1,2-HEXANEDIOL

(CAS #6920-22-5)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: February 22, 2024

Expiration Date: February 22, 2029

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GreenScreen® Executive Summary for 1,2-Hexanediol (CAS #6920-22-5)

1,2-Hexanediol is a slightly volatile, non-flammable colorless liquid at standard temperature and pressure. It is a short chain 1,2-glycol commonly used as a skin and hair conditioning agent and viscosity controlling agent in personal care products. It is also used as a humectant and solvent in pharmaceuticals, inks and toners, perfumes, and fragrances. It is produced via catalytic oxidation of the corresponding alkene oxide or reduction of the corresponding 2-hydroxy acid.

1,2-Hexanediol was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard scores:

- Benchmark 3c
  - Moderate Group II Human Toxicity (neurotoxicity single exposure-Ns)
  - High Group II Human Toxicity (eye irritation-IrE)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,2-hexanediol meets requirements for a GreenScreen Benchmark™ Score of 3 despite the hazard data gap. In a worst-case scenario, if 1,2-hexanediol were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, aquatic toxicity, persistence, and bioaccumulation, and *in vitro* testing for mutagenicity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

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

Type I (input data) uncertainties in 1,2-hexanediol's NAMs dataset include lack of/insufficient experimental data for carcinogenicity, endocrine activity, respiratory sensitization, and aquatic toxicity, and lack of validated test methods for respiratory sensitization. 1,2-Hexanediol's Type II (extrapolation output) uncertainties include the lack of defined applicability domains in some modeling programs, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the uncertain *in vivo* relevance of *in silico* modeling of receptor activities due to lack of consideration of toxicokinetics, and the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without accounting for non-immunologic mechanisms of respiratory sensitization.

GreenScreen® Hazard Summary Table for 1,2-Hexanediol

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

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of

repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after “repeat” for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for 1,2-Hexanediol (CAS #6920-22-5)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Margaret H. Rabotnick, M.P.H.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: January 21, 2024

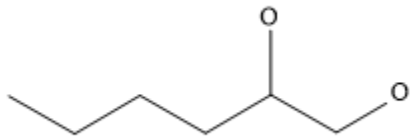
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: February 22, 2024

Expiration Date: February 22, 2029[2]

Chemical Name: 1,2-Hexanediol

CAS Number: 6920-22-5

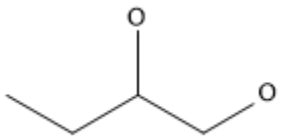
Chemical Structure(s):



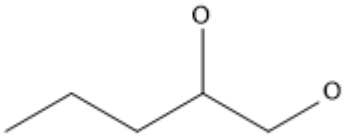
Also called: DL-1,2-Hexanediol; 1,2-Dihydroxyhexane; 5,6-Dihydroxyhexane; dl-hexane-1,2-diol; 1,2-Hexylene Glycol (PubChem 2024)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
1,2-Hexanediol has an incomplete toxicological dataset; limited data exist for most endpoints and no data for carcinogenicity were identified. Therefore, to support the available information on the target substance, data on the structurally related short chain 1,2-glycols 1,2-butanediol (CAS #584-03-2) and 1,2-pentanediol (CAS #5343-92-0) were considered. These chemicals have been evaluated as a group by the Cosmetic Ingredient Review (CIR) Expert Panel in their review of 1,2-glycols (CIR 2012). These surrogates differ from the target chemical only in the length of the carbon backbone attached to the hydroxyl groups at the 1 and 2 positions, with 1,2-butanediol having 2 less carbons than 1,2-hexanediol and 1,2-pentanediol having 1 less carbon than 1,2-hexanediol. Due to their close structural similarity, they are both strong surrogates; however, data on 1,2-pentanediol are prioritized as it is more similar in molecular size to the target substance. No data were identified for the target substance or its surrogates for the carcinogenicty endpoint, therefore, ToxServices used a shorter 1,2-glycol, propylene glycol (CAS #57-55-6) as a conservative surrogate and performed modeling to evaluate this endpoint. Propylene glycol is 3 carbons shorter than 1,2-hexanediol.

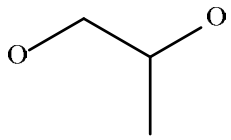
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment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



1,2-Butanediol (CAS #584-03-2)



1,2-Pentanediol (CAS #5343-92-0)



Propylene glycol (CAS #57-55-6)

Identify Applications/Functional Uses: (EC 2024, U.S. EPA 2023, CIR 2012)
1. Skin conditioning agent
2. Solvent
3. Hair conditioning agent
4. Viscosity increasing agent

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

GreenScreen® Summary Rating for 1,2-Hexanediol[4,5 6,7]: 1,2-Hexanediol was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement") (CPA 2018b). This score is based on the following hazard scores:

- Benchmark 3c
    - Moderate Group II Human Toxicity (neurotoxicity single exposure-Ns)
    - High Group II Human Toxicity (eye irritation-IrE)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,2-hexanediol meets requirements for a

[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.

GreenScreen Benchmark™ Score of 3 despite the hazard data gap. In a worst-case scenario, if 1,2-hexanediol 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 1,2-Hexanediol

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As 1,2-hexanediol is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

1,2-Hexanediol is a short chain 1,2-glycol. It is synthesized via catalytic oxidation of the corresponding alkene oxide or reduction of the corresponding 2-hydroxy acid (CIR 2012).

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

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

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

1,2-Hexanediol is listed on the U.S. EPA SCIL as a solvent with a Full Green Circle.

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 2024) 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

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

scores for each human health and environmental endpoint. The output for 1,2-hexanediol can be found in Appendix C.

- 1,2-Hexanediol is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 1,2-Hexanediol is not listed on the U.S. DOT list.
- 1,2-Hexanediol is on the following list for multiple endpoints. It is not present on any GreenScreen®-specified lists for single endpoints.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements (H-Statements) that are harmonized across the European Union (EU) were identified for 1,2-hexanediol. H-Statements reported in the ECHA REACH dossier 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 1,2-Hexanediol (CAS #6920-22-5) (ECHA, CAS #6920-22-5, 2024)

H Statement	H Statement Details
H319	Causes serious eye irritation

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for 1,2-Hexanediol (CAS #6920-22-5)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Safety glasses and/or face shields; protective gloves and clothing; respiratory protection when exposure limits are exceeded or irritation or other symptoms are experienced	ThermoFisher Scientific 2021	None identified	N/A

Physicochemical Properties of 1,2-Hexanediol

1,2-Hexanediol is a colorless liquid at standard temperature and pressure. It is highly soluble in water and volatile. The log K_{ow} of 0.58 indicates a low bioaccumulation potential.

Table 3: Physical and Chemical Properties of 1,2-Hexanediol (CAS #6920-22-5)

Property	Value	Reference
Molecular formula	$C_6H_{14}O_2$	PubChem 2024
SMILES Notation	CCCCC(CO)O	PubChem 2024
Molecular weight	118.17 g/mol	PubChem 2024
Physical state	Liquid	ECHA, CAS #6920-22-5, 2024
Appearance	Colorless	ECHA, CAS #6920-22-5, 2024
Melting point	2°C (ISO 1392)	ECHA, CAS #6920-22-5, 2024

Table 3: Physical and Chemical Properties of 1,2-Hexanediol (CAS #6920-22-5)		
Property	**Value**	**Reference**
Boiling point	228.3°C (OECD Guideline 103)	ECHA, CAS #6920-22-5, 2024
Vapor pressure	0.576 Pa at 25°C (EU Method A.4)	ECHA, CAS #6920-22-5, 2024
Water solubility	> 9,000 g/g water at 23.5°C	ECHA, CAS #6920-22-5, 2024
Dissociation constant	n/a	
Density/specific gravity	0.95 at 20°C (EU Method A.3)	ECHA, CAS #6920-22-5, 2024
Partition coefficient	Log K_{ow} = 0.58 at 25°C (EU Method A.8)	ECHA, CAS #6920-22-5, 2024

Toxicokinetics

No experimental toxicokinetic data are identified for 1,2-hexanediol, specifically.

When a 1 g/kg dose of the surrogate 1,2-butanediol was intravenously infused into rabbits, metabolism was described as slow, it was excreted in the urine either unchanged or as the glucuronide, and there was no accumulation in tissues (CIR 2012).

1,2-Hexanediol is proposed to distribute rapidly to the blood, liver, and kidney and estimated to be excreted in the urine unchanged or conjugated to glucuronide form (ECHA, CAS #6920-22-5, 2024).

Due to high water solubility and expected efficient metabolism to soluble degradation products, 1,2-hexanediol is unlikely to accumulate in the body (ECHA, CAS #6920-22-5, 2024).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

1,2-Hexanediol was assigned a score of Low for carcinogenicity based on negative experimental data for the surrogate propylene glycol, and the weight of evidence from rule-based (VEGA, Toxtree, and OncoLogic) and statistical-based (Danish QSAR) modeling programs. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high based on reliable data on a conservative surrogate supported by modeled data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2001, ECHA, CAS #57-55-6, 2024, CIR 2012
  - *Oral: Surrogate: Propylene glycol (CAS #57-55-6):* A non-GLP compliant 2-year chronic toxicity/carcinogenicity study (guideline not reported) was conducted using male and female Crj: CD(SD) rats (30/sex/dose group). Rats were provided diets containing propylene glycol (purity not specified) at 0, 6,250, 12,500, 25,000, or 50,000 ppm (reported to be equivalent to 0, 200, 400, 900, and 1,700 mg/kg/day for males and 0, 300, 500, 1,000, and 2,100 mg/kg/day for females, respectively) for 2 years. No evidence of treatment-related tumor

induction was observed with treatment (Klimisch 2, reliable with restrictions) (Gaunt et al. 1972).

