ETHYLHEXYLGLYCERIN

(CAS #70445-33-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 17, 2023

Expiration Date: April 17, 2028

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GreenScreen® Executive Summary for Ethylhexylglycerin (CAS #70445-33-9)

Ethylhexylglycerin is an alkyl glyceryl ether. It is used in cosmetic products at concentrations up to 8% (as of 2013) as a skin conditioning agent and to enhance the efficacy of preservatives. Ethylhexylglycerin is a liquid at room temperature.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R)
- Benchmark 2f
    - Very High Group II Human Toxicity (eye irritation-IrE)

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

The GreenScreen® Benchmark score for ethylhexylglycerin has not changed over time. The original GreenScreen® assessment was performed in 2016 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in the current GreenScreen® assessment.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and *in vitro* assays for genotoxicity. 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 ethylhexylglycerin's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Ethylhexylglycerin's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to evaluate ethylhexylglycerin's carcinogenic potential, the uncertain *in vivo* relevance of *in silico* prediction of endocrine receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of ethylhexylglycerin's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Ethylhexylglycerin

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

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

GreenScreen® Chemical Assessment for Ethylhexylglycerin (CAS #70445-33-9)

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

GreenScreen® Assessment (v1.3) Prepared By:
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Organization: ToxServices LLC
Date: March 16, 2016, December 4, 2015 (update)

Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 14, 2015, December 15, 2015, January 19, 2016

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: March 29, 2023

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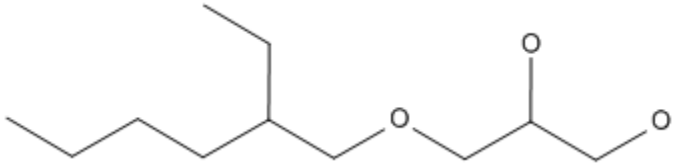
Organization: ToxServices LLC
Date: April 17, 2023

Expiration Date: April 17, 2028[2]

Chemical Name: Ethylhexylglycerin

CAS Number: 70445-33-9

Chemical Structure(s):

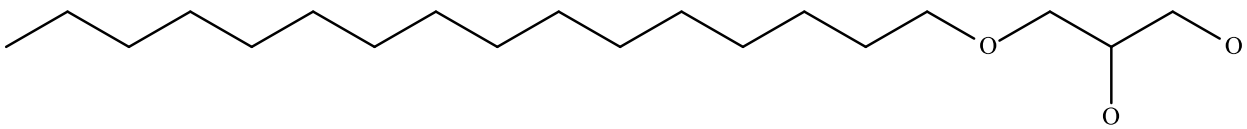


Also called: 3-[2-(Ethylhexyl)oxyl]-1,2-propandiol; Ethylhexylglycerin; Octoxyglycerin; 3-(2-ethylhexyloxy)propane-1,2-diol; 3-(2-ethylhexoxy)propane-1,2-diol; 3-((2-Ethylhexyl)oxy)propane-1,2-diol; 3-(2-ethylhexyloxy)-1,2-propanediol; 1,2-Propanediol, 3-((2-ethylhexyl)oxy)- (PubChem 2023).

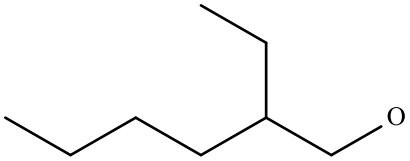
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Data for ethylhexylglycerin were not identified for all endpoints. Therefore, ToxServices used data for the similar alkyl glyceryl ether, chimyl alcohol (CAS #506-03-6), for the evaluation of toxicokinetic endpoints. Chimyl alcohol is the condensation product of cetyl alcohol and glycerin, and data suggest that the ester linkage may be broken *in vivo* after intestinal absorption. Based on structural similarity to chimyl alcohol, it is likely that the ester linkage in ethylhexylglycerin may also be broken to produce 2-ethylhexanol and glycerin. Therefore, ToxServices used 2-ethylhexanol and glycerin as surrogates to evaluate the carcinogenicity of ethylhexylglycerin. However, because there are no data regarding the

[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).

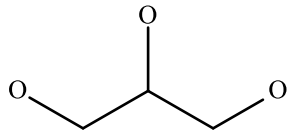
rate and extent of *in vivo* ether breakage for ethylhexylglycerin, it is unclear to what extent do the metabolites contribute to the overall toxicity of the parent compound, and therefore ToxServices considered these compounds weak surrogates. All three chemical surrogates are illustrated below. Ethylhexylglycerin and surrogate chimyl alcohol were evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel in its safety assessment of alkyl glyceryl ethers used in cosmetics (CIR 2013).



Chimyl Alcohol (CAS #506-03-6)



2-Ethylhexanol (CAS #104-76-7)



Glycerin (CAS #56-81-5)

Identify Applications/Functional Uses:
1. Deodorizer, fragrance, preservative, softener, and conditioner (PubChem 2023).
2. Skin conditioning agent and efficacy enhancer of preservatives at concentrations up to 8% in cosmetic products (CIR 2013).

Known Impurities[3]:
Sensiva SC 50, a tradename for ethylhexylglycerin, contains > 99% ethylhexylglycerin, with a small amount of α-tocopherol added for molecule stabilization (CIR 2013). It also contains impurities 2-ethylhexyl-glycidylether and water. The screen is performed on the theoretical pure substance.

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

[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.

