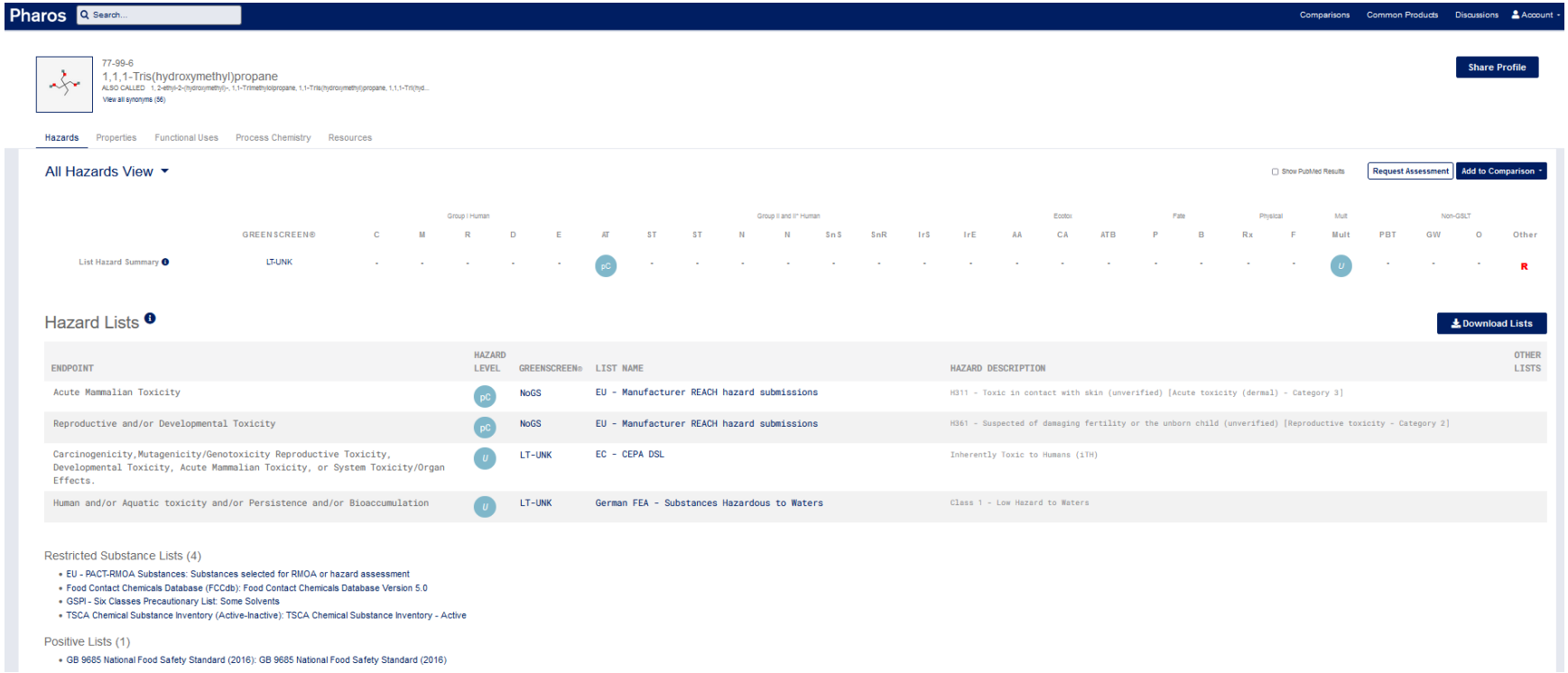
Chemical Name	Final GreenScreen® Benchmark Score
2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol	2

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-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)



APPENDIX D: VEGA Carcinogenicity Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.945
P(NON-Carcinogen): 0.055
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

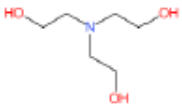
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 57-55-6
Dataset id:677 (Training Set)
SMILES: OCC(O)C
Similarity: 0.826
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #2

CAS: 3296-90-0
Dataset id:93 (Training Set)
SMILES: OCC(CO)(CBr)CBr
Similarity: 0.821
Experimental value : Carcinogen
Predicted value : Carcinogen

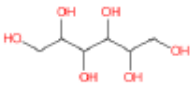


Compound #3

CAS: 102-71-6
Dataset id:772 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

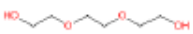
Compound #4

CAS: 111-46-6
Dataset id:240 (Training Set)
SMILES: OCCOCCO
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 69-65-8
Dataset id:421 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.803
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 112-27-6
Dataset id:773 (Training Set)
SMILES: OCCOCCOCCO
Similarity: 0.788
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.762 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.823 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✗	Concordance for similar molecules Concordance index = 0.498 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✓	Model class assignment reliability Pos/Non-Pos difference = 0.89 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 Carcinogen, but the result shows some critical aspects, which require to be checked:
- Accuracy of prediction for similar molecules found in the training set is not optimal
The following alerts have been found: SA41 Substituted n-alkylcarboxylic acids

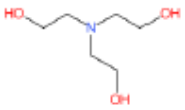
Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
Structural Alerts: SA41 Substituted n-alkylcarboxylic acids
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 3296-90-0
Dataset id:303 (Training Set)
SMILES: OCC(CO)(CBr)CBr
Similarity: 0.821
Experimental value : Carcinogen
Predicted value : Carcinogen

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

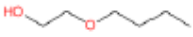


Compound #2

CAS: 102-71-6
Dataset id:652 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

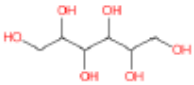
Compound #3

CAS: 111-46-6
Dataset id:860 (Training Set)
SMILES: OCCOCCO
Similarity: 0.808
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



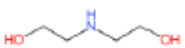
Compound #4

CAS: 111-76-2
Dataset id:596 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.807
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 69-65-8
Dataset id:86 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.803
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 111-42-2
Dataset id:600 (Training Set)
SMILES: OCCNCCO
Similarity: 0.788
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.762 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.82 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.501 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