- *Oral: Surrogate: Propylene glycol (CAS #57-55-6):* A non-GLP compliant 2-year chronic toxicity/carcinogenicity study (guideline not reported) was conducted using male and female rats (strain not specified). Animals were exposed via drinking water at 0, 1, 2, 5, 10, 25, and 50% (reported to be equivalent to 0, 1,600, 3,680, 7,700, 13,200, 21,000, and 37,000 mg/kg/day) for 140 days (5/sex/dose). Animals were evaluated based on food and water consumption, body weights, urinalysis, gross pathology, and histopathology of the kidneys, heart, spleen, and liver. All animals exposed at ≥ 25% died within the first 9 days of exposure. Food intake was slightly reduced in the 10% group compared to controls; however, there were no significant effects on water consumption or body weights in groups exposed at up to 10%. Albuminuria, cells, or casts in the urine were identified in animals administered 1 to 10% solutions (no further details provided). There were no significant findings based on gross pathology or histopathology in rats exposed at up to 10%. The NOAEL was assigned at 13,200 mg/kg/day (Klimisch 2, reliable with restrictions) (Seidenfeld and Hanzlik 1932).
- *Oral: Surrogate: Propylene glycol (CAS #57-55-6):* Albino rats were provided diets containing propylene glycol (purity not specified) at 0, 2.45 and 4.9% in the diet for 2 years (6 males and 4 females/dose). Animals were evaluated based on cage side observations, food and water consumption, body weights, food efficiency, gross pathology, and histopathology of the lung, heart, liver, kidney, adrenal, and testis (routinely), and the pancreas, stomach, intestines, and lymph in about half of the animals, and other organs occasionally. Slight chronic liver damage was the only effect reported (no further details provided). The NOAEL was assigned at 4.9% in the diet (Klimisch 2, reliable with restrictions) (Morris et al. 1941).
- *Oral: Surrogate: Propylene glycol (CAS #57-55-6):* A non-GLP compliant 2-year chronic toxicity/carcinogenicity study (method not reported) was conducted using male and female Beagle dogs (5/sex/dose group). Dogs were provided food containing propylene glycol (USP) at 0, 8%, or 20% (equivalent to 0, 2,000, and 5,000 mg/kg/day, respectively) for 2 years. Tumor incidences were unchanged in male and female dogs when compared to the controls (Klimisch 2, reliable with restrictions) (Weil et al. 1971).
- *Dermal: Surrogate: Propylene glycol (CAS #57-55-6):* In a skin painting study, propylene glycol was administered to female mice at 2, 10 or 21 mg/day over the lifetime. No increase in dermal tumors was observed (Klimisch 2, reliable with restrictions) (Stenbäck and Shubik 1974).
- *Inhalation: Surrogate: Propylene glycol (CAS #57-55-6):* Groups of 20 white rats were exposed to a supersaturated atmosphere with propylene glycol vapor (> 350 mg/m^3), whole-body, 24 hours/day, for up to 18 months. The number of rats was increased by birth of young. Observations in life were recorded for body weight gain, coat color, conjunctival effects, number of young born, and general conditions. Rats were sacrificed at intervals of 3 to 18 months from the beginning of exposure. Urine was aspirated from the bladder for urinalysis, gross pathological and histopathological (lungs, liver, kidney, and spleen) examinations were performed. There were no increases in tumor incidence observed (Klimisch 2, reliable with restrictions) (Robertson et al. 1947).
- *Inhalation: Surrogate: Propylene glycol (CAS #57-55-6):* Two groups of Macaca Rhesus monkeys were exposed to propylene glycol vapor at 100 to 220 mg/m^3 (about 60% saturation), and > 350 mg/m^3 (supersaturation), whole-body, 24 hours/day, for 1 to 13 months (14-15 animals/sex/ group, and 16/sex in the control group). Animals were evaluated based on body weight changes, texture and color of hair and skin, condition of

eyes, appetite, activity, and any abnormal signs or symptoms. Complete blood counts were performed at the beginning of the experiment, and again just prior to sacrifice. Tests for the ability of the kidneys to concentrate urine were conducted at the end of the observation period. Gross pathology and microscopic examinations of the liver, kidneys, spleen, mesenteric glands, adrenals and in certain cases stomach, intestines and tested were performed. Infections with parasitic nematodes and lung mites were found in almost all of the animals. There were no increases in tumor incidence observed (Klimisch 2, reliable with restrictions) (Robertson et al. 1947).

- VEGA 2023
  - ToxServices predicted the carcinogenicity potential of 1,2-hexanediol using the following six VEGA v1.2.3 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/ISSCAN-CGX v1.0.2, IRFMN/Antares v1.0.2, IRFMN oral classification v1.0.1, and IRFMN inhalation classification v1.0.1. 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 1,2-hexanediol to be a carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix D).
    - ISS v1.0.3 model predicts 1,2-hexanediol to be a non-carcinogen with low confidence. The ADI is 0.632, indicating that the prediction is not reliable (Appendix D).
    - IRFMN/ISSCAN-CGX v1.0.2 model predicts 1,2-hexanediol to be a possible **non-carcinogen** with moderate confidence. The ADI is **0.729**, indicating that the prediction is reliable (Appendix D).
    - IRFMN/Antares v1.0.2 model predicts 1,2-hexanediol to be a possible **non-carcinogen** with high confidence. The ADI is **0.929**, indicating that the prediction is reliable (Appendix D).
    - IRFMN oral classification v1.0.2 model predicts 1,2-hexanediol to be a carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix D).
    - IRFMN inhalation classification v1.0.2 model predicts 1,2-hexanediol to be a **non-carcinogen** with high confidence. The ADI is **0.932**, indicating that the prediction is reliable (Appendix D).
- Toxtree 2018
  - 1,2-Hexanediol does not contain a structural alert for genotoxic or nongenotoxic carcinogenicity (Appendix E).
- DTU 2024
  - Danish (Q)SAR Database for the CAS number 6920-22-5 reports that 1,2-hexanediol is in the domains of six of the seven of the E Ultra FDA RCA cancer databases and is predicted to be negative for carcinogenicity in all six databases (female rat, rat, male mouse, female mouse, mouse, and rodent). 1,2-Hexanediol is in the domain of one of the seven Leadscope FDA RCA cancer databases, and is predicted it to be negative for carcinogenicity in the one system (female rat). Regarding the liver specific cancer in rat or mouse model, 1,2-hexanediol is within the domain of all three models (CASE Ultra, Leadscope, and SciQSAR) and the overall battery, and is predicted to be negative in all four (Appendix F).
- U.S. EPA 2019, 2021

  - Attempts were made to evaluate the carcinogenic potential of 1,2-hexanediol using the most current version of OncoLogic (v9.0); however, OncoLogic indicated that its chemical class is not supported in the current version of software. Since the knowledge base used in this version of the program has not changed from the last version, ToxServices used the previous version (v8.0) to evaluate the carcinogenic potential of 1,2-hexanediol. ToxServices evaluated this chemical as an aliphatic alcohol. Medium sized alcohols (C 6-20) are of carcinogenic concern when they can be oxidized to metabolically persistent carboxylic acids (e.g., ω – 1 branched fatty acids). As 1,2-hexanediol is not metabolically persistent, and was negative for genotoxicity in *in vitro* assays (see genotoxicity section below), it has a low concern for carcinogenicity (Appendix G).
- Based on a weight of evidence, a score of Low was assigned. 1,2-Hexanediol does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity according to Toxtree. Three of the six models in VEGA produced reliable predictions for carcinogenicity for 1,2-hexanediol, and it was predicted to be a non-carcinogen in all three models. Danish QSAR modeling database gave consistently negative predictions for carcinogenicity. OncoLogic suggests a low concern for carcinogenicity. The weight of evidence from rule-based (VEGA, Toxtree, and OncoLogic) and statistical-based (Danish QSAR) modeling programs indicates that 1,2-hexanediol is not likely to be carcinogenic.

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

1,2-Hexanediol was assigned a score of Low for mutagenicity/genotoxicity based on consistently negative results in *in vitro* genotoxicity studies with 1,2-hexanediol. 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.
- ECHA, CAS #6920-22-5, 2024
  - *In vitro:* 1,2-Hexanediol was negative for mutagenicity in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471. *Salmonella typhimurium* strains TA1538, TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP_2 *uvr* A pKM 101 were exposed to 1,2-hexanediol (99.5% purity) in water at concentrations of 25, 75, 200, 600, 1,800, and 5,000 µg/plate with and without metabolic activation (Aroclor 1254 rat liver S9 mix). Positive controls were 2-aminoanthracene, sterigmatocystin, 2-nitrofluorene, sodium azide, 9-aminoacridine, and methylmethanesulfonate. Cytotoxicity was reported in the highest dose tested in the *S. typhimurium* strains without metabolic activation only. There were no increases in the frequency of revertants with treatment. Vehicle, untreated negative, and positive controls were reported to be valid (Klimisch 1, reliable without restriction).
  - *In vitro:* 1,2-Hexanediol was negative for clastogenicity in a GLP-compliant chromosome aberration assay conducted according to OECD Guideline 473. Chinese hamster Ovary (CHO) cells were exposed to 1,2-hexanediol (purity not reported) in distilled water at concentrations of 295, 590 and 1180 µg/mL with and without metabolic activation (induced by Aroclor in rat liver) in an initial test and at 148, 295, 590 and 1180 µg/mL without metabolic activation in a repeated assay. Positive controls were mitomycin C and cyclophosphamide. There was no cytotoxicity reported. A significant increase in chromosomal aberrations was reported in the non-activated initial assay, but no significant

increase was reported in the repeat assay without metabolic activation. There were no increases in the frequency of cells with chromosomal aberrations in the metabolically activated cells in either the initial or repeat experiment. Untreated negative and positive controls were reported to be valid (Klimisch 1, reliable without restriction).

- *In vitro:* 1,2-Hexanediol was negative for mutagenicity in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476 and EU Method B.17. Chinese hamster lung fibroblasts (V79) were exposed to 1,2-hexanediol (99.6% purity) in dimethylsulfoxide (DMSO) at concentrations of 36.94, 73.88, 147.75, 295.5, 591 and 1,182 µg/mL with and without metabolic activation (Phenobarbital/beta-naphthoflavone induced rat liver S9). Positive controls were ethylmethanesulphonate and 7,12-dimethylbenzanthracene. There was no cytotoxicity reported. There were no increases in the frequency of mutants with treatment. Untreated negative and positive controls were reported to be valid (Klimisch 1, reliable without restriction).