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R)
- Benchmark 2f
    - Very High Group II Human Toxicity (eye irritation-IrE)

Data gaps (DG) exist for endocrine activity-E and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), ethylhexylglycerin meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if ethylhexylglycerin 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 Ethylhexylglycerin

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

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

Environmental Transformation Products

Ethylhexylglycerin is not expected to undergo hydrolysis under environmental conditions. It is expected to undergo biodegradation in the environment at a moderate rate; however, there are no reports of measured biodegradation products. Therefore, it is unknown whether this compound will produce relevant and feasible biodegradation products.

Introduction

Ethylhexylglycerin is an alkyl glyceryl ether that is produced through the splitting of ethylhexyl glycidyl ether followed by addition of water and purification. Ethylhexylglycerin is used in cosmetic products at concentrations up to 8% (as of 2013) as a skin conditioning agent and to enhance the efficacy of preservatives (CIR 2013).

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

Ethylhexylglycerin is not currently present on the SCIL.

GreenScreen® List Translator Screening Results

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

- Ethylhexylglycerin is a BM-2 chemical based on an expired GreenScreen® assessment under version 12 criteria conducted in 2016 by ToxServices, when screened using Pharos, and therefore the current GreenScreen® brings that assessment up to date.
- Ethylhexylglycerin is not listed on the U.S. DOT list.
- Ethylhexylglycerin is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - GHS – Australia – H412 – Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 3]
    - EU – GHS (H-Statements) Annex 6 Table 3-1 – H412 – Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 3]
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters

Hazard Statement and Occupational Control

Harmonized Hazard (H) Statements from European Chemicals Agency (ECHA)'s C&L Inventory are included in Table 1, below. 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 Ethylhexylglycerin (CAS #70445-33-9) (ECHA 2023a)

H Statement	H Statement Details
H318	Causes serious eye damage
H412	Harmful to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Ethylhexylglycerin (CAS #70445-33-9)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear protective gloves, protective clothing, eye protection, face protection, and hearing protection	ECHA 2023b	None identified	

Physicochemical Properties of Ethylhexylglycerin

Ethylhexylglycerin is a liquid at room temperature. Its vapor pressure of 0.0023 mmHg indicates a slight potential to volatilize. It is soluble in water (1.8 g/L) and its log K_{ow} of 2.53 indicates it's more soluble in octanol than water.

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

Table 3: Physical and Chemical Properties of Ethylhexylglycerin (CAS #70445-33-9)		
Property	**Value**	**Reference**
Molecular formula	$C_{11}H_{24}O_3$	PubChem 2023
SMILES Notation	CCCCC(CC)COCC(CO)O	PubChem 2023
Molecular weight	204.31 g/mole	PubChem 2023
Physical state	Liquid	ECHA 2023b
Appearance	Clear, colorless-nearly colorless	Schulke Undated
Melting point	< -76°C (OECD Guideline 102)	ECHA 2023b, Schulke Undated
Boiling point	> 285°C (OECD Guideline 103)	ECHA 2023b
Vapor pressure	0.003 hPa (0.0023 mmHg) (OECD Guideline 104)	ECHA 2023b, Schulke Undated
Water solubility	1.8 g/L at 22.5°C (OECD Guideline 105)	ECHA 2023b, Schulke Undated
Dissociation constant	Not applicable	
Density/specific gravity	0.95 g/cm^3 at 20°C (OECD Guideline 109)	ECHA 2023b, Schulke Undated
Partition coefficient	Log K_{ow} = 2.53 (OECD Guideline 107)	ECHA 2023b, Schulke Undated

Toxicokinetics

No toxicokinetic data were identified for ethylhexylglycerin. Absorption and metabolism data in rats administered surrogate (1-^{14}C)-chimyl alcohol (5 mg) in 0.5 mL olive oil via stomach tube, indicate 95% absorption with 45-59% of total absorbed activity (whole body) recovered in the lymph lipids as free and esterified chimyl alcohol. The remaining 5% of the [^{14}C]-labeled chimyl alcohol was recovered in the unsaponifiable fraction of the fecal lipids (CIR 2013). Analysis of the intestinal lumen of rats fed α-(1-C^{14})-chimyl alcohol as free alcohol or as chimyl dioleate (in olive oil) (via stomach tube) revealed an intact ether linkage during absorption followed by rapid conversion of more than 50% of the compound into palmitic acid once it was absorbed into the intestinal mucosa (CIR 2013).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Ethylhexylglycerin was assigned a score of Low for carcinogenicity based on negative results in chronic oral carcinogenicity studies of surrogates 2-ethylhexanol and glycerin, which are the expected metabolites of ether breakage, and negative weight of evidence from modeling. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on modeling and there are no data regarding the rate and extent of ether breakage for ethylhexylglycerin.

- 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 2019, 2021
  - An attempt was made to use EPA's OncoLogic (v 8.0 and v 9.0) to evaluate this chemical, but it does not fit into any of the existing chemical classes. Therefore, it cannot be assessed by Oncologic.