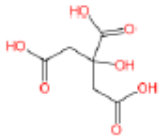
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: SA41 Substituted n-alkylcarboxylic acids

Substituted n-alkylcarboxylic acids

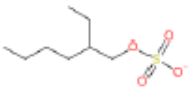
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 77-92-9
Dataset id:829 (Training Set)
SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Similarity: 0.722

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids



CAS: 126-92-1
Dataset id:77 (Training Set)
SMILES: O=S(=O)([O-])OCC(CC)CCCC
Similarity: 0.695

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids

CAS: 103-23-1
Dataset id:52 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.606

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids

Alerts (not found also in the target): SA42 Phthalate diesters and monoesters

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

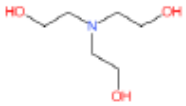
Prediction is Possible NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar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

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
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

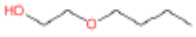
CAS: 3296-90-0
Dataset id:245 (Training Set)
SMILES: OCC(CO)(CBr)CBr
Similarity: 0.821
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

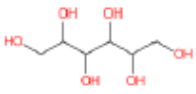
CAS: 102-71-6
Dataset id:533 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 34



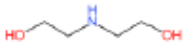
Compound #3

CAS: 111-76-2
Dataset id:498 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.807
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

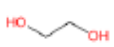
CAS: 69-65-8
Dataset id:69 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.803
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 111-42-2
Dataset id:500 (Training Set)
SMILES: OCCNCCO
Similarity: 0.788
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 34



Compound #6

CAS: 107-21-1
Dataset id:667 (Training Set)
SMILES: OCCO
Similarity: 0.776
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 = 0.816 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.335 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, the result appears reliable.
Anyhow, you should check it through the evaluation of the information given in the following sections.Anyway some issues could be not optimal:
- some similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

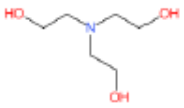
Compound #1

CAS: 57-55-6
Dataset id:677 (Training Set)
SMILES: OCC(O)C
Similarity: 0.826
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #2

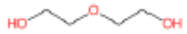
CAS: 3296-90-0
Dataset id:93 (Training Set)
SMILES: OCC(CO)(CBr)CBr
Similarity: 0.821
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 58; Carcinogenity alert no. 59



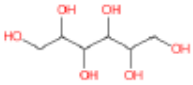
Compound #3

CAS: 102-71-6
Dataset id:772 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



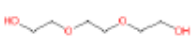
Compound #4

CAS: 111-46-6
Dataset id:240 (Training Set)
SMILES: OCCOCCO
Similarity: 0.808
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 69-65-8
Dataset id:421 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.803
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #6

CAS: 112-27-6
Dataset id:773 (Training Set)
SMILES: OCCOCCOCCO
Similarity: 0.788
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.819 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.822 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
⚠	Concordance for similar molecules Concordance index = 0.667 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

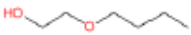
Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 57-55-6
Dataset id:661 (Training Set)
SMILES: OCC(O)C
Similarity: 0.826
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #2

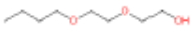
CAS: 111-76-2
Dataset id:509 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.807
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #3

CAS: 71-36-3
Dataset id:362 (Training Set)
SMILES: OCCCC
Similarity: 0.791
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

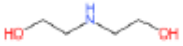
Compound #4

CAS: 75-85-4
Dataset id:336 (Training Set)
SMILES: OC(C)(C)CC
Similarity: 0.79
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 112-34-5
Dataset id:453 (Test Set)
SMILES: OCCOCCOCCCC
Similarity: 0.79
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 111-42-2
Dataset id:451 (Test Set)
SMILES: OCCNCCO
Similarity: 0.788
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.903 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.816 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 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:

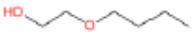
Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
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: 57-55-6
Dataset id:650 (Test Set)
SMILES: OCC(O)C
Similarity: 0.826
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id:482 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.807
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #3

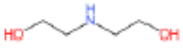
CAS: 71-36-3
Dataset id:314 (Training Set)
SMILES: OCCCC
Similarity: 0.791
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #4

CAS: 75-85-4
Dataset id:283 (Training Set)
SMILES: OC(C)(C)CC
Similarity: 0.79
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #5

CAS: 112-34-5
Dataset id:420 (Test Set)
SMILES: OCCOCCOCCCC
Similarity: 0.79
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 111-42-2
Dataset id:418 (Training Set)
SMILES: OCCNCCO
Similarity: 0.788
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.903 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.816 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

APPENDIX E: Danish QSAR Carcinogenicity Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