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

1,2-Hexanediol was assigned a score of Low for reproductive toxicity based on the lack of effect to male sperm parameters and female estrous cyclicity in an OECD Guideline 411 subchronic dermal repeated dose toxicity study in rats, and a lack of adverse effects on reproduction in an OECD Guideline 422 combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats with the surrogate 1,2-butanediol. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is primarily based on a screening study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Dermal:* In a GLP-compliant subchronic dermal toxicity study conducted according to OECD Guideline 411, male and female Sprague-Dawley rats (15/sex/dose) were administered 1,2-hexanediol (99.6% purity) in water at doses of 0, 350, 700, and 1,000 mg/kg/day for 90 days. Male animals were evaluated for sperm motility, total sperm count, and sperm morphology. Females estrous cycle data were evaluated and compared to control animals. There were no adverse effects on these parameters in treated males or females (Klimisch 1, reliable without restriction).
  - *Oral: Surrogate: 1,2-Butanediol (CAS #584-03-2)*: In a GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Crj: CD(SD) rats (10/sex/dose group) were administered 1,2-butanediol (> 99% purity) in water at doses of 0, 40, 200, or 1,000 mg/kg/day via gavage. Male rats were exposed for 42 days. Reproductive phase females were dosed from two weeks prior to mating to day 3 of lactation (total of 37 days). There were no mortalities and no adverse effects on body weight, food consumption, hematology parameters, clinical chemistry parameters, organ weight, or pathological examination between the treated and control animals. There was no effect on reproduction/developmental parameters of copulation, implantation, pregnancy, parturition, and lactation. There were no developmental toxicities. The study authors identified a reproductive toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on a lack of effects (Klimisch 2, reliable with restrictions).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L

1,2-Hexanediol was assigned a score of Low for developmental toxicity based on lack of adverse effects in two OECD Guideline 414 prenatal developmental toxicity studies in rats and in an OECD Guideline 422 combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats with the surrogate 1,2-butanediol. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data on the target chemical and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Oral:* In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, pregnant female Crl: CD (SD) IGS BR rats (24/dose) were administered 1,2-hexanediol (purity and vehicle not reported) at doses of 0, 30, 100, and 300 mg/kg/day via gavage on gestation days (GD) 5-19. Animals were sacrificed on GD 20. There were no treatment-related effects on numbers of live litters, implantations, resorptions, live and dead fetuses, sex ratio of the fetuses, average fetus weight, or fetal external examinations. The study authors assigned a maternal and developmental toxicity NOAEL of 300 mg/kg/day, the highest dose tested, based on a lack of effects (Klimisch 1, reliable with restrictions).
  - *Oral:* In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, pregnant female Crl: CD (SD) rats (25/dose) were administered 1,2-hexanediol (purity not reported) in water at doses of 0, 250, 500, and 750 mg/kg/day via gavage on GD 6-19. Animals were sacrificed on GD 20. Maternal body weight gain and body weights were significantly reduced in the highest dose group. Absolute feed consumption was also significantly reduced in the highest dose group. There were no treatment-related effects on numbers of live litters, implantations, resorptions, live and dead fetuses, sex ratio of the fetuses, average fetus weight, or fetal external examinations. The study authors assigned a maternal toxicity NOAEL of 500 mg/kg/day based on reduced weight and a developmental toxicity NOAEL of 750 mg/kg/day, the highest dose tested, based on a lack of effects in offspring (Klimisch 1, reliable with restrictions).
  - *Oral: Surrogate: 1,2-Butanediol (CAS #584-03-2)*: In a GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Crj: CD(SD) rats (10/sex/dose group) were administered 1,2-butanediol (>99% purity) in water at doses of 0, 40, 200, or 1,000 mg/kg/day via gavage. Male rats were exposed for 42 days. Reproductive phase females were dosed from two weeks prior to mating to day 3 of lactation (total of 37 days). There were no mortalities and no adverse effects on body weight, food consumption, hematology parameters, clinical chemistry parameters, organ weight, or pathological examination between the treated and control animals. There was no effect on reproduction/developmental parameters of copulation, implantation, pregnancy, parturition, and lactation. There were no developmental toxicities. The study authors identified a developmental toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on a lack of effects (Klimisch 2, reliable with restrictions).

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

1,2-Hexanediol was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2024
  - 1,2-Hexanediol was inactive for estrogen receptor agonism, antagonism, and binding using the CERAPP Potency Level (from literature) models in ToxCast (Appendix H).

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

1,2-Hexanediol was assigned a score of Low for acute toxicity based on an oral LD_{50} value > 5,000 mg/kg in rats and, with the surrogate 1,2-pentanediol, oral LD_{50} values > 2,000 mg/kg in rats, mice, rabbits, and guinea pigs, a dermal LD_{50} > 2,000 mg/kg in rats, and a 4-hour aerosol inhalation LC_{50} > 7.015 mg/L in rats. 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 and inhalation LC_{50} values are greater than 5 mg/L for dusts/mists/fumes (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Oral:* LD_{50} (male and female Sprague-Dawley rats) > 5,000 mg/kg (non-GLP, OECD Guideline 401) (Klimisch 2, reliable with restrictions)
  - *Dermal: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* LD_{50} (male and female Tif:RAIf (SPF) rats) > 2,000 mg/kg (non-GLP, OECD Guideline 402) (Klimisch 2, reliable with restrictions)
  - *Inhalation: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* 4-hour aerosol LC_{50} (male and female Tif:RAIf (SPF) rats) > 7,015 mg/m^3 (7.015 mg/L) aerosol (non-GLP, similar to OECD Guideline 403) (Klimisch 2, reliable with restrictions)
- CIR 2012
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* LD_{50} (rat, sex and strain not specified) = 12,700 mg/kg
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* LD_{50} (mouse, sex and strain not specified) = 7,400 mg/kg
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* LD_{50} (rabbit, sex and strain not specified) = 3,700 mg/kg
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* LD_{50} (guinea pig, sex and strain not specified) = 5,200 mg/kg

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

1,2-Hexanediol was assigned a score of Low for systemic toxicity (single dose) based on a lack of specific target organ toxicity in an acute oral study in rats and a kinematic viscosity exceeding the GHS

aspiration hazard classification criteria. This is supported by a lack of oral, dermal, and inhalation toxicity studies in rats with the surrogate 1,2-pentanediol. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance and a strong surrogate.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
    - *Oral:* In a non-GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Sprague-Dawley rats (5-10/sex/dose) were administered 1,2-hexanediol (purity not reported) unchanged at doses of 2,043 (males only), 4,408, 6,339, 6,470, 7,838, and 9,500 mg/kg (females only) via gavage and observed for 14 days. A reduction in muscle tonicity and effects on coordination were observed with increased doses. At the dose of 6,339 mg/kg mortality was observed in 1 out of 5 males and in 3 out of 5 females. At the highest dose of 7,838 mg/kg in males and 9,500 mg/kg in females, 4 out of 5 males and 5 out of 10 females died, respectively. There were no adverse effects reported at necropsy (Klimisch 2, reliable with restrictions).
    - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Tif:RAIf (SPF) rats (5/sex/dose) were administered 1,2-pentanediol (purity not reported) in water at a dose of 5,000 mg/kg via gavage and observed for 14 days. There were no mortalities and no adverse effects on body weights. Clinical signs included sedation (up to 5 hours after administration), dyspnea (up to 12 days after administration), exophthalmos (up to 11 days after administration), ruffled fur (up to 8 days after administration), and a curved body position (up to 7 days after administration). There were no adverse effects at necropsy (Klimisch 2, reliable with restrictions).
    - *Dermal: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute dermal toxicity study conducted according to OECD Guideline 402, male and female Tif:RAIf (SPF) rats (5/sex/dose) were administered unchanged 1,2-pentanediol (purity not reported) to the skin at a dose of 2,000 mg/kg for 24 hours under occlusive conditions. There were no mortalities and no adverse effects on body weights. Clinical signs included sedation (up to 5 hours after administration), dyspnea (up to 8 days after administration), exophthalmos (up to 7 days after administration), ruffled fur (up to 8 days after administration), and erythema and edema. There were no adverse effects at necropsy (Klimisch 2, reliable with restrictions).
    - *Inhalation: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute inhalation toxicity study conducted similar to OECD Guideline 403, male and female Tif:RAIf (SPF) rats (10/sex/concentration) were exposed nose only to 1,2-pentanediol (purity not reported) aerosol in air at concentrations of 3,380 and 7,015 mg/m^3 for 4 hours. There were no mortalities and no adverse effects on body weight. Clinical signs included dyspnea, ruffled fur, and curved body position up to 1 day after treatment. Mottled or reddish lungs were noted at necropsy in some animals (Klimisch 2, reliable with restrictions).
    - 1,2-Hexanediol has a dynamic viscosity of 27.7 mPa·s at 40°C in a GLP-compliant OECD Guideline 114 assay (Klimisch 1, reliable without restriction).
        - *According to GHS (UN 2023), the kinematic viscosity (mm^2/s) is calculated as dynamic viscosity (mPa·s) / density (g/cm^3). Therefore, based on a density of 0.95*

g/cm^3 for 1,2-hexanediol, the dynamic viscosity is calculated as 27.7 (mPa·s) / 0.95 g/cm^3 = 29.2 mm^2/s.

- *GHS criteria classify chemicals as aspiration hazards Category 1 or 2 when they are hydrocarbons, alcohols or ketones with a kinematic viscosity of ≤ 20.5 or ≤ 14 mm^2/s at 40°C, respectively, along with consideration of surface tension, water solubility, boiling point and volatility (UN 2023). Although 1,2-hexanediol is a diol with 6 carbons, it has a kinematic viscosity of 29.2 mm^2/s at 40°C. Therefore, a GHS classification for aspiration hazard is not warranted.*

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

1,2-Hexanediol was assigned a score of Low for systemic toxicity (repeated dose) based on an oral LOAEL of 750 mg/kg/day for maternal toxicity in an oral prenatal developmental toxicity study in rats, and a dermal NOAEL of 1,000 mg/kg/day in a 90-day study in rats on itself, and an oral NOAEL of 1,000 mg/kg/day in a 90-day study in rats with the surrogate 1,2-pentanediol. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when the oral LOAEL is greater than 100 mg/kg/day for 90-day studies, and 640 mg/kg/day for 14-day studies, and the dermal LOAEL is greater than 200 mg/kg/day for 90-day studies (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Oral:* In a GLP-compliant oral prenatal toxicity study conducted according to OECD Guideline 414, male and female Crj: CD(SD) rats (25/sex/dose) were administered 1,2-hexanediol (purity not reported) in water at doses of 250, 500, and 750 mg/kg/day on GDs 6 through 19. No toxicologically relevant clinical signs of toxicity or mortality were observed. Maternal body weight gain and maternal weight were significantly reduced in the highest dose group. Absolute and relative feed consumption values were slightly reduced in the 750 mg/kg/day dosage group, but these reductions were only significant on GDs 9 to 12 (absolute only). The study authors identified a maternal systemic toxicity NOAEL of 500 mg/kg/day (LOAEL of 750 mg/kg/day) based on reductions in body weight gain and reduced feed consumption in the highest dose tested (Klimisch 1, reliable without restriction).
    - *GHS criteria classify chemicals as an oral specific target organ toxicity – repeat dose Category 2 when the LOAEL is > 10 – 100 mg/kg/day (UN 2023). Based on the 14-day duration of treatment for females in this study, the guidance values were multiplied by 6.4 (i.e., 100 mg/kg/day * 6.4 = 640 mg/kg/day), as 90 days is approximately 6.4 times the duration of 14-days. As the maternal systemic LOAEL of 750 mg/kg/day is greater than the adjusted guidance value of 640 mg/kg/day, classification is not warranted.*
  - *Dermal:* In a GLP-compliant subchronic dermal toxicity study conducted according to OECD Guideline 411, male and female Sprague-Dawley rats (15/sex/dose) were administered 1,2-hexanediol (purity not reported) in water at doses of 0, 350, 700, and 1,000 mg/kg/day for 90 days. There were no mortalities. Clinical signs included rough coat, fur staining, and slight dermal irritation at 1,000 mg/kg/day. Slight body weight decreases were noted in high dose males; however, they were not considered to be toxicologically relevant. There were no toxicologically relevant effects on hematology parameters or clinical

chemistry parameters. Changes in urinalysis parameters were considered to be non-adverse. There were slight changes in heart and kidney weights; however, there were no associated histopathological alternations. The study authors identified a systemic toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on a lack of toxicologically significant adverse effects (Klimisch 2, reliable with restrictions).