- Toxtree 2018
    - Ethylhexylglycerin has a structural alert for nongenotoxic carcinogenicity (substituted n-alkylcarboxylic acids) (Appendix D). This refers to the tertiary carbon portion of the 2-ethylhexyl moiety, which is also present in the metabolite 2-ethylhexanol. Substances with this alert may act as peroxisome proliferators (PPs) that can cause liver cancer in rodents via non-genotoxic mechanisms. 2-Ethylhexanoic acid and some compounds containing this moiety are known PPs (OECD 2014).
- DTU 2023
    - Ethylhexylglycerin was modeled in the Danish (Q)SAR Database. The E Ultra model predicted ethylhexylglycerin would be non-carcinogenic based on data from 6 of 7 FDA rodent databases, and the compound was within the applicability domain for these 6 predictions. The 7th model predicted ethylhexylglycerin would be carcinogenic but the compound was outside of the applicability domain. The Leadscope model predicted ethylhexylglycerin would be carcinogenic based on data from 3 of the FDA rodent databases for which the compound was within the applicability domain, and with the remaining 3 of 4 of the databases, the predictions were negative or inconclusive but the compound was outside the applicability domain, and the 4th model was positive and within the applicability domain. The model output noted a structural alert for nongenotoxic carcinogenicity associated with substituted n-alkylcarboxylic acids and not classified, using the alerts by ISS and OECD QSAR Toolbox v 4.2, respectively. Lastly, ethylhexylglycerin was predicted to be negative for liver specific cancer in rats and mouse according to the Leadscope, and positive in the CASE Ultra within the applicability domains of the DTU-developed models, as well as inconclusive and outside the applicability domain for the SciQSAR model and the overall model battery (Appendix E).
- VEGA 2021
    - The CAESAR model predicted ethylhexylglycerin as a NON-carcinogen with moderate reliability (Global applicability domain (AD) Index = 0.635). Only moderately similar compounds with experimental values were found in the training set and similar molecules found in the training set have experimental values that disagree with the predicted value (Appendix F).
    - The ISS model predicted ethylhexylglycerin as a carcinogen with low reliability (Global AD Index = 0). The 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, and the predicted compound is outside of the applicability domain (Appendix F).
    - The IRFMN/Antares model predicted ethylhexylglycerin as a possible NON-carcinogen with strong reliability (Global AD Index = 0.895) (Appendix F).
    - The IRFMN/ISSCAN-CGX model predicted ethylhexylglycerin as a carcinogen, however the reliability is low (Global AD Index = 0). The 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, and the predicted compound is outside of the applicability domain (Appendix F).
    - The IRFMN oral classification model predicted ethylhexylglycerin as a NON-carcinogen with good reliability (Global AD Index = 0.907) (Appendix F).
    - The IRFMN inhalation classification model predicted ethylhexylglycerin as a NON-carcinogen with good reliability (Global AD Index = 0.907) (Appendix F).
- ECHA 2023c, WHO 1993

  - *Oral: Surrogate: 2-Ethylhexanol (CAS # 104-76-7):* 2-Ethylhexanol was tested in a GLP-compliant chronic oral carcinogenicity study in male and female Fischer 344 rats (50/sex/dose) that were administered 2-ethylhexanol (>99% purity) at doses of 50, 150, and 500 mg/kg/day via gavage 5 days/week for 24 months. Histopathology was performed on gross lesions, all tissues from control and high dose groups, and on kidneys, fore- and glandular stomachs, livers, lungs, and testes from low and mid dose groups. In both sexes the sum of primary tumors, malignant tumors, and benign tumors was lower than the control groups. Authors concluded that 2-ethylhexanol was not oncogenic under the conditions of the assay (Klimisch score 1, reliable without restriction).
  - *Oral: Surrogate: 2-Ethylhexanol (CAS # 104-76-7):* 2-Ethylhexanol was tested in a GLP-compliant chronic oral carcinogenicity study in male and female B6C3F1 mice (50/sex/dose) that were administered 2-ethylhexanol (>99% purity) at doses of 50, 200, and 750 mg/kg/day via gavage 5 days/week for 18 months. Histopathology was performed on gross lesions, all tissues from control and high dose groups, and on kidneys, fore- and glandular stomachs, livers, lungs, and testes from low and mid dose groups. Body weights were significantly decreased in both males (26% reduction) and females (24% reduction) at the high dose; feed consumption was reduced in these animals as well. Mortality rates for male and females at this dose were both 30% (compared to 4% in vehicle control males and 8% in vehicle control females. There was a slight but statistically significant increase in hepatocellular carcinomas in females at the high dose when compared to the vehicle control (water with Polyoxyl 35 Castor Oil as an emulsifier), but not when compared to a water control (0/50, 1/50, 1/50, 3/50, 5/50 in the vehicle control, water control, 50, 200, and 750 mg/kg/day groups, respectively). There was no increase in tumors in male rats. Based on comparisons to historical control data and a lack of metastases, authors concluded that the tumor incidence was incidental and not biologically relevant and concluded that 2-ethylhexanol was not carcinogenic under the conditions of the assay (Klimisch score 1, reliable without restriction).
- ECHA 2023d
  - *Oral: Surrogate: Glycerin (CAS #56-81-5):* In a 2-year carcinogenicity study (1 year for high dose group), male and female Long-Evans rats (22/sex/dose; 26/sex/controls) were administered 5, 10, and 20% glycerin (natural: purity not reported; synthetic: 99.5% purity) in the diet (2,000, 4,000, and 8,000 mg/kg for males and 2,500, 5,000, and 10,000 mg/kg for females). Animals were observed daily, weighed weekly, and examined pathologically (liver, spleen, adrenals, kidney, small intestine, gonads, and urinary bladder) upon death or at study conclusion. No increase in tumor formation was observed in rats administered natural or synthetic glycerin compared to controls (Klimisch score 2, reliable with restrictions).
- UNEP 2002
  - *Oral: Surrogate: Glycerin (CAS #56-81-5):* As part of a study of tumor promoting effects of glycerol, a group of male ddY mice (number not reported) were administered 5% glycerin in water for 20 weeks. Treatment with glycerol alone did not increase the number of tumor-bearing mice compared to controls. Additional details were not provided.
- Based on the weight of evidence, a score of Low was assigned. No data were identified for ethylhexylglycerin, but Toxtree and Danish (Q)SAR identified a structural alert for nongenotoxic carcinogenicity. VEGA predicted positive results in two model with low confidence but negative in four models with good to low confidence. However, the positive predictions were based on chemicals with additional structural alerts for carcinogenicity. Therefore, ToxServices did not consider these predictions reliable. Based on data for a similar alkyl glyceryl ether, the ether linkage