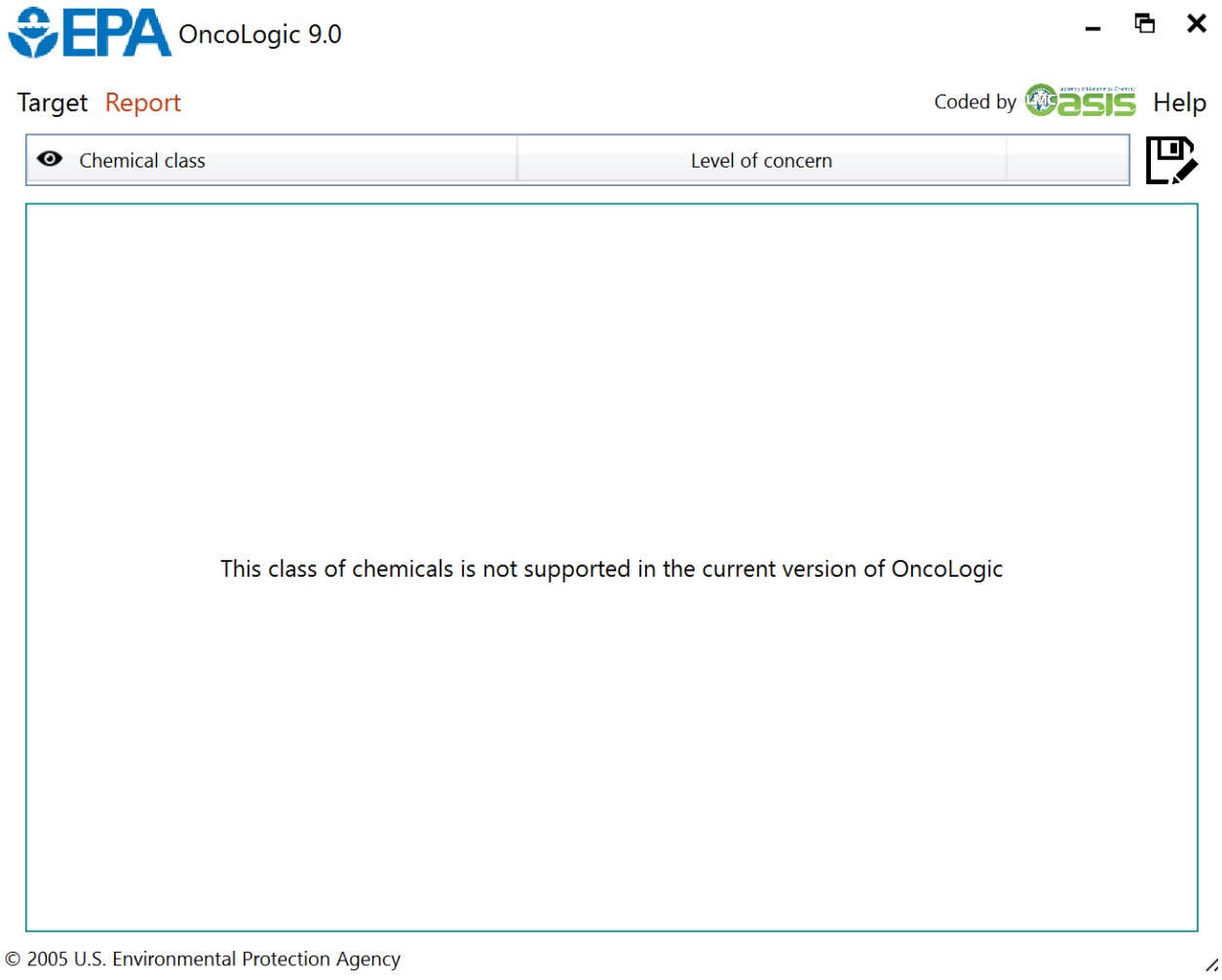
Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	POS_IN
FDA RCA Cancer Female Rat	NEG_IN	NEG_IN
FDA RCA Cancer Rat	POS_OUT	NEG_OUT
FDA RCA Cancer Male Mouse	NEG_IN	POS_IN
FDA RCA Cancer Female Mouse	NEG_IN	NEG_OUT
FDA RCA Cancer Mouse	NEG_IN	NEG_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		

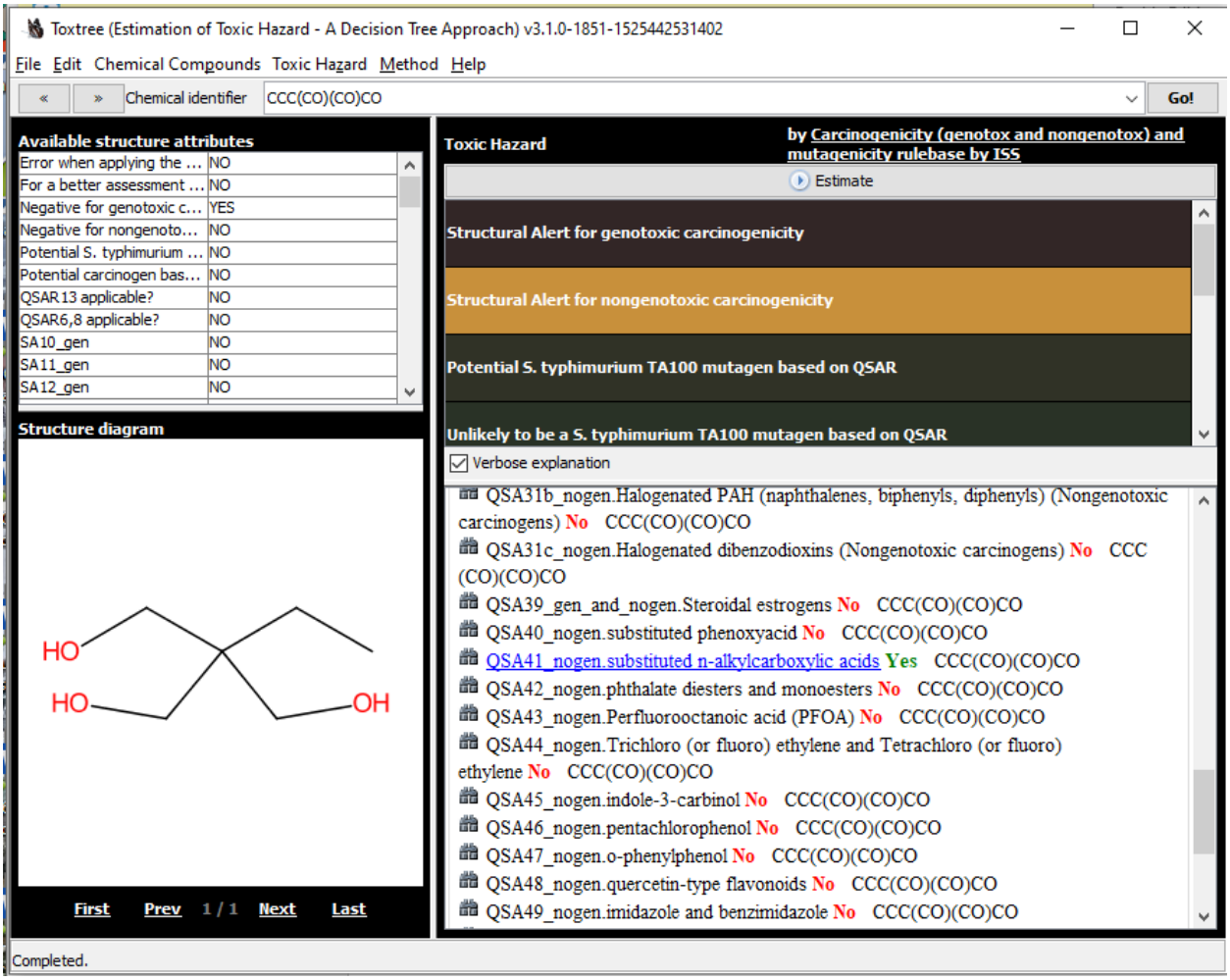
Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	Structural alert for nongenotoxic carcinogenicity; Substituted n-alkylcarboxylic acids (Nongenotox)
Oncologic Primary Classification, alerts in:	
- parent only	Not classified
OECD QSAR Toolbox v.4.2 profilers	
Profiler predictions are supporting information to be used together with the relevant QSAR predictions	