- *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a GLP-compliant 90-day repeated dose toxicity study conducted according to OECED Guideline 408, male and female Wistar rats (10/sex/dose) were administered 1,2-pentanediol (99.7% purity) in water at doses of 0, 50, 150, and 1,000 mg/kg/day via gavage for 91 (males) or 92 (females) days. There were no mortalities or clinical signs of toxicity reported, and there were no adverse effects on body weight, food consumption and efficiency, hematology parameters, clinical chemistry parameters, urinalysis, organ weight, or pathological examination between the treated and control animals. The study authors identified a systemic toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on a lack of effects (Klimisch 1, reliable without restriction).

- CIR 2012
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* A TD_{Lo} of 2,450 mg/kg is reported following intermittent oral administration of 1,2-pentanediol to rats over a 28-week period. No further details were provided.

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

1,2-Hexanediol was assigned a score of Moderate for neurotoxicity (single dose) based on the reversible behavioral/neurological clinical signs of toxicity detected following single oral, dermal, and inhalation doses of 1,2-hexanediol or the surrogate 1,2-pentanediol,leading ToxServices to conservatively classifying 1,2-hexanediol as a GHS Category 3 specific target organ toxicant following single exposures for narcotic effects. 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 it is unclear if these effects have a neurological etiology or are merely reflective of general signs of discomfort.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Oral:* In a non-GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Sprague-Dawley rats (5-10/sex/dose) were administered 1,2-hexanediol (purity not reported) unchanged at doses of 2,043 (males only), 4,408, 6,339, 6,470, 7,838, and 9,500 mg/kg (females only) via gavage and observed for 14 days. Clinical signs included a reduction in muscle tonicity and effects on coordination with increased doses, beginning at the lowest dose tested. There were no adverse effects reported at necropsy (Klimisch 2, reliable with restrictions).
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Tif:RAIf (SPF) rats (5/sex/dose) were administered 1,2-pentanediol (purity not reported) in water at a dose of 5,000 mg/kg via gavage and observed for 14 days. There were no mortalities. Clinical signs included sedation (up to 5 hours after administration), dyspnea (up to 12 days after administration), exophthalmos (up to 11 days after administration), ruffled fur (up to 8 days after administration), and a curved body position (up to 7 days after administration). There were no adverse effects at necropsy (Klimisch 2, reliable with restrictions).

- *Dermal: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute dermal toxicity study conducted according to OECD Guideline 402, male and female Tif:RAIf (SPF) rats (5/sex/dose) were administered unchanged 1,2-pentanediol (purity not reported) to the skin at a dose of 2,000 mg/kg for 24 hours under occlusive conditions. There were no mortalities. Clinical signs included sedation (up to 5 hours after administration), dyspnea (up to 8 days after administration), exophthalmos (up to 7 days after administration), and ruffled fur (up to 8 days after administration). There were no adverse effects at necropsy (Klimisch 2, reliable with restrictions).
- *Inhalation: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In a non-GLP-compliant acute inhalation toxicity study conducted similar to OECD Guideline 403, male and female Tif:RAIf (SPF) rats (10/sex/concentration) were exposed nose only to 1,2-pentanediol (purity not reported) aerosol in air at concentrations of 3,380 and 7,015 mg/m^3 for 4 hours. There were no mortalities. Clinical signs included dyspnea, ruffled fur, and curved body position up to 1 day after treatment. Mottled or reddish lungs was noted at necropsy in some animals (Klimisch 2, reliable with restrictions).

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

1,2-Hexanediol was assigned a score of Low for neurotoxicity (repeated dose) based on lack of effects in neurobehavioral examinations at dermal doses up to 1,000 mg/kg/day in a 90-day study in rats on itself, and at oral doses up to 1,000 mg/kg/day in a 90-day study in rats with the surrogate 1,2-pentanediol. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when the oral neurotoxicity LOAEL is greater than 100 mg/kg/day for 90-day studies and the dermal neurotoxicity LOAEL is greater than 200 mg/kg/day for 90-day studies (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Dermal:* In a GLP-compliant subchronic dermal toxicity study conducted according to OECD Guideline 411, male and female Sprague-Dawley rats (15/sex/dose) were administered 1,2-hexanediol (purity not reported) in water at doses of 0, 350, 700, and 1,000 mg/kg/day for 90 days. Hand-held and open-field observations were performed weekly and animals were evaluated for elicited behaviors (forelimb and hindlimb grip strength and tail flick) during the last week of the study. Ther were no adverse effects on these parameters. A neurotoxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, can be established based on a lack of adverse effects (Klimisch 2, reliable with restrictions).
  - *Oral: Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* In the previously described GLP-compliant 90-day repeated dose toxicity study conducted according to OECD Guideline 408, male and female Wistar rats (10/sex/dose) were administered 1,2-pentanediol (99.7% purity) in water at doses of 0, 50, 150, and 1,000 mg/kg/day via gavage for 91 (males) or 92 (females) days. A functional observational battery (FOB) as well as measurement of motor activity (MA) were carried out at the end of the administration period. There were no adverse effects reported. Thus, a neurotoxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, can be established for this study based on a lack of effects (Klimisch 1, reliable without restriction).

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

1,2-Hexanediol was assigned a score of negative results for skin sensitization in an OECD Guideline 429 local lymph node assay (LLNA. 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 substance and surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - 1,2-Hexanediol was considered to be non-sensitizing in a GLP-compliant LLNA conducted according to OECD Guideline 429. Female CBA mice (5 animals) were treated with a topical application of 25 µL of 1,2-hexanediol at 100%, 50%, or 10% (w/w) to the entire dorsal surface of each ear, once daily over three days. Five days after the first topical application, all mice were dosed with 20 µCi 3H-methyl thymidine by intravenous injection (tail vein) of 250 µl of 3H-methyl thymidine, diluted to a working concentration of 80 µCi/mL. Animals were sacrificed and within 5 hours the amount of 3H-methyl thymidine – incorporation in the auricular lymph nodes was measured. A substance is regarded as a sensitizer in the LLNA if at least one concentration of the test item results in a 3 fold or greater increase in 3H-methyl thymidine - incorporation into lymph node cells of the lymph nodes of the test group animals, relative to that recorded for the lymph nodes of control group animals (Stimulation Index equal to or greater than 3.0.). The stimulation indices at concentrations of 100%, 50% and 10% were 0.6, 1.9 and 1.6, respectively. Therefore, the study authors did not consider the test substance to be sensitizing under the conditions of the test (Klimisch 1, reliable without restriction).

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

1,2-Hexanediol was assigned a score of Low for respiratory sensitization based on a lack of skin sensitization potential according to ECHA (2017)'s guidance on respiratory sensitization. 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
  - 1,2-Hexanediol does not contain any structural alerts for respiratory sensitization (Appendix I)
- 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 1,2-hexanediol 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 1,2-hexanediol, and as 1,2-hexanediol does not

contain any structural alerts for respiratory sensitization (OECD 2023), 1,2-hexanediol is not expected to be a respiratory sensitizer.

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

1,2-Hexanediol was assigned a score of Low for skin irritation/corrosivity based on negative results for skin irritation in one acute dermal irritation assay 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 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.
- ECHA, CAS #6920-22-5, 2024
  - *In vivo:* 1,2-Hexanediol was not irritating to the skin in a non-GLP-compliant acute dermal irritation assay conducted according to OECD Guideline 404. In this assay, 0.5 mL unchanged 1,2-pentanediol (> 97% purity) was applied to clipped skin of Russian Albino white rabbits (3 males and 3 females) for 72 hours under occlusive conditions. The mean 24, 48, and 72 hour erythema and edema scores for intact skin were all 0/4 (Klimisch 2, reliable with restrictions).