may break after absorption from the GI tract. Therefore, data for the 2-ethylhexanol and glycerin were evaluated. The structural alert is also found in the metabolite 2-ethylhexanol and is associated with liver cancers in rodents through the peroxisome proliferation mechanism. Peroxisomal proliferation mechanism in the liver has not been found in humans for chemicals known to cause these effects in the liver of rodents (IARC 1994, Youssef and Badr 2011). Therefore, the relevance of this structural alert to humans is low. In addition, measured data in rodents on 2-ethylhexanol provide no evidence of carcinogenicity, as described above and concluded by WHO (1993). Therefore, a score of Low was assigned. Confidence in this score is reduced because there are no data regarding the rate and extent of ether breakage for ethylhexylglycerin.

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

Ethylhexylglycerin was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* bacterial and mammalian cell mutagenicity assays and an *in vivo* micronucleus assay. 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 based on reliable experimental 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.
- CIR 2013, AICIS 2001
  - Ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was negative in an Ames reverse mutation assay that was conducted according to OECD Guideline 471 (GLP status not reported) in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested at concentrations up to 1.5 µg/plate with and without metabolic activation. Cytotoxicity was observed at the highest dose. Positive and negative controls were reported as valid.
  - Ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was negative with and without metabolic activation in an *in vitro* mammalian cell mutagenicity assay in mouse lymphoma L5178Y cells. No additional details were provided.
  - *Oral:* Ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was negative in an *in vivo* micronucleus assay (OECD Guideline 474) in 60 male and female BOR:NMRI mice (30/sex) that received a single oral dose of 1,000 or 2,000 mg/kg via gavage and were evaluated 24 or 48 hours after administration. Clinical signs of toxicity seen within the first hour after dosing included reduced activity, alterations in tone, and abnormal gait. There was a statistically significant decrease in the number of polychromatic erythrocytes (PCEs) in bone marrow of females at all doses. There were no statistically significant increases in micronucleated PCEs at any dose, and authors concluded that the substance was not clastogenic.

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

Ethylhexylglycerin was assigned a score of Moderate for reproductive toxicity based on reduced fertility rates in the high dose group in a 1-generation reproductive toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animals (CPA 2018b). The confidence in the score is low as there was some evidence of maternal toxicity in the 1-generation reproductive toxicity study and it is not possible to conclusively determine if reduced fertility may be secondary to systemic effects.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2013
  - Ethylhexylglycerin was evaluated in a 1-generation reproductive toxicity study in male and female rats (strain not specified) that were administered 0, 50, 200, or 800 mg/kg/day ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) orally (specific route not specified) for 10 weeks prior to mating and through sacrifice (males) or for 2 weeks prior to mating and through gestation and post-partum day 20 (females). There were 17-23 females/group with live pups on post-partum day 21. Clinical signs of toxicity in parental animals included rales and salivation in males at the high dose. A total of 12 females did not become pregnant (doses not reported). There were no effects on estrus cycle, pre-birth loss, or gestation length. The fertility index was decreased in the high dose group compared to the control group. Authors identified a NOEL of 50 mg/kg/day.
    - Based on the study description, ToxServices determined that the NOEL established by the study authors was for systemic toxicity, based on clinical signs of toxicity. Therefore, ToxServices identified a reproductive NOAEL of 200 mg/kg/day and LOAEL of 800 mg/kg/day based on reduced fertility index.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Ethylhexylglycerin was assigned a score of Low for developmental toxicity based on lack of fetotoxicity and teratogenicity in oral reproductive and prenatal developmental toxicity studies in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the limited availability of study details.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2013
  - *Oral*: In a prenatal developmental toxicity test in rats (strain not specified), dams (number not specified) were administered ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) via gavage at doses of 0, 50, 200, or 800 mg/kg/day. The specific gestation days of dosing were not reported. Clinical signs of toxicity seen in the mid and high dose groups included salivation and rales. There were no effects on body weight, uterine weight, or weight gain. There were also no effects on visceral, skeletal, or external malformations. Authors identified a NOAEL of 800 mg/kg/day for developmental toxicity.
  - *Oral*: In the 1-generation reproductive toxicity study that was described previously for reproductive toxicity, male and female rats (strain not specified) that were administered 0, 50, 200, or 800 mg/kg/day ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) orally (specific route not specified) for 10 weeks prior to mating and through sacrifice (males) or for 2 weeks prior to mating and through gestation and post-partum day 20 (females). There were 17-23 females/groups with live pups on post-partum day 21. There were no treatment-related effects on pre-birth loss.