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	NEG_IN	NEG_IN	NEG_OUT
DTU-developed models					

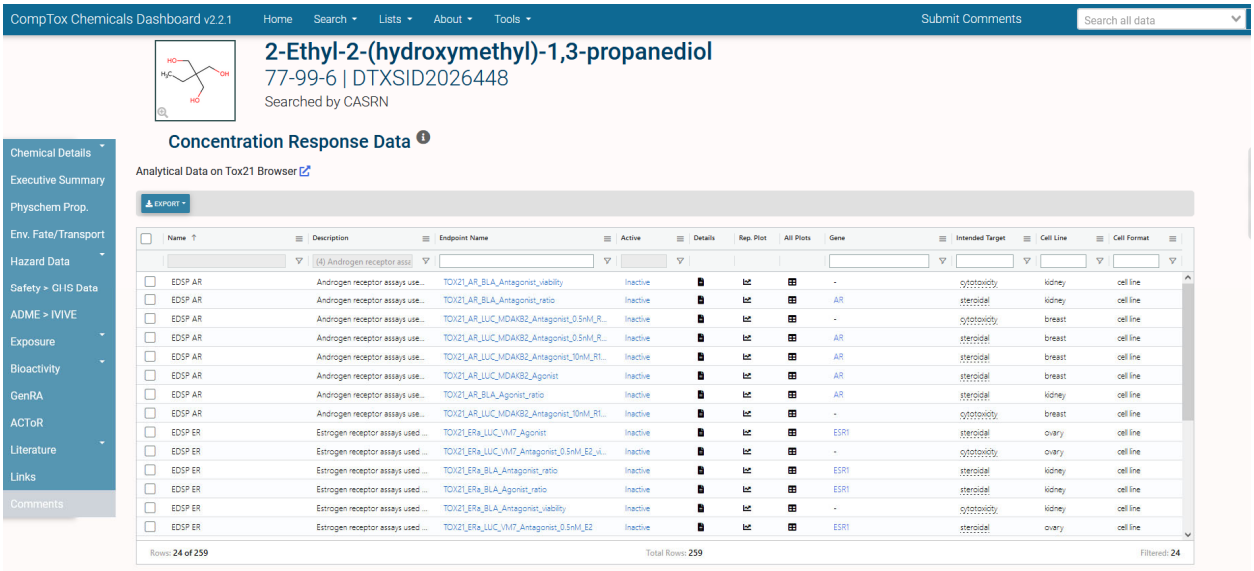
APPENDIX F: OncoLogic™ Carcinogenicity Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

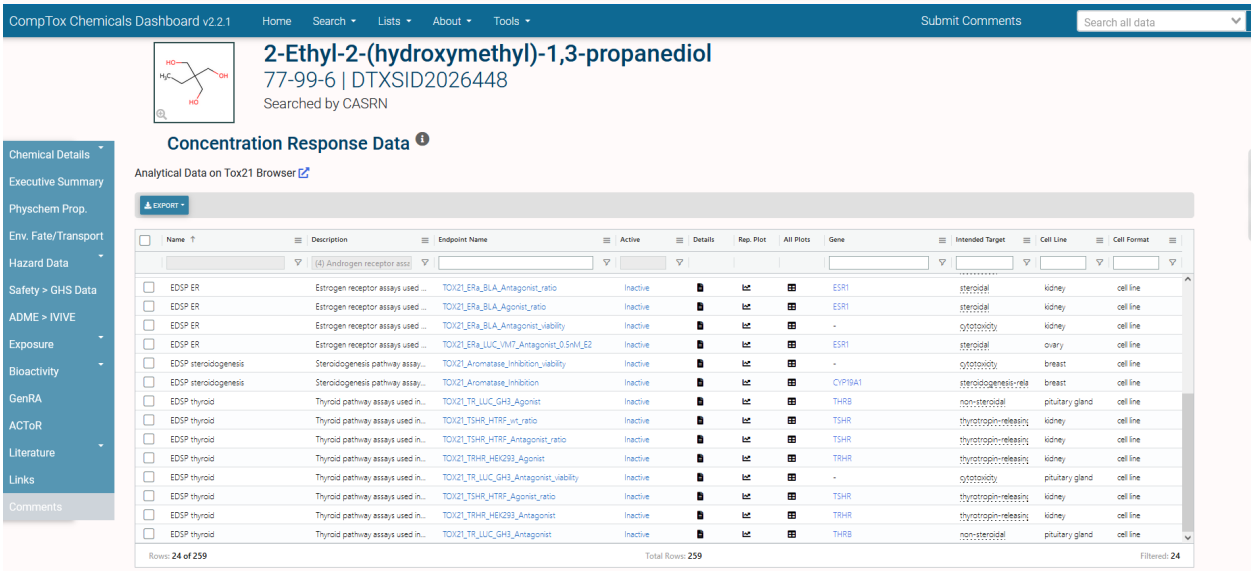


APPENDIX G: Toxtree Carcinogenicity Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)