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

1,2-Hexanediol was assigned a score of High for eye irritation/corrosivity based on the mean 24, 48, and 72 hours scores of ≥ 1 for corneal opacity in an ATSM 1055-85 ocular irritation assay in rabbits with 1,2-hexanediol. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they cause irritating effects to the eyes and a GHS Category 2A classification is warranted (CPA 2018b). The confidence in the score is low as individual animal scores were not available in the study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *In vivo:* 1,2-Hexanediol was irritating to the eye in a GLP-compliant acute ocular irritation assay conducted according to ASTM E 1055-85. One eye of New Zealand White rabbits (n=3) was instilled with 10 µL unchanged 1,2-hexanediol (purity not reported) and observed for 14 days. The mean corneal opacity, iris, conjunctivae, and chemosis scores were 2, 1, 2, and 2, respectively, at 24 hours; 2, 1, 2, and 2, respectively, at 48 hours; and 2, 0.67, 1.33, and 1.33, respectively, at 72 hours. Individual animal scores were not reported. Effects were reversible by day 10 (Klimisch 1, reliable without restriction).
    - *Based on GHS guidance (UN 2023), a GHS Category 2A classification is warranted when, in at least two of three animals, effects on the cornea and/or iris mean 24, 48, and 72 hours score is ≥ 1, conjunctivae/chemosis mean 24, 48, and 72 hours score is ≥ 2. A GHS Category 2B classification is warranted when the effects listed above are fully reversible within 7 days of observation. As the mean 24, 48, and 72 hours scores meet the criteria of ≥ 1 for corneal opacity, 1,2-hexanediol meets the classification criteria for a GHS Category 2A eye irritant.*

<u>Ecotoxicity (Ecotox)</u>

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

1,2-Hexanediol was assigned a score of Low for acute aquatic toxicity based on experimental L/EC_{50} values > 100 mg/L in all three trophic levels for the target chemical and/or surrogate 1,2-pentanediol. This is supported by the modeled acute values > 100 mg/L. 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 reliable experimental data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - 48-hour mobility EC_{50} (*Daphnia magna*, daphnia) > 110 mg/L (nominal) (GLP-compliant, OECD Guideline 202; EU Method C.2) (Klimisch 1, reliable without restriction).
  - *Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* 96-hour LC_{50} (*Danio rerio*, zebrafish) > 1,096 mg/L (measured) (GLP, OECD Guideline 203) (Klimisch 1, reliable without restriction).
  - *Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* 48-hour mobility EC_{50} (*D. magna*, daphnia) > 500 mg/L (nominal) (non-GLP, EU Directive 79/831/EWG Appendix V, part C) (Klimisch 2, reliable with restrictions).
  - *Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* 72-hour growth rate EC_{50} (*Desmodesmus subspicatus*, green algae) = 9,334.69 (nominal) (non-GLP, DIN 38412 part 9) (Klimisch 2, reliable with restrictions).
- U.S. EPA 2022
  - 1,2-Hexanediol belongs to the neutral organics ECOSAR chemical class. The most conservative predicted L/EC_{50} values are 1,450 mg/L in fish (96h), 731 mg/L in daphnia (48h), and 331 mg/L in green algae (96h) (Appendix J).

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

1,2-Hexanediol was assigned a score of Low for chronic aquatic toxicity based on modeled chronic aquatic toxicity values > 10 mg/L in all three trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeling and experimental data were not available for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - *Surrogate: 1,2-Pentanediol (CAS #5343-92-0):* 72-hour growth rate EC_{10} (*D. subspicatus*, green algae) = 5,477.33 mg/L (nominal) (non-GLP, DIN 38412 part 9) (Klimisch 2, reliable with restrictions).
- U.S. EPA 2022
  - 1,2-Hexanediol belongs to the neutral organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 123 mg/L in fish, 51.0 mg/L in daphnia, and 66.2 mg/L in green algae (Appendix J).

Environmental Fate (Fate)

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

1,2-Hexanediol was assigned a score of Very Low for persistence based on the results of an OECD Guideline 301 B assay indicating it meets the 10-day window for biodegradability. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they meet the 10-day window and are mainly distributed to water, soil, or sediment (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.
- ECHA, CAS #6920-22-5, 2024
  - 1,2-Hexanediol was readily biodegradable and met the 10-day window in a GLP-compliant OECD Guideline 301 B ready biodegradability (CO2 Evolution Test) assay. In this assay, two flasks of 10 mg/L 1,2-hexanediol (purity not reported) were exposed to non-adapted, activated sludge for 28 days. After 28 days, the test substance degraded 82.1% and 83.7% in the two flasks, respectively. The study authors stated that the 10-day window was met under the conditions of the test and 1,2-hexanediol is considered readily biodegradable (Klimisch 2, reliable with restrictions).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that 1,2-hexanediol is expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 57% will partition to soil with a half-life of 17.3 days, 41.3% will partition to water with a half-life of 8.7 days, and 2.1% will partition to air with a half-life of 13.7 hours, and 0.0731% will partition to sediment with a half-life of 77.9 days (Appendix K).

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

1,2-Hexanediol was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 0.58 and an estimated BCF of 1.093. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when they 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 a measured log K_{ow} with support from modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #6920-22-5, 2024
  - 1,2-Hexanediol has a measured log K_{ow} of 0.58 in a GLP-compliant EU Method A.8 shake-flask method test (Klimisch 1, reliable without restriction).
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 3.162 L/kg wet-wt using the regression based model based on a measured log K_{ow} of 0.58, and a BCF of 1.093 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix K).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*

1,2-Hexanediol was assigned a score of Low for reactivity based on NFPA ratings of 1 for stability and 0 for physical hazards indicating that the target substance is not inherently reactive. 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.
- ECHA, CAS #6920-22-5, 2024
  - 1,2-Hexanediol does not contain chemical groups associated with explosive properties.
  - 1,2-Hexanediol is incapable of reacting exothermically with combustible materials on the basis of chemical structure.
- ThermoFisher Scientific 2021
  - An SDS for 1,2-hexanediol (> 95% purity) has a stability rating of 1 and physical hazard rating of N/A from NFPA ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").

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

1,2-Hexanediol was assigned a score of Low for flammability based on its flash point of 114℃ and it not being classified as a flammable liquid under GHS. 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 reliable 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, CAS #6920-22-5, 2024
  - 1,2-Hexanediol has a flash point of 114℃ measured according to a non-GLP-compliant EU Method A.8 in a closed cup assay (Klimisch 1, reliable without restriction).
    - *As 1,2-hexanediol has a flash point >93℃, a flammable liquid classification under GHS is not warranted (UN 2023).*
  - 1,2-Hexanediol has an auto-ignition point of 350℃ measured according to a non-GLP EU Method A.15 in a self-ignition assay (Klimisch 1, reliable without restriction).

Use of New Approach Methodologies (NAMs)[9] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 4, Type I (input data) uncertainties in 1,2-hexanediol's NAMs dataset include lack of/insufficient experimental data for carcinogenicity, endocrine activity, respiratory sensitization and aquatic toxicity, and lack of validated test methods for respiratory sensitization. 1,2-Hexanediol's Type II (extrapolation output) uncertainties include the lack of defined applicability domains in some modeling programs, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the uncertain *in vivo* relevance of *in silico* modeling of receptor activities due to lack of consideration of toxicokinetics, and the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without accounting for non-immunologic mechanisms of respiratory sensitization.

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 on the target chemical. **Endocrine activity**: No experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Aquatic toxicity:** Insufficient experimental data are available on the target chemical.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). Only three of the six VEGA models produced reliable (i.e., Global AD index > 0.7) predictions. **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

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

	does not entirely mimic *in vivo* conditions[10]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[11] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[12]. **Endocrine activity:** ToxCast models don't define applicability domain. The *in vivo* relevance of *in silico* modeling of receptor activities is uncertain due to lack of consideration of toxicokinetics. **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/OncoLogic™/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: ToxCast
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

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

Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD Guideline 301 B Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for 1,2-Hexanediol (CAS #6920-22-5)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**1,2-Hexanediol**	**6920-22-5**	**L**	**L**	*L*	**L**	DG	**L**	**L**	**L**	*M*	**L**	**L**	*L*	**L**	*H*	**L**	*L*	**vL**	**vL**	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
1,2-Hexanediol	3

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

Table 6

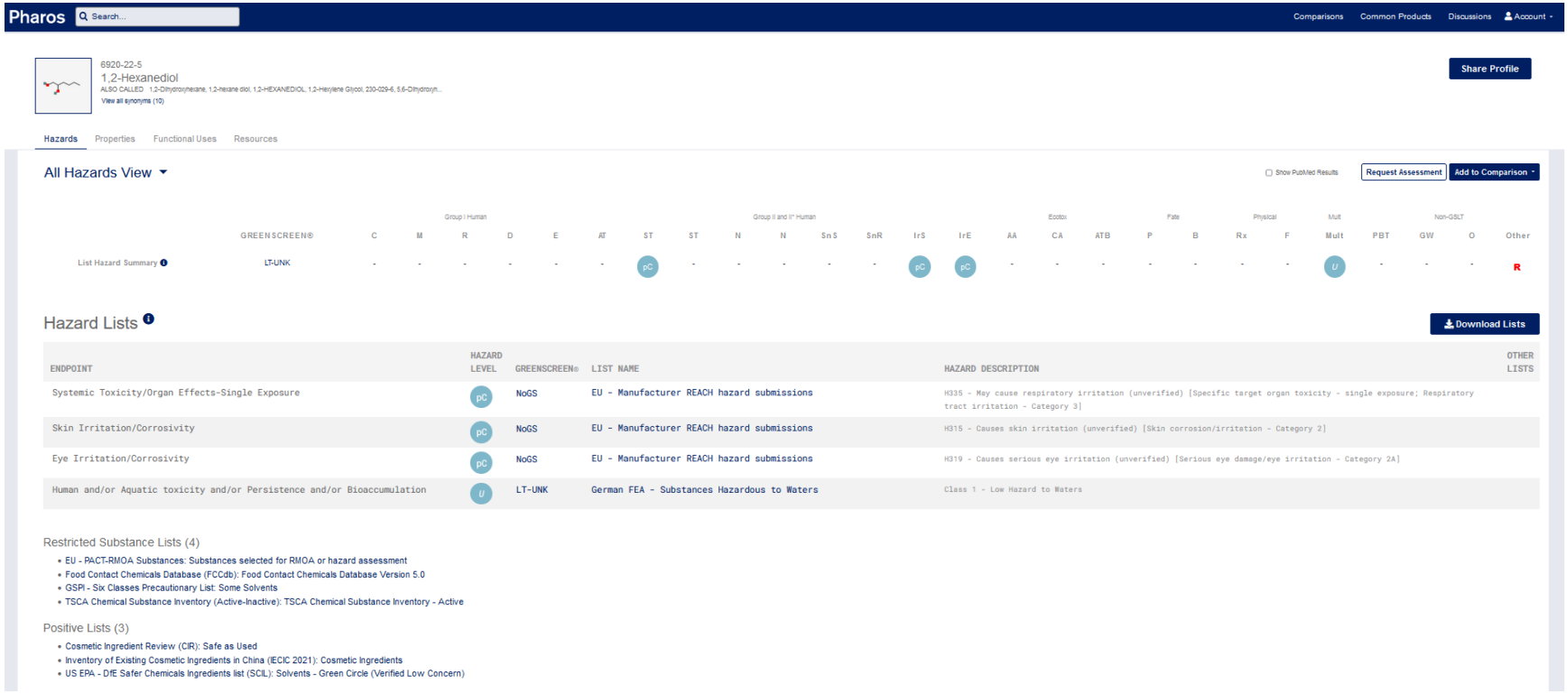
Chemical Name	Final GreenScreen® Benchmark Score
1,2-Hexanediol	3

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												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

APPENDIX C: Pharos Output for 1,2-Hexanediol (CAS #6920-22-5)

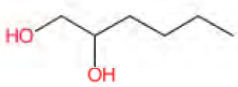


APPENDIX D: VEGA Carcinogenicity Results for 1,2-Hexanediol (CAS #6920-22-5)

VEGA Carcinogenicity model (CAESAR) 2.1.10 page 1

1. Prediction Summary

Prediction for compound Molecule 0 -

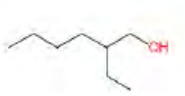


Prediction: Reliability:

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

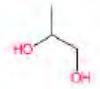
Compound: Molecule 0
Compound SMILES: OCC(O)CCCC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.502
P(NON-Carcinogen): 0.498
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



Compound #1

CAS: 104-76-7
Dataset id:314 (Training Set)
SMILES: OCC(CC)CCCC
Similarity: 0.882
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



Compound #2

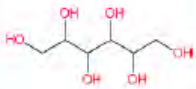
CAS: 57-55-6
Dataset id:677 (Training Set)
SMILES: OCC(O)C
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #3

CAS: 60-32-2
Dataset id:47 (Training Set)
SMILES: O=C(O)CCCCCN
Similarity: 0.841
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

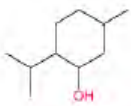
Compound #4

CAS: 35449-36-6
Dataset id:345 (Training Set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.825
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 69-65-8
Dataset id:421 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.808
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 89-78-1
Dataset id:427 (Training Set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.804
Experimental value : NON-Carcinogen
Predicted value : 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 = 0.875
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 0.495
Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..