Endocrine Activity (E) Score (H, M, or L): DG
Ethylhexylglycerin was assigned a score of Data Gap for endocrine activity based on insufficient data available.

- 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 2023b
  - No Bioactivity – ToxCast Models were identified for ethylhexylglycerin on the CompTox Dashboard.
- DTU 2023 (only predictions that are within their applicability domains are reported below)
  - Ethylhexylglycerin is predicted to be negative by the Battery, CASE Ultra, Leadscope, and SciQSAR models for the estrogen receptor α binding, balanced training set and negative by the CASE Ultra model for the estrogen receptor α binding, full training set. It is also predicted to be negative by the CASE Ultra model for estrogen receptor α activation but positive by the SciQSAR model (Appendix G).
  - Ethylhexylglycerin is predicted to be negative by the Battery, CASE Ultra, Leadscope, and SciQSAR models for androgen receptor inhibition (Appendix G).
  - Ethylhexylglycerin and its predicted metabolites are predicted to be non-binders for estrogen receptor binding (Appendix G).
  - Ethylhexylglycerin is predicted to be negative for TPO inhibition QSAR2 by the Leadscope model (Appendix G).
- VEGA 2021
  - Ethylhexylglycerin was predicted to be inactive in the Estrogen Receptor Binding Affinity model (IRFMN) with strong reliability (Global AD Index = 0.891).
  - Ethylhexylglycerin was predicted to be NON-active in the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with strong reliability (Global AD = 0.948).
  - Ethylhexylglycerin was predicted to be NON-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with strong reliability (Global AD = 0.946).
- Pharos 2023
  - *Surrogate: 2-Ethylhexanol (CAS #104-76-7):* 2-Ethylhexanol is listed by TEDX as a potential endocrine disruptor.
    - The following studies were used to support the TEDX listing of 2-ethylhexanol as a potential endocrine disruptor:
      - Kassotis et al. 2015
        - Male C57BL/6J mice were administered prenatal exposures to a mixture of 23 oil and gas operation chemicals (presumable including 2-ethyl-1-hexanol but this could not be verified via the study abstract) at 3, 30, or 300 µg/kg/day and assessed for reproductive and developmental outcomes. Prenatal exposure to this mixture resulted in decreased sperm counts, increased body, testes, heart, and thymus weights, and increased serum testosterone levels.
        - Human endometrial cancer cells with a reporter gene were exposed to 24 chemicals used (presumable including 2-ethyl-1-hexanol but this could not be verified via the study abstract) and/or produced by oil and gas operations. Twenty-three of these chemicals activated or inhibited the estrogen, androgen, glucocorticoid, progesterone, and/or thyroid receptors. Furthermore, mixtures of these chemicals

acted synergistically, additively, or antagonistically in this cell system.

- Kassotis et al. 2014
    - Water samples collected from a hydraulic fracturing-dense region were solid-phase extracted and measured for estrogen and androgen receptor activities using human cell lines with reporter gene assays. Estrogenic, anti-estrogenic, androgenic, and anti-androgenic activities were detected in 89%, 41%, 12%, and 46% of 39 unique water samples, respectively. Evaluation of a subset of natural gas drilling chemicals (presumable including 2-ethyl-1-hexanol but this could not be verified via the study abstract) revealed novel anti-estrogenic, novel anti-androgenic, and limited estrogenic activities.

- There are no data for the potential endocrine activity of ethylhexylglycerin. The overall weight of evidence from modeling indicate a low concern for endocrine activity. Evidence of endocrine effects exist for surrogate 2-ethylhexanol as a constituent of natural gas drilling and gas operation chemicals. However, collectively, data are insufficient to determine if ethylhexylglycerin is endocrine active.

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

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

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

Ethylhexylglycerin was assigned a score of Moderate for acute toxicity based on an inhalation LC_{50} of 3.07 mg/L in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when inhalation LC_{50} values are between 1 and 5 mg/L for dust/mist/fumes (CPA 2018b). The confidence in the score is high as it is based on experimental data from a well conducted 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.
- CIR 2013
    - *Oral*: LD_{50} (rat, male and female Wistar) > 2,000 mg/kg (OECD Guideline 401)
    - *Dermal*: LD_{50} (rat, male and female Wistar) > 2,000 mg/kg (OECD Guideline 402)
    - *Inhalation*: LC_{50} (rat, male and female Sprague-Dawley) = 3.07 mg/L (aerosol) (OECD Guideline 403)

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

Ethylhexylglycerin was assigned a score of Moderate for systemic toxicity (single dose) based on evidence of respiratory tract irritation in an acute inhalation study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when available data indicate that GHS Category 3 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on experimental data from a guideline 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.
- CIR 2013