APPENDIX H: CompTox Endocrine Disruption Screening Program (EDSP) for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)





APPENDIX I: Danish QSAR Endocrine Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

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

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			21462.87	5070.466	5.564008
- µM			159955.8	37788.54	41.46675
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			4341.982	390.3622	16.2925
- µM			32359.38	2909.243	121.4227
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at max. 10 µM (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at any concentration (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Retinoic Acid Receptor (RAR) inhibition at max. 10 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A

DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, non cyclic structure
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	Non binder, non cyclic structure
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

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

APPENDIX J: VEGA Endocrine Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER non-activity alert no. 29

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted ER-mediated effect: NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 1
No. alerts for possible non-activity: 0
Structural Alerts: ER non-activity alert no. 29
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

Compound #1

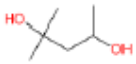
CAS: N.A.
Dataset id:526 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29

Compound #2

CAS: N.A.
Dataset id:612 (Training Set)
SMILES: OCC(C)(C)CO
Similarity: 0.906
Experimental value : NON-active
Predicted value : NON-active

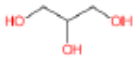
Alerts (found also in the target): ER non-activity alert no. 29



Compound #3

CAS: N.A.
Dataset id:423 (Training Set)
SMILES: OC(C)CC(O)(C)C
Similarity: 0.89
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29



Compound #4

CAS: N.A.
Dataset id:45 (Training Set)
SMILES: OCC(O)CO
Similarity: 0.886
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29

Alerts (not found also in the target): ER possible non-activity alert no. 3

Compound #5

CAS: N.A.
Dataset id:466 (Training Set)
SMILES: OCCCCO
Similarity: 0.876
Experimental value : NON-active
Predicted value : Not predicted

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

Compound #6

CAS: N.A.
Dataset id:136 (Training Set)
SMILES: OCC(N)(CO)CO
Similarity: 0.867
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29

Alerts (not found also in the target): ER non-activity alert no. 33

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.952
Explanation: The predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.906
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: Accuracy of prediction for similar molecules found in the training set is good..

Concordance for similar molecules
Concordance index = 1
Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..

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.

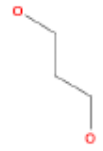
The feature has a non optimal assessment, this aspect should be reviewed by an expert.

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

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: ER non-activity alert no. 29



Fragment related to non-activity for ER-mediated effect, defined by the SMARTS: OCCCO

Following, the most similar compounds from the model's dataset having the same fragment.

CAS: N.A.
Dataset id:526 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925

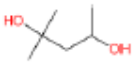
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29

CAS: N.A.
Dataset id:612 (Training Set)
SMILES: OCC(C)(C)CO
Similarity: 0.906

Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29



CAS: N.A.
Dataset id:423 (Training Set)
SMILES: OC(C)CC(O)(C)C
Similarity: 0.89

Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29

1. Prediction Summary

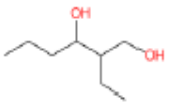
Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is Inactive, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.Anyway some issues could be not optimal:
- Only moderately similar compounds with known experimental value in the training set have been found

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 4
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

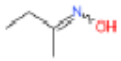


Compound #1

CAS: 94-96-2
Dataset id:17 (Training Set)
SMILES: OCC(CC)C(O)CCC
Similarity: 0.852
Experimental value : Inactive
Predicted value : Inactive

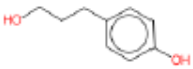
Compound #2

CAS: 107-21-1
Dataset id:22 (Training Set)
SMILES: OCCO
Similarity: 0.776
Experimental value : Inactive
Predicted value : Inactive



Compound #3

CAS: 96-29-7
Dataset id:7 (Training Set)
SMILES: ON=C(C)CC
Similarity: 0.713
Experimental value : Inactive
Predicted value : Inactive

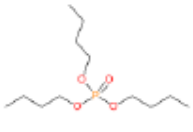


Compound #4

CAS: 10210-17-0
Dataset id:252 (Training Set)
SMILES: Oc1ccc(cc1)CCCO
Similarity: 0.693
Experimental value : Active
Predicted value : Active

Compound #5

CAS: 108-93-0
Dataset id:876 (Test Set)
SMILES: OC1CCCCC1
Similarity: 0.683
Experimental value : Inactive
Predicted value : Inactive



Compound #6

CAS: 126-73-8
Dataset id:18 (Training Set)
SMILES: O=P(OCCCC)(OCCCC)OCCCC
Similarity: 0.679
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.9 Explanation: The predicted compound is into the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.809 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER alert no. 59, inactive

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 1
Structural Alerts: ER alert no. 59, inactive
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

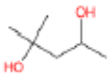
CAS: 115-77-5
Dataset id:922 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER alert no. 59, inactive

Compound #2

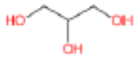
CAS: 126-30-7
Dataset id:930 (Training Set)
SMILES: CC(C)(CO)CO
Similarity: 0.906
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER alert no. 59, inactive



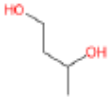
Compound #3

CAS: 107-41-5
Dataset id:544 (Training Set)
SMILES: CC(O)CC(C)(C)O
Similarity: 0.89
Experimental value : NON-active
Predicted value : NON-active



Compound #4

CAS: 56-81-5
Dataset id:363 (Training Set)
SMILES: OC(CO)CO
Similarity: 0.886
Experimental value : NON-active
Predicted value : NON-active