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

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

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

Model class assignment reliability
Pos/Non-Pos difference = 0.003
Explanation: model class assignment is uncertain..

Neural map neurons concordance
Neurons concordance = 0.75
Explanation: predicted value disagrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

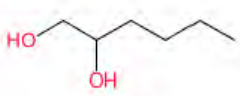
The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

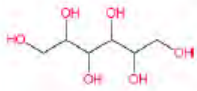
Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules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

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

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

Compound #1

CAS: 111-76-2
Dataset id:596 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.868
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

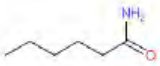


Compound #2

CAS: 69-65-8
Dataset id:86 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.808
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

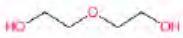
Compound #3

CAS: 107-21-1
Dataset id:306 (Training Set)
SMILES: OCCO
Similarity: 0.795
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



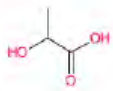
Compound #4

CAS: 628-02-4
Dataset id:387 (Training Set)
SMILES: O=C(N)CCCCC
Similarity: 0.791
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 111-46-6
Dataset id:860 (Training Set)
SMILES: OCCOCCO
Similarity: 0.783
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 814-80-2
Dataset id:815 (Training Set)
SMILES: O=C(O)C(O)C
Similarity: 0.78
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.632 Explanation: The predicted compound is outside the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.835 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.478 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.478 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

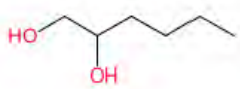
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

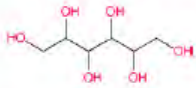
Prediction is Possible NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- Accuracy of prediction for similar molecules found in the training set is not optimal
- some similar molecules found in the training set have experimental values that disagree with the predicted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

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

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

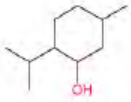
Compound #1

CAS: 111-76-2
Dataset id:498 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.868
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

CAS: 69-65-8
Dataset id:69 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.808
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

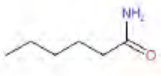


Compound #3

CAS: 15356-70-4
Dataset id:654 (Training Set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.804
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #4

CAS: 107-21-1
Dataset id:667 (Training Set)
SMILES: OCCO
Similarity: 0.795
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 628-02-4
Dataset id:317 (Training Set)
SMILES: O=C(N)CCCCC
Similarity: 0.791
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #6

CAS: 556-52-5
Dataset id:536 (Training Set)
SMILES: OCC1OC1
Similarity: 0.775
Experimental value : Carcinogen
Predicted value : Carcinogen

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

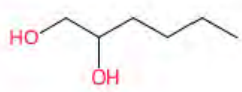
⚠	Global AD Index AD index = 0.729 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.823 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.646 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
⚠	Concordance for similar molecules Concordance index = 0.646 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0 -

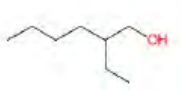


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: OCC(O)CCCC
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: 104-76-7
Dataset id:314 (Training Set)
SMILES: OCC(CC)CCCC
Similarity: 0.882
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #2

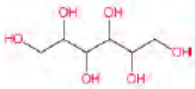
CAS: 57-55-6
Dataset id:677 (Training Set)
SMILES: OCC(O)C
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #3

CAS: 60-32-2
Dataset id:47 (Training Set)
SMILES: O=C(O)CCCCCN
Similarity: 0.841
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

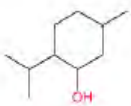
Compound #4

CAS: 35449-36-6
Dataset id:345 (Training Set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.825
Experimental value : NON-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: 0.808
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #6

CAS: 89-78-1
Dataset id:427 (Training Set)
SMILES: OC1CC(C)CCC1(C(C)C)
Similarity: 0.804
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.929 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.862 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:

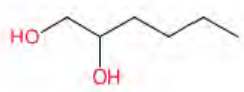
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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 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:
- similar molecules found in the training set have experimental values that disagree with the predicted value

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

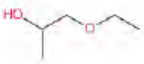
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 111-76-2
Dataset id:509 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #2

CAS: 57-55-6
Dataset id:661 (Training Set)
SMILES: OCC(O)C
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

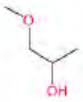


Compound #3

CAS: 1569-02-4
Dataset id:663 (Training Set)
SMILES: OC(C)COCC
Similarity: 0.839
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #4

CAS: 71-36-3
Dataset id:362 (Training Set)
SMILES: OCCCC
Similarity: 0.834
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 107-98-2
Dataset id:664 (Training Set)
SMILES: OC(C)COC
Similarity: 0.825
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #6

CAS: 78-92-2
Dataset id:363 (Training Set)
SMILES: OC(C)CC
Similarity: 0.823
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.868 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 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

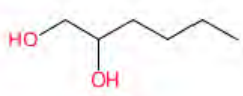
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

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

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

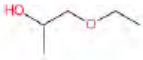
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 111-76-2
Dataset id:482 (Training Set)
SMILES: OCCOCCCC
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #2

CAS: 57-55-6
Dataset id:650 (Test Set)
SMILES: OCC(O)C
Similarity: 0.868
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

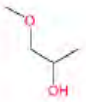


Compound #3

CAS: 1569-02-4
Dataset id:652 (Training Set)
SMILES: OC(C)COCC
Similarity: 0.839
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #4

CAS: 71-36-3
Dataset id:314 (Training Set)
SMILES: OCCCC
Similarity: 0.834
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 107-98-2
Dataset id:653 (Training Set)
SMILES: OC(C)COC
Similarity: 0.825
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #6

CAS: 78-92-2
Dataset id:316 (Training Set)
SMILES: OC(C)CC
Similarity: 0.823
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✔	Global AD Index AD index = 0.932 Explanation: The predicted compound is into the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.868 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..

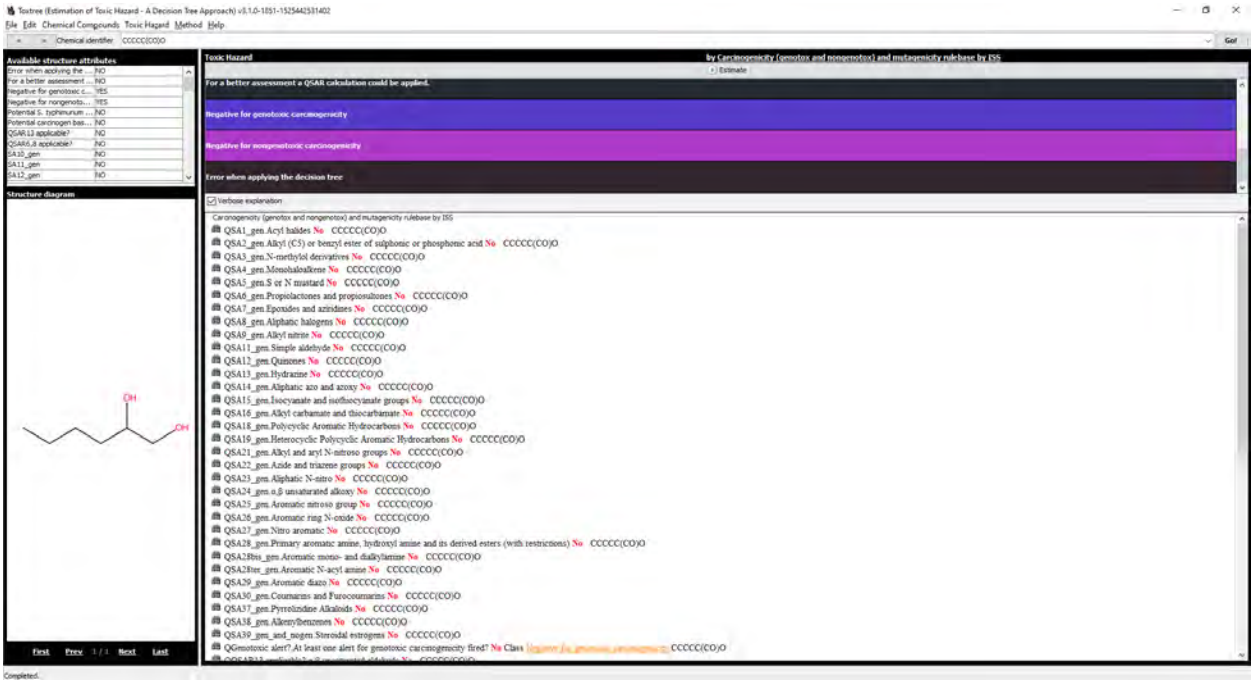
Symbols explanation:

✔ 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: Toxtree Carcinogenicity Results for 1,2-Hexanediol (CAS #6920-22-5)



APPENDIX F: Danish QSAR Carcinogenicity Results for 1,2-Hexanediol (CAS #6920-22-5)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	NEG_OUT
FDA RCA Cancer Female Rat	NEG_IN	NEG_IN
FDA RCA Cancer Rat	NEG_IN	INC_OUT
FDA RCA Cancer Male Mouse	NEG_IN	NEG_OUT
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	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