- *Oral:* In the acute oral toxicity study (OECD Guideline 401) that identified an LD_{50} of > 2,000 mg/kg in Wistar rats, animals (5/sex) were administered a single dose of 2,000 mg/kg ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) via gavage. There was no unscheduled mortality. Clinical signs included irregular respiration and hemorrhagic nasal discharge for the first 24 hours. There were no gross pathological changes.
- *Dermal:* In the acute dermal toxicity study (OECD Guideline 402) that identified an LD_{50} of > 2,000 mg/kg in Wistar rats, animals (5/sex) were administered a single dose of 2,000 mg/kg ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) to shaved, intact skin for 24 hours under semiocclusion. There was no unscheduled mortality, and there were no treatment-related clinical signs or dermal irritation. There were no abnormal necropsy findings.
- *Inhalation:* In the acute inhalation toxicity study (OECD Guideline 403) that identified an LC_{50} of 3.07 mg/L in Sprague-Dawley rats, animals (5/sex/dose) were administered aerosolized ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) at concentrations of 1.89, 2.96, or 4.98 mg/L via nose-only inhalation for 4 hours and were observed for 14 days. The following mortalities were reported: 4.98 mg/L (4 males, 5 females), 2.96 mg/L (3 males, 2 females), and 1.89 mg/L (1 male). Clinical signs of toxicity included labored/noisy respiration, sneezing, ataxia, and gasping. Pathological changes to the lungs included dark and reddened appearance, pale patches, enlargement, and isolated hemorrhage. An abnormally dark liver was also reported for the male in the lowest dose group that died. Authors concluded that there was clear evidence of respiratory tract irritation and that the lung was a target organ.

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

Ethylhexylglycerin was assigned a score of Moderate for systemic toxicity (repeated dose) based on hepatocyte hypertrophy at a dose of 100 mg/kg/day in a 28-day study in rats and increased liver weights at a dose of 50 mg/kg/day in a 90-day study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when evidence of systemic toxicity is seen between the guidance values of 30 and 300 mg/kg/day for a 28-day study and 10 and 100 mg/kg/day for a 90-day study (CPA 2018b). The confidence in the score is low as it is not possible to determine if effects would have been seen below the guidance values for a High, as no NOAELs were identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2013
  - *Oral*: In a subacute oral toxicity study (guideline and GLP status not reported) in male and female rats (strain not specified), animals (10/dose) were administered ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) at doses of 0, 100, 500, or 1,500 mg/kg/day via gavage for 28 days. No unscheduled mortality was observed, and the only clinical sign observed was increased salivation. At the mid and high doses, body weight was significantly reduced (magnitude not reported) and food consumption was non-significantly reduced in both sexes. There were no treatment-related effects on eye and ear function, hematology, urinalysis, or necropsy. Aminotransferase (ALT) was increased in the high dose group. Liver and adrenal weights were increased in animals at the high dose, and this effect was reported to be more apparent in females. Histopathology revealed slight to moderate hypertrophy in all dose groups, fatty infiltration of hepatocytes in males at the

high dose, and hepatocyte necrosis in some animals in the mid and high dose groups (1 rat/dose). Authors identified a NOAEL of 100 mg/kg/day and LOAEL of 500 mg/kg/day based on the assumption that slight hypertrophy of the liver, which was seen in 5/10 animals at the low dose, was not toxicologically significant.

- As the above study included an exposure period less than 90 days, ToxServices adjusted the GHS oral guidance value of 100 mg/kg/day (UN 2021) by a factor of 3 (28 days is approximately one-third of 90 days) to 300 mg/kg/day.

- *Oral*: In a subchronic oral toxicity study conducted according to OECD Guideline 407[9] (GLP status not reported) in male and female Sprague-Dawley rats, animals (10/sex/dose) were administered ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) via gavage at doses of 0, 50, 200, or 800 mg/kg/day for 90 days. There was no unscheduled mortality, and the only clinical sign reported was noisy respiration and an increased incidence of subcutaneous masses at the high dose. There were no effects on body weight, ophthalmoscopic examination, or clinical chemistry. Although no details were provided, the Cosmetic Ingredient Review (CIR) Expert Panel reports that there were some statistically significant changes in hematology, including a significant decrease in lymphocytes that were not considered by authors to be toxicologically significant. There were no treatment-related effects on gross pathology of organs. There was a statistically significant increase in absolute and relative liver weights in males at all doses and in females at the high dose. The magnitude of this effect was not reported. The increase in relative liver weights remained increased in males at the end of a 4-week recovery period (no details were provided regarding dose groups involved in the recovery study). Generalized hepatocyte hypertrophy was seen in animals at the high dose, and this effect was significant in males. Absolute and relative kidney weights were increased in females of the low and high dose groups at the end of treatment but not after the 4 week recovery period. Females at the high dose had an increase in renal mineralization at the end of treatment but not at the end of the recovery period. Study authors did not consider effects on liver weight to be toxicologically significant in the absence of other effects and identified a NOAEL of 50 mg/kg/day and LOAEL of 200 mg/kg/day. CIR Expert Panel reports that in its review of this study, Australian Industrial Chemicals Introduction Scheme (AICIS) identified a LOAEL of 50 mg/kg/day based on increased liver weights at the low dose (no additional details are provided in the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), now known as AICIS summary (AICIS 2001)).