Compound #5

CAS: 107-88-0
Dataset id:900 (Training Set)
SMILES: CC(O)CCO
Similarity: 0.882
Experimental value : NON-active
Predicted value : NON-active

Compound #6

CAS: 110-63-4
Dataset id:757 (Training Set)
SMILES: OCCCCO
Similarity: 0.876
Experimental value : NON-active
Predicted value : NON-active

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.957 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.915 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	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.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: ER alert no. 59, inactive Fragment related to ER inactivity (high reliability), defined by the SMARTS:OCC(C)(C)CO Following, the most similar compounds from the model's dataset having the same fragment.	
	CAS: 115-77-5 Dataset id:922 (Training Set) SMILES: OCC(CO)(CO)CO Similarity: 0.925 Experimental value : NON-active Predicted value : NON-active Alerts (found also in the target): ER alert no. 59, inactive
	CAS: 126-30-7 Dataset id:930 (Training Set) SMILES: CC(C)(CO)CO Similarity: 0.906 Experimental value : NON-active Predicted value : NON-active Alerts (found also in the target): ER alert no. 59, inactive
	CAS: 3296-90-0 Dataset id:278 (Training Set) SMILES: OCC(CBr)(CBr)CO Similarity: 0.821 Experimental value : NON-active Predicted value : NON-active Alerts (found also in the target): ER alert no. 59, inactive

1. Prediction Summary

Prediction for compound Molecule 0 -

EXPERIMENTAL DATA

E xperimental value is Inactive. Model prediction is Inactive (GOOD reliability).

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: Inactive
Predicted TR alpha class: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

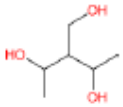
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 77-99-6
Dataset id:4630 (Training Set)
SMILES: OCC(CO)(CO)CC
Similarity: 1
Experimental value : Inactive
Predicted value : Inactive

Compound #2

CAS: 77-85-0
Dataset id:4614 (Training Set)
SMILES: OCC(C)(CO)CO
Similarity: 0.956
Experimental value : Inactive
Predicted value : Inactive

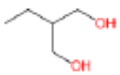


Compound #3

CAS: 921-20-0
Dataset id:4611 (Training Set)
SMILES: OCC(C(O)C)C(O)C
Similarity: 0.953
Experimental value : Inactive
Predicted value : Inactive

Compound #4

CAS: 115-77-5
Dataset id:4631 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : Inactive
Predicted value : Inactive



Compound #5

CAS: 2612-29-5
Dataset id:4634 (Training Set)
SMILES: OCC(CO)CC
Similarity: 0.916
Experimental value : Inactive
Predicted value : Inactive

Compound #6

CAS: 126-30-7
Dataset id:4613 (Training Set)
SMILES: OCC(C)(C)CO
Similarity: 0.906
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: The predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: Accuracy of prediction for similar molecules found in the training set is good..

Concordance for similar molecules
Concordance index = 1
Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..

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 -

EXPERIMENTAL DATA

E xperimental value is Inactive. Model prediction is Inactive (GOOD reliability).

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: Inactive
Predicted TR beta class: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

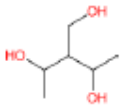
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 77-99-6
Dataset id:4648 (Training Set)
SMILES: OCC(CO)(CO)CC
Similarity: 1
Experimental value : Inactive
Predicted value : Inactive

Compound #2

CAS: 77-85-0
Dataset id:4632 (Training Set)
SMILES: OCC(C)(CO)CO
Similarity: 0.956
Experimental value : Inactive
Predicted value : Inactive

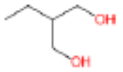


Compound #3

CAS: 921-20-0
Dataset id:4629 (Training Set)
SMILES: OCC(C(O)C)C(O)C
Similarity: 0.953
Experimental value : Inactive
Predicted value : Inactive

Compound #4

CAS: 115-77-5
Dataset id:4649 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : Inactive
Predicted value : Inactive



Compound #5

CAS: 2612-29-5
Dataset id:4652 (Training Set)
SMILES: OCC(CO)CC
Similarity: 0.916
Experimental value : Inactive
Predicted value : Inactive

Compound #6

CAS: 126-30-7
Dataset id:4631 (Training Set)
SMILES: OCC(C)(C)CO
Similarity: 0.906
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 1 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 1 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	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 Inactive, 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: OCC(CO)(CO)CC
Experimental value: -
Predicted Receptor Activity: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

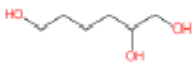
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: N.A.
Dataset id:1343 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : Inactive
Predicted value : Inactive

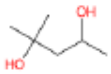
Compound #2

CAS: N.A.
Dataset id:1400 (Training Set)
SMILES: CC(C)(CO)CO
Similarity: 0.906
Experimental value : Inactive
Predicted value : Inactive



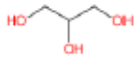
Compound #3

CAS: N.A.
Dataset id:1227 (Training Set)
SMILES: OCCCCC(O)CO
Similarity: 0.9
Experimental value : Inactive
Predicted value : Inactive



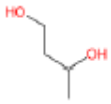
Compound #4

CAS: N.A.
Dataset id:1242 (Training Set)
SMILES: CC(O)CC(C)(C)O
Similarity: 0.89
Experimental value : Inactive
Predicted value : Inactive



Compound #5

CAS: N.A.
Dataset id:1621 (Training Set)
SMILES: OCC(O)CO
Similarity: 0.886
Experimental value : Inactive
Predicted value : Inactive



Compound #6

CAS: N.A.
Dataset id:1250 (Training Set)
SMILES: CC(O)CCO
Similarity: 0.882
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.957 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.915 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	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:

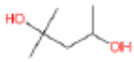
Prediction is INA, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted TPO: INA
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

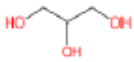
Compound #1

CAS: N.A.
Dataset id:540 (Training Set)
SMILES: OCC(CO)(CO)CO
Similarity: 0.925
Experimental value : INA
Predicted value : INA