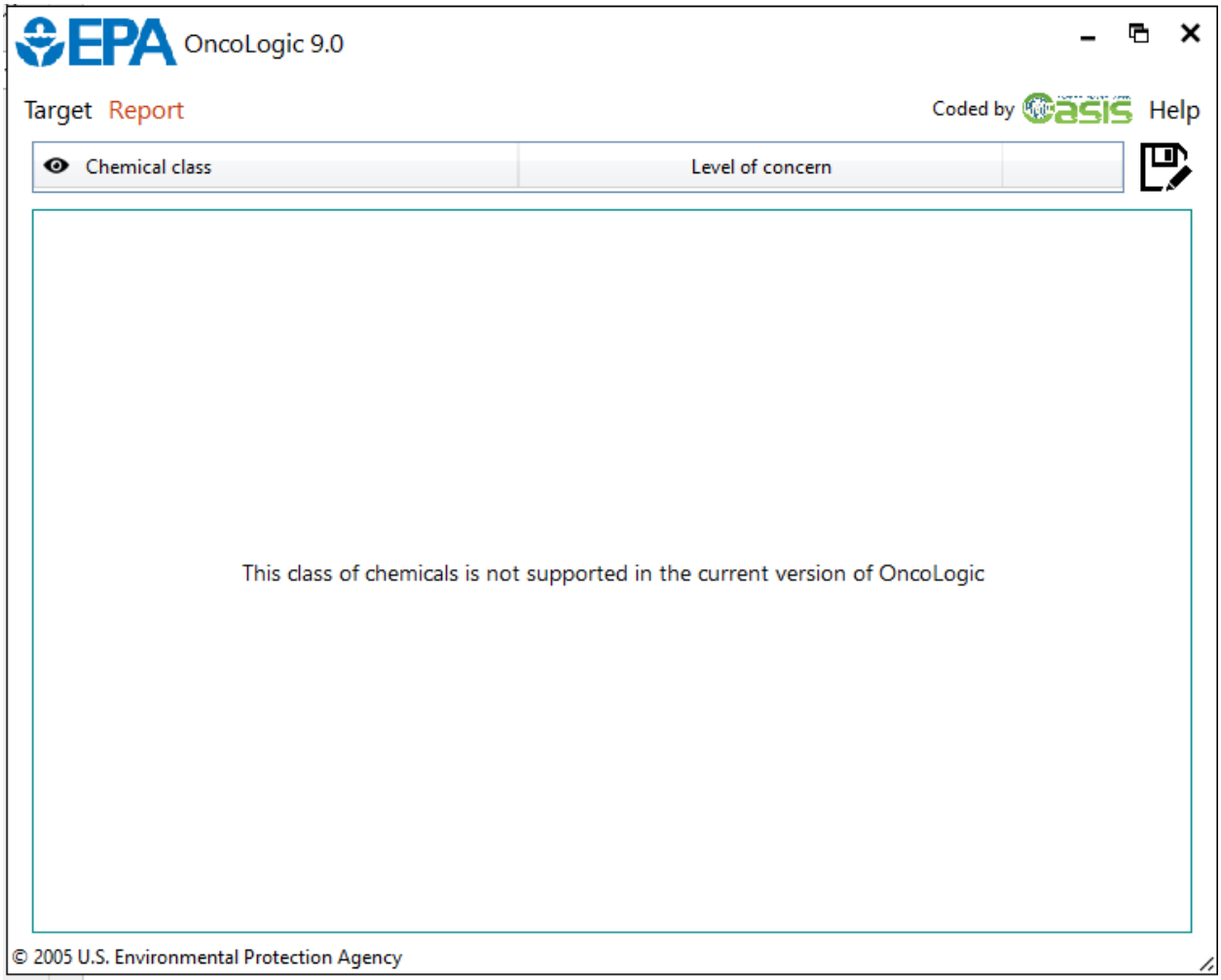
OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

APPENDIX G: OncoLogic Carcinogenicity Results for 1,2-Hexanediol (CAS #6920-22-5)



OncoLogic Justification Report

SUMMARY :

CODE NUMBER : 6920-22-5

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Alcohols*

Aliphatic alcohols (R-OH) may be loosely divided into (a) high M.W.alcohols (C > 20), (b) medium size alcohols (C = 6 to 20), and (c) low M.W. alcohols (C < 6). In general, high M.W. aliphatic alcohols have low potential to be significant carcinogens. A number of medium size alcohols (e.g., CF3(CF2)6CH2OH; 2-ethylhexanol) that can be oxidized to metabolically persistent aliphatic carboxylic acids (e.g., perfluorinated fatty acid like perfluoroooctanoic; ω – 1 branched fatty acids like 2-ethylhexanoic acid) are potential nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Low M.W. alcohols, (especially methanol and ethanol) are of carcinogenic concern because of possible oxidation to reactive aldehydes. The concern for carcinogenic risk is especially higher in individuals who are genetically deficient in aldehyde dehydrogenase which detoxifies aldehydes to carboxylic acids. A number of low M.W. tertiary alcohols (e.g., t-butyl, t-amyl) have been shown to induce kidney tumors in male rats by a mechanism (alpha-2-mu nephropathy) not relevant to humans. In addition, low M.W. alcohols with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens.

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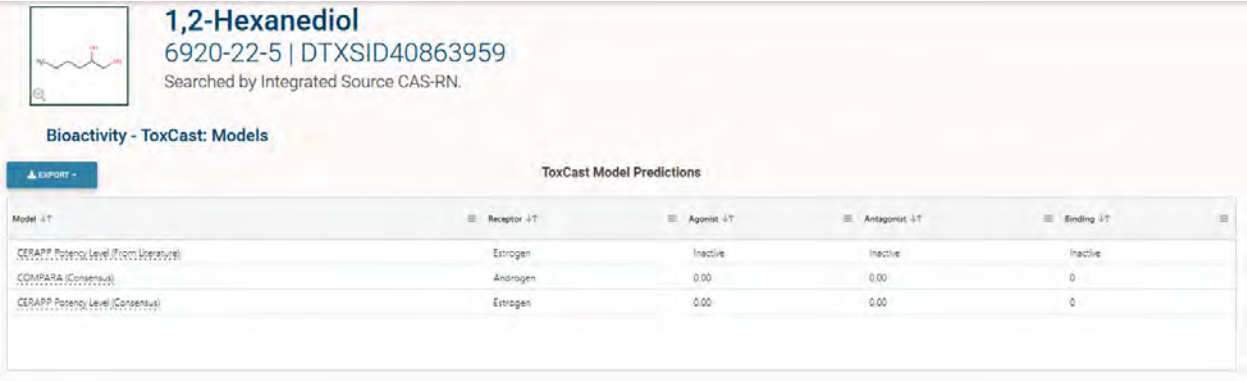
*This is only a brief summary of the structure activity relationships (SAR) knowledge of this class. A more detailed decision logic will be developed in future version of OncoLogic. If the compound of your interest has been tested in any short-term predictive tests, the results of the tests should be entered into OncoLogic’s Functional Arm to give an evaluation of carcinogenic potential based on short-term predictive tests.

APPENDIX H: ToxCast Model Results for 1,2-Hexanediol (CAS #6920-22-5)



1,2-Hexanediol

6920-22-5 | DTXSID40863959

Searched by Integrated Source CAS-RN.