- Based on the weight of evidence, a score of Moderate was assigned. Both the 28-day and 90-day oral toxicity studies in rats demonstrate treatment-related effects on the liver. In the 28-day study, authors reported a NOAEL of 100 mg/kg/day based on evidence of hepatocyte necrosis and decreased body weights at the mid dose of 500 mg/kg/day. In their identification of the NOAEL, authors of this study did not consider liver hypertrophy to be toxicologically significant. In the 90-day study, authors did not consider effects on liver weight to be toxicologically significant and identified a NOAEL of 50 mg/kg/day and LOAEL of 200 mg/kg/day, while AICIS identified a more conservative LOAEL of 50 mg/kg/day based on effects on liver weight at the low dose. While liver enlargement and hypertrophy may indicate an adaptive response due to induction of drug metabolizing enzymes, such responses are not typically associated with ALT elevations or necrosis (as was seen in the 28-day study) and tend to be reversible following a recovery period (which was not seen in the 90-day study) (Hall et al. 2012). While the effects may be related to peroxisomal

[9] CIR reports that this study was conducted according to OECD Guideline 407, which is a guideline for a 28-day study. ToxServices assumes that the test was conducted according to OECD Guideline 408 (90-day study) but did not have access to the full study report to confirm the study design.

proliferation that is not relevant to humans, as the compound has a structural alert for peroxisomal proliferation (see carcinogenicity endpoint), experimental data are insufficient to substantiate this mode of action. Therefore, ToxServices conservatively considered hypertrophy and increased liver weights to be early signs of hepatotoxicity and identified a LOAEL of 100 mg/kg/day in the 28-day study and LOAEL of 50 mg/kg/day in the 90-day study. These values fall between the guidance values of 30-300 mg/kg/day (28-day study) and 10-100 mg/kg/day (90-day study) corresponding to a Moderate. Confidence in this score is reduced because it is not possible to determine if effects would have been seen below the guidance values for a High, as no NOAELs were identified.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Ethylhexylglycerin was assigned a score of Low for neurotoxicity (single dose) based on a lack of neurotoxic effects in acute oral and dermal toxicity studies, and signs of labored/noisy respiration, sneezing, ataxia, and gasping in the inhalation toxicity studies likely secondary to evidence of respiratory tract irritation. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as it is based on studies with limited neurotoxicity examination.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2013
  - *Oral:* In the acute oral toxicity study (OECD Guideline 401) that identified an LD_{50} of > 2,000 mg/kg in Wistar rats, animals (5/sex) were administered a single dose of 2,000 mg/kg ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) via gavage. There was no unscheduled mortality. Clinical signs included irregular respiration and hemorrhagic nasal discharge for the first 24 hours. There were no gross pathological changes.
  - *Dermal:* In the acute dermal toxicity study (OECD Guideline 402) that identified an LD_{50} of > 2,000 mg/kg in Wistar rats, animals (5/sex) were administered a single dose of 2,000 mg/kg ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) to shaved, intact skin for 24 hours under semiocclusion. There was no unscheduled mortality, and there were no treatment-related clinical signs or dermal irritation. There were no abnormal necropsy findings.
  - *Inhalation:* In the acute inhalation toxicity study (OECD Guideline 403) that identified an LC_{50} of 3.07 mg/L in Sprague-Dawley rats, animals (5/sex/dose) were administered aerosolized ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) at concentrations of 1.89, 2.96, or 4.98 mg/L via nose-only inhalation for 4 hours and were observed for 14 days. The following mortalities were reported: 4.98 mg/L (4 males, 5 females), 2.96 mg/L (3 males, 2 females), and 1.89 mg/L (1 male). Clinical signs of toxicity included labored/noisy respiration, sneezing, ataxia, and gasping. Pathological changes to the lungs included dark and reddened appearance, pale patches, enlargement, and isolated hemorrhage. An abnormally dark liver was also reported for the male in the lowest dose group that died. Authors concluded that there was clear evidence of respiratory tract irritation and that the lung was a target organ.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Ethylhexylglycerin was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of neurotoxicity at doses up to 800 mg/kg/day in a 90-day oral toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when there is no evidence of

neurotoxicity below the guidance value of 100 mg/kg/day for an oral study (CPA 2018b). The confidence in the score is high based on reliable 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.
- CIR 2013, AICIS 2001
  - *Oral*: In the OECD Guideline 407 subchronic oral toxicity study in male and female Sprague-Dawley rats that was described above for systemic toxicity, animals (10/sex/dose) were administered ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) via gavage at doses of 0, 50, 200, or 800 mg/kg/day for 90 days. There were no effects on neurotoxicity endpoints, including a functional observation battery and motor activity evaluation. No additional details were provided.

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

Ethylhexylglycerin was assigned a score of Moderate for skin sensitization based on it being an infrequent skin sensitizer in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when they are classified to GHS category 1B (low frequency of occurrence) (CPA 2018b). The confidence in the score is low due to inconsistent results among human and animal studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2013
  - Ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was negative in a guinea pig maximization test that was conducted according to OECD Guideline 406 in male and female guinea pigs (strain not specified). Animals (10/sex/group) were induced intradermally with a 0.5% solution and topically with undiluted test substance and were challenged with a 50% solution. There was no evidence of sensitization in any of the animals. No additional details were provided.
  - Ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was negative in a mouse local lymph node assay (LLNA) when tested at concentrations up to 50%. The EC3 value did not reach 3 at any concentration tested, and authors concluded that the substance was not a sensitizer. No additional details were provided.
  - The CIR Expert Panel reported on human repeat insult patch tests (HRIPT) of several cosmetic ingredients containing ethylhexylglycerin. There was no evidence of sensitization in HRIPTs of a formulation containing 0.4975% ethylhexylglycerin in 600 subjects, a formulation containing 0.5% ethylhexylglycerin in 105 subjects, a formulation containing 0.4975% ethylhexylglycerin in 115 subjects, a formulation containing 0.995% ethylhexylglycerin in 111 subjects, or a formulation containing 0.6965% ethylhexylglycerin in 108 subjects.
- Anderson 2012
  - Ethylhexylglycerin is an infrequent skin sensitizer in humans. Anderson reported that there were four previously published case reports of ethylhexylglycerin-induced allergic contact dermatitis that were diagnosed by targeted testing with 5-10% solutions of ethylhexylglycerin in petrolatum. The case reports involved four women that had positive patch tests to the suspected culprit cosmetics in addition to positive patch tests for ethylhexylglycerin. The Department of Dermatology, Odense University Hospital and Allergy Centre includes ethylhexylglycerin in the baseline series of patch tests and identified

one positive patch test result in 785 tested individuals (0.13%). The author concluded that ethylhexylglycerin is a weak cosmetic allergen.