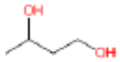
Compound #2

CAS: N.A.
Dataset id:334 (Training Set)
SMILES: OC(C)CC(O)(C)C
Similarity: 0.89
Experimental value : INA
Predicted value : INA



Compound #3

CAS: N.A.
Dataset id:606 (Test Set)
SMILES: OCC(O)CO
Similarity: 0.886
Experimental value : INA
Predicted value : INA

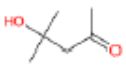


Compound #4

CAS: N.A.
Dataset id:746 (Training Set)
SMILES: OCCC(O)C
Similarity: 0.882
Experimental value : INA
Predicted value : INA

Compound #5

CAS: N.A.
Dataset id:886 (Training Set)
SMILES: OCC(O)C
Similarity: 0.826
Experimental value : INA
Predicted value : INA



Compound #6

CAS: N.A.
Dataset id:836 (Test Set)
SMILES: O=C(C)CC(O)(C)C
Similarity: 0.824
Experimental value : INA
Predicted value : INA

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.948 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.899 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 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

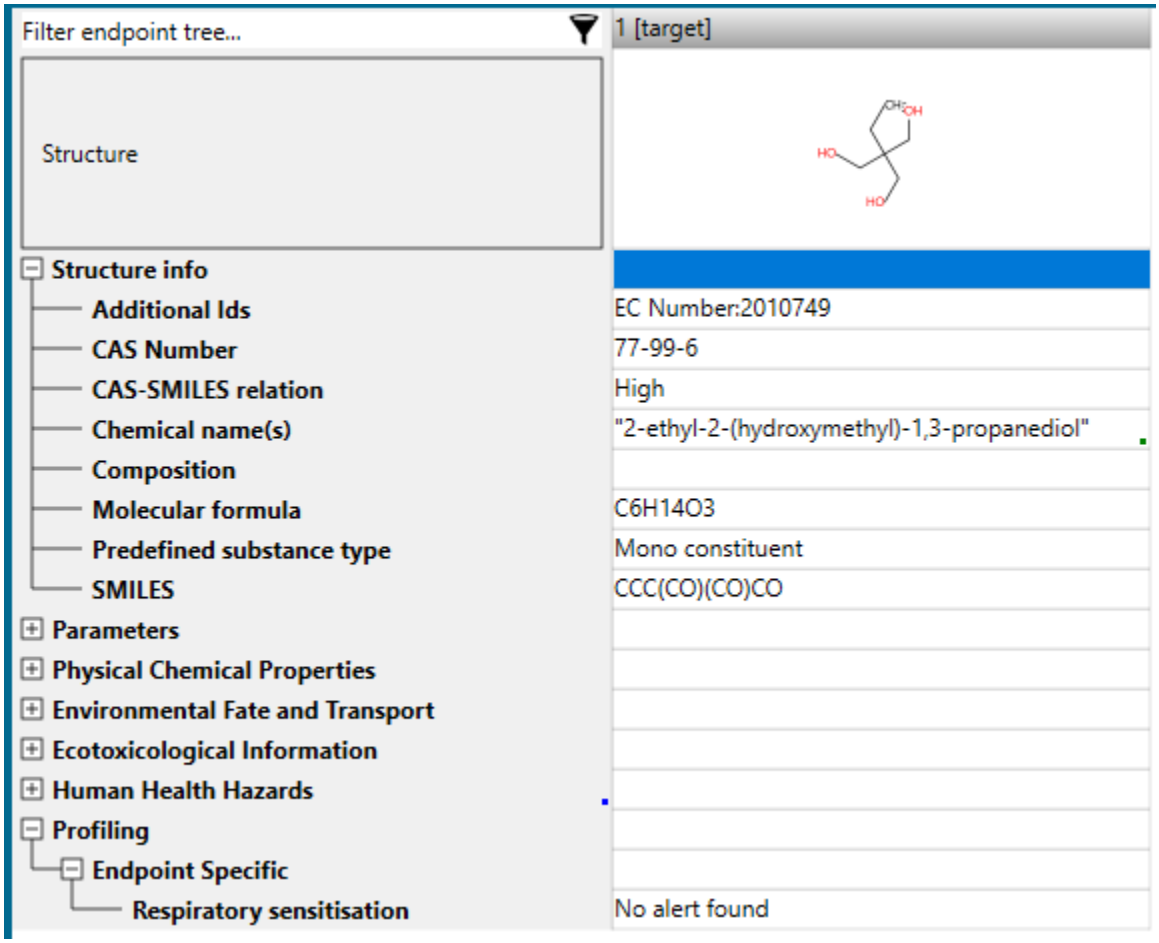
Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is Inactive, it is not possible to perform an assessment.

Compound: Molecule 0
Compound SMILES: OCC(CO)(CO)CC
Experimental value: -
Predicted ED activity: Inactive
ED activity reason: -
Reliability: -
Remarks:
[Model] Unable to perform Applicability Domain check

APPENDIX K: OECD Toolbox Respiratory Sensitization Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)



Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:2010749
CAS Number	77-99-6
CAS-SMILES relation	High
Chemical name(s)	"2-ethyl-2-(hydroxymethyl)-1,3-propanediol"
Composition	
Molecular formula	C6H14O3
Predefined substance type	Mono constituent
SMILES	CCC(CO)(CO)CO
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Endpoint Specific	
Respiratory sensitisation	No alert found

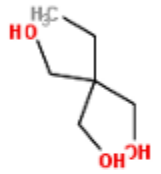
APPENDIX L: ECOSAR Modeling Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
77996	1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-	OCC(CC)(CO)CO

Structure



Details	
Mol Wt	134.18
Selected LogKow	0.19
Selected Water Solubility (mg/L)	1000000
Selected Melting Point (°C)	58
Estimated LogKow	0.19
Estimated Water Solubility (mg/L)	1000000
Measured LogKow	-1.48
Measured Water Solubility (mg/L)	1000000
Measured Melting Point (°C)	58