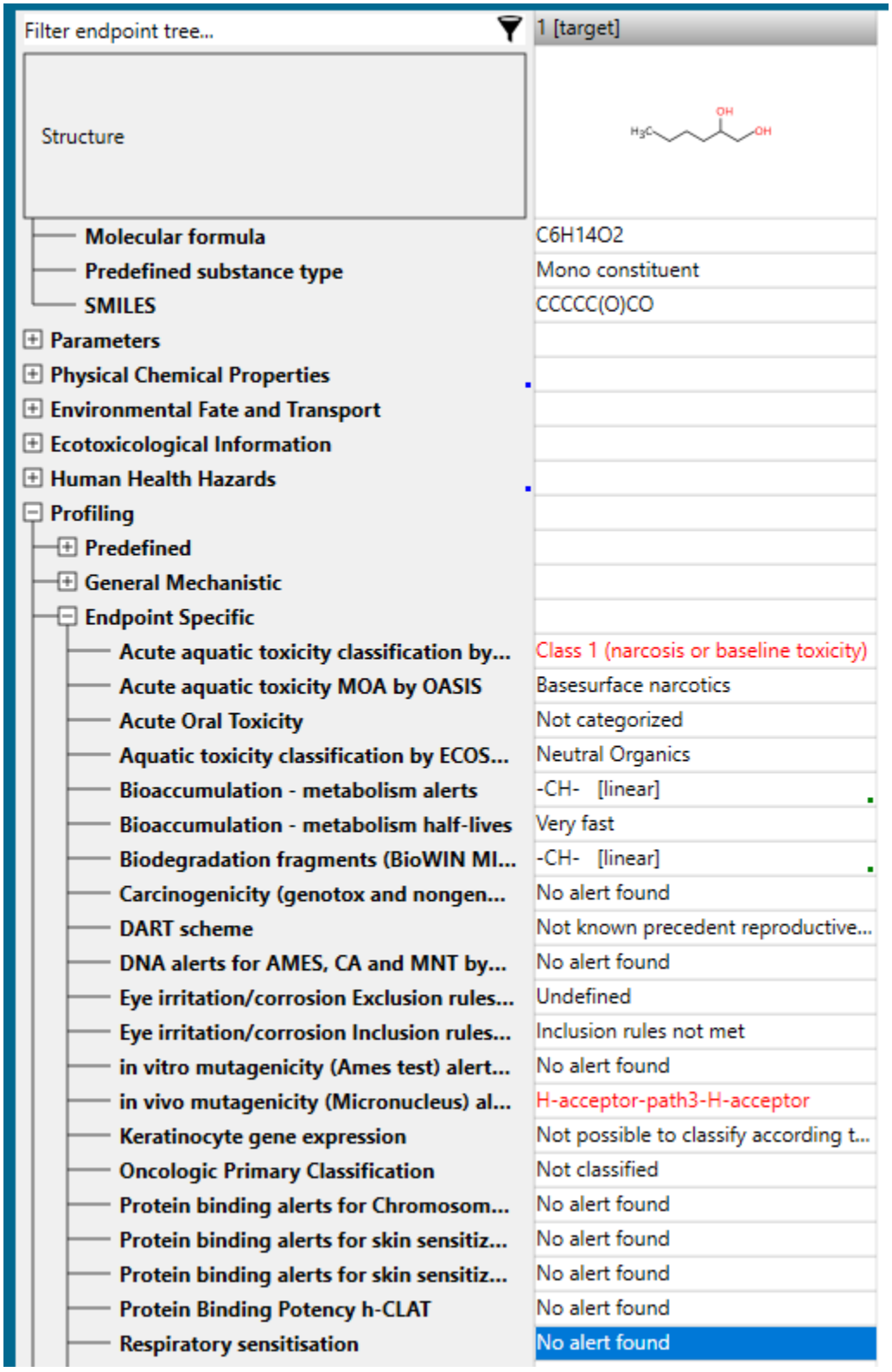
Bioactivity - ToxCast: Models

EXPORT

ToxCast Model Predictions

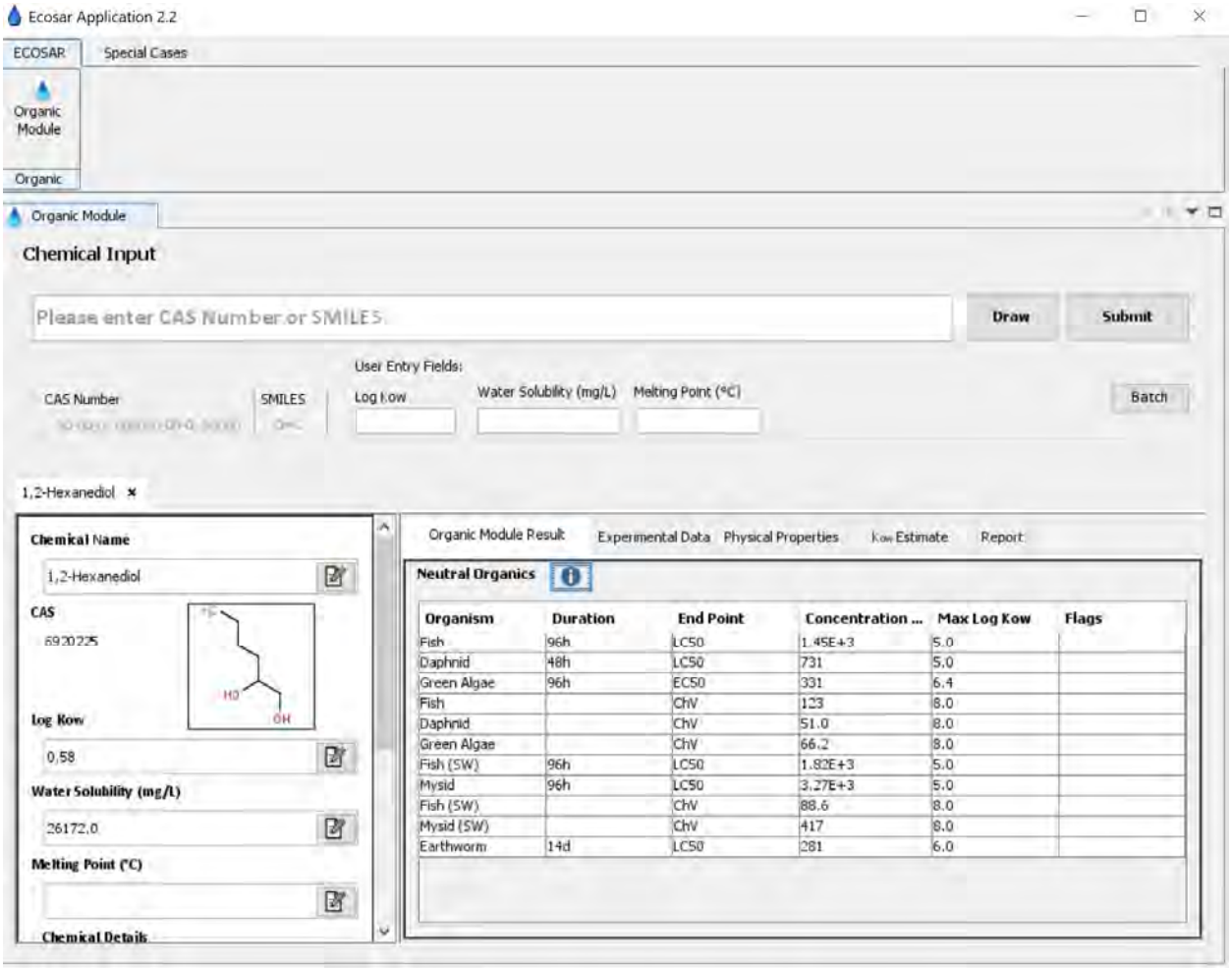
Model	Receptor	Agonist	Antagonist	Binding
CERAPP Potency Level (From Literature)	Estrogen	Inactive	Inactive	Inactive
COMPARA (Consensus)	Androgen	0.00	0.00	0
CERAPP Potency Level (Consensus)	Estrogen	0.00	0.00	0

APPENDIX I: OECD Toolbox Respiratory Sensitization Results for 1,2-Hexanediol (CAS #6920-22-5)



Filter endpoint tree...	1 [target]
Structure	
Molecular formula	C6H14O2
Predefined substance type	Mono constituent
SMILES	CCCCC(O)CO
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Predefined	
General Mechanistic	
Endpoint Specific	
Acute aquatic toxicity classification by...	Class 1 (narcosis or baseline toxicity)
Acute aquatic toxicity MOA by OASIS	Basesurface narcotics
Acute Oral Toxicity	Not categorized
Aquatic toxicity classification by ECOS...	Neutral Organics
Bioaccumulation - metabolism alerts	-CH- [linear]
Bioaccumulation - metabolism half-lives	Very fast
Biodegradation fragments (BioWIN MI...	-CH- [linear]
Carcinogenicity (genotox and nongen...	No alert found
DART scheme	Not known precedent reproductive...
DNA alerts for AMES, CA and MNT by...	No alert found
Eye irritation/corrosion Exclusion rules...	Undefined
Eye irritation/corrosion Inclusion rules...	Inclusion rules not met
in vitro mutagenicity (Ames test) alert...	No alert found
in vivo mutagenicity (Micronucleus) al...	H-acceptor-path3-H-acceptor
Keratinocyte gene expression	Not possible to classify according t...
Oncologic Primary Classification	Not classified
Protein binding alerts for Chromosom...	No alert found
Protein binding alerts for skin sensitiz...	No alert found
Protein binding alerts for skin sensitiz...	No alert found
Protein Binding Potency h-CLAT	No alert found
Respiratory sensitisation	No alert found

APPENDIX J: ECOSAR Modeling Results for 1,2-Hexanediol (CAS #6920-22-5)



Organism	Duration	End Point	Concentration ...	Max Log Kow	Flags
Fish	96h	LC50	1.45E+3	5.0	
Daphnid	48h	LC50	731	5.0	
Green Algae	96h	EC50	331	6.4	
Fish		ChV	123	8.0	
Daphnid		ChV	51.0	8.0	
Green Algae		ChV	66.2	8.0	
Fish (SW)	96h	LC50	1.82E+3	5.0	
Mysid	96h	LC50	3.27E+3	5.0	
Fish (SW)		ChV	88.6	8.0	
Mysid (SW)		ChV	417	8.0	
Earthworm	14d	LC50	281	6.0	

APPENDIX K: EPI Suite™ Modeling Results for 1,2-Hexanediol (CAS #6920-22-5)

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

CAS Number: 6290-22-5
SMILES : CCCCC(CO)O
CHEM : 1,2-Hexanediol
MOL FOR: C6 H14 O2
MOL WT : 118.18
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 0.58
Boiling Point (deg C) : 228.30
Melting Point (deg C) : 2.00
Vapor Pressure (mm Hg) : 0.0043204
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.69

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 216.64 (Adapted Stein & Brown method)
Melting Pt (deg C): 1.85 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00843 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.12 (Mean VP of Antoine & Grain methods)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 6.881e+004
log Kow used: 0.58 (user entered)
melt pt used: 2.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 3.3602e+005 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 4.06E-007 atm-m3/mole (4.11E-002 Pa-m3/mole)
Group Method: 3.70E-010 atm-m3/mole (3.75E-005 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: 9.763E-009 atm-m3/mole (9.893E-004 Pa-m3/mole)
VP: 0.00432 mm Hg (source: User-Entered)
WS: 6.88E+004 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 0.58 (user entered)
Log Kaw used: -4.780 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 5.360
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.1172
Biowin2 (Non-Linear Model) : 0.9955
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.5563 (days-weeks)
Biowin4 (Primary Survey Model) : 4.2052 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7170
Biowin6 (MITI Non-Linear Model): 0.8724
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6424
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): 0.576 Pa (0.00432 mm Hg)
Log Koa (Koawin est): 5.360
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 5.21E-006
Octanol/air (Koa) model: 5.62E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000188
Mackay model : 0.000416
Octanol/air (Koa) model: 4.5E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 18.7157 E-12 cm3/molecule-sec
Half-Life = 0.571 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 6.858 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000302 (Junge-Pankow, Mackay avg)
4.5E-006 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1 L/kg (MCI method)
Log Koc: 0.000 (MCI method)
Koc : 2.649 L/kg (Kow method)

Log Koc: 0.423 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.6002 days (HL = 0.02511 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.039 (BCF = 1.093)
Log BAF Arnot-Gobas method (upper trophic) = 0.039 (BAF = 1.093)
log Kow used: 0.58 (user entered)

Volatilization from Water:
Henry LC: 4.06E-007 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1569 hours (65.37 days)
Half-Life from Model Lake : 1.721E+004 hours (716.9 days)

Removal In Wastewater Treatment:
Total removal: 1.88 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.77 percent
Total to Air: 0.02 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**2.09**	**13.7**	**1000**
Water	**41.3**	**208**	**1000**
Soil	**56.5**	**416**	**1000**
Sediment	**0.0731**	**1.87e+003**	**0**

Persistence Time: 250 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.09	13.7	1000
Water	41.3	208	1000
water	(41.3)		
biota	(7.86e-006)		
suspended sediment	(6.2e-005)		
Soil	56.5	416	1000
Sediment	0.0731	1.87e+003	0

Persistence Time: 250 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.08	13.7	1000

Water	40.9	208	1000
water	(40.9)		
biota	(7.77e-006)		
suspended sediment	(9.55e-005)		
Soil	57	416	1000
Sediment	0.0731	1.87e+003	0
Persistence Time: 251 hr			

APPENDIX L: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for 1,2-hexanediol. The original GreenScreen® assessment was performed in 2024 under version 1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score.

Table 5: Change in GreenScreen® Benchmark™ for 1,2-Hexanediol

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
February 22, 2024	BM-3	v. 1.4	Original GreenScreen® assessment.

Licensed GreenScreen® Profilers

1,2-Hexanediol GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

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

1,2-Hexanediol GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

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