- Based on the weight of evidence, a score of Moderate was assigned. GHS criteria allow for classification as a Category 1A sensitizer based on "diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to a relatively low exposure" and as a Category 1B sensitizer when there is "diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to a relatively high exposure" (UN 2021). Although there were no positive responses to ethylhexylglycerin in several patch tests of cosmetic formulations containing up to 0.995% ethylhexylglycerin, and all the animal studies were negative, there have been 5 case reports of sensitization to ethylhexylglycerin following exposure to low use levels in cosmetics. This ingredient is widely used and produced positive patch test responses in only 0.13% of individuals in a dermatology clinic. Therefore, the incidence of sensitization responses is relatively low in relation to a relatively low exposure. Furthermore, GHS guidance specifies that evidence from animal studies is usually more reliable than evidence from human exposure, and that isolated episodes of allergic contact dermatitis should be considered only on a case-by-case basis when seen in conjunction with positive results in epidemiological studies, non-guideline studies, or analogs, or borderline positive animal studies. Based on the positive human reports, ToxServices conservatively classified ethylhexylglycerin to GHS category 1B. Confidence in this score is reduced due to consistently negative results in a guinea pig maximization test, mouse LLNA, and HRIPT.

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

Ethylhexylglycerin was assigned a score of Data Gap for respiratory sensitization based on insufficient 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.
- OECD 2022
  - Ethylhexylglycerin does not contain any structural alerts for respiratory sensitization (Appendix I)
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of ethylhexylglycerin according to ECHA's guideline (ECHA 2017), which 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). Ethylhexylglycerin does not contain any structural alerts but is a weak skin sensitizer based on infrequent positive experimental data in humans. According to the ECHA guidance, the positive skin sensitization results in humans and lack of structural alerts and evidence of respiratory sensitization indicate that there are insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Due to the positive predictions for skin sensitization and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Data Gap was assigned.

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

Ethylhexylglycerin was assigned a score of Low for skin irritation/corrosivity based on negative results in dermal irritation studies in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental 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.
- CIR 2013
  - In a dermal irritation study that was conducted according to OECD Guideline 404 (GLP status not reported), 0.5 mL undiluted test substance (>99% ethylhexylglycerin with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was administered to the intact skin of 3 New Zealand White rabbits for 4 hours under semiocclusion and animals were observed for 4 days. Erythema was seen in 2 rabbits (score of 1) during the observation period and resolved by day 4. There was no evidence of edema in any of the rabbits. Authors concluded that ethylhexylglycerin is a mild skin irritant.
  - In a dermal irritation study that was conducted according to OECD Guideline 404 (GLP status not reported), 0.5 mL undiluted test substance (>99% ethylhexylglycerin with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was administered to the intact skin of 3 rabbits (strain not specified) for 4 hours under semiocclusion. Very slight erythema was seen in 2/3 rabbits at the 24 and 48 hour observations (scores not reported). Authors concluded that ethylhexylglycerin was not a skin irritant.
- Based on the weight of evidence, a score of Low was assigned. GHS classification as a skin irritant requires mean scores of > 1.5 and < 2.3 for erythema or edema in at least 2/3 animals. Although scores were not reported in one study, only "very slight" erythema was reported. In a second study, scores did not exceed 1 for erythema, and no edema was seen. Therefore, ethylhexylglycerin does not warrant GHS classification for irritation.

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

Ethylhexylglycerin was assigned a score of Very High for eye irritation/corrosivity based on the harmonized EU classification of ethylhexylglycerin as a GHS Category 1 eye irritant (H318). GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when they classified as GHS Category 1 eye irritants by the EU (CPA 2018b). The confidence in the score is high as it is based on an authoritative listing and reliable measure data.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU – GHS (H-Statements) Annex 6 Table 3-1 – H318 – Causes serious eye damage [Serious eye damage/eye irritation – Category 1]
  - *Screening:*
    - GHS – Australia – H318 – Causes serious eye damage [Serious eye damage/eye irritation – Category 1]
- CIR 2013
  - In an ocular irritation study that was conducted according to OECD Guideline 405 (GLP status not reported) in 3 New Zealand White rabbits (sex not reported), 0.1 mL test substance (>99% ethylhexylglycerin with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) was instilled into the eyes and animals were observed for 21 days. Conjunctival redness and chemosis were seen in all animals, and "irritation scores of 2 or 3 predominated" (exact scores were not reported). Conjunctival irritation persisted until day

14 and corneal opacity persisted in one animal through the 21-day observation period. Authors concluded that the substance caused severe damage to the eye.
    - In an ocular irritation study according to the same procedures described above, a 5% solution of ethylhexylglycerin (>99% with < 1% α-tocopherol, 2-ethylhexyl-glycidylether, and water) produced conjunctival erythema scores of 1 in each animal one