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	4664.73	5	
Daphnid	48h	LC50	2240.79	5	
Green Algae	96h	EC50	836.03	6.4	
Fish		ChV	374.34	8	
Daphnid		ChV	137.21	8	
Green Algae		ChV	150.87	8	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)	96h	LC50	5809.22	5	
Mysid	96h	LC50	14724.59	5	
Fish (SW)		ChV	208.65	8	
Mysid (SW)		ChV	2176.87	8	
Earthworm	14d	LC50	359.49	6	

APPENDIX M: EPI Suite™ Modeling Results for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol (CAS #77-99-6)

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

CAS Number: 000077-99-6
SMILES : OCC(CC)(CO)CO
CHEM : 1,1,1-TRIS(HYDROXYMETHYL)PROPANE
MOL FOR: C6 H14 O3
MOL WT : 134.18
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): -1.48
Boiling Point (deg C) : 289.00
Melting Point (deg C) : 58.00
Vapor Pressure (mm Hg) : 4.49E-005
Water Solubility (mg/L): 1E+006
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.19
Log Kow (Exper. database match) = -1.48
Exper. Ref: TSCATS

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 280.83 (Adapted Stein & Brown method)
Melting Pt (deg C): 59.71 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 4.22E-005 (Modified Grain method)
VP (Pa, 25 deg C) : 0.00563 (Modified Grain method)
MP (exp database): 58 deg C
BP (exp database): 289 deg C
VP (exp database): 4.49E-05 mm Hg (5.99E-003 Pa) at 25 deg C
Subcooled liquid VP: 9.52E-005 mm Hg (25 deg C, user-entered VP)
: 0.0127 Pa (25 deg C, user-entered VP)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1e+006
log Kow used: -1.48 (user entered)
melt pt used: 58.00 deg C
Water Sol (Exper. database match) = 1e+006 mg/L (deg C)
Exper. Ref: WEAST,RC (1972)

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

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.48E-008 atm-m3/mole (1.50E-003 Pa-m3/mole)
Group Method: 3.08E-015 atm-m3/mole (3.12E-010 Pa-m3/mole)
Exper Database: 7.93E-12 atm-m3/mole (8.04E-007 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: 7.927E-012 atm-m3/mole (8.032E-007 Pa-m3/mole)
VP: 4.49E-005 mm Hg (source: User-Entered)
WS: 1E+006 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -1.48 (user entered)
Log Kaw used: -9.489 (exp database)
Log Koa (KOAWIN v1.10 estimate): 8.009
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.9759
Biowin2 (Non-Linear Model) : 0.9390
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1704 (weeks)
Biowin4 (Primary Survey Model) : 3.8891 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7724
Biowin6 (MITI Non-Linear Model): 0.7791
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.9245
Ready Biodegradability Prediction: YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.0127 Pa (9.52E-005 mm Hg)
Log Koa (Koawin est): 8.009
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.000236
Octanol/air (Koa) model: 2.51E-005
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.00846
Mackay model : 0.0186
Octanol/air (Koa) model: 0.002

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 13.7987 E-12 cm3/molecule-sec
Half-Life = 0.775 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 9.302 Hrs

Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.0135 (Junge-Pankow, Mackay avg)
0.002 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.499 L/kg (MCI method)
Log Koc: 0.176 (MCI method)
Koc : 0.1921 L/kg (Kow method)
Log Koc: -0.716 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.4773 days (HL = 0.003332 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.8936)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.8936)
log Kow used: -1.48 (user entered)

Volatilization from Water:
Henry LC: 7.93E-012 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 8.552E+007 hours (3.563E+006 days)
Half-Life from Model Lake : 9.33E+008 hours (3.887E+007 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.75 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.000185**	**18.6**	**1000**
Water	**37.2**	**360**	**1000**
Soil	**62.8**	**720**	**1000**
Sediment	**0.0703**	**3.24e+003**	**0**

Persistence Time: 591 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000185	18.6	1000
Water	37.2	360	1000

water (37.2)
biota (6.15e-008)
suspended sediment (8.36e-005)
Soil 62.8 720 1000
Sediment 0.0703 3.24e+003 0
Persistence Time: 591 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000189	18.6	1000
Water	39	360	1000
water	(39)		
biota	(6.46e-008)		
suspended sediment	(7.94e-007)		
Soil	60.9	720	1000
Sediment	0.0713	3.24e+003	0

Persistence Time: 579 hr

APPENDIX N: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for 2-ethyl-2-(hydroxymethyl)-1,3-propanediol. The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in 2022 and in this current 2023 update.

Table 5: Change in GreenScreen® Benchmark™ for 2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
July 16, 2015	BM-2	v. 1.2	New assessment.
January 17, 2022	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with v.1.4 criteria and template.
November 20, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with the current template.

Licensed GreenScreen® Profilers

2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol GreenScreen® Evaluation (v 1.2) Prepared by:

SIGNATURE BLOCK

Lindsay Ward, M.S., M.P.H.
Associate Toxicologist
ToxServices LLC

2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol GreenScreen® Evaluation (v 1.2) QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC

2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol GreenScreen® Evaluation (v 1.4) Prepared by:

SIGNATURE BLOCK

Rachel Doerer, M.P.H.
Toxicologist
ToxServices LLC

2-Ethyl-2-(Hydroxymethyl)-1,3-Propanediol GreenScreen® Evaluation (v 1.4) QC'd by:

SIGNATURE BLOCK

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

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol GreenScreen® Evaluation (v 1.4) Updated by:

SIGNATURE BLOCK

Margaret H. Rabotnick, M.P.H.
Associate Toxicologist
ToxServices LLC

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol GreenScreen® Evaluation (v 1.4) QC'd by:

SIGNATURE BLOCK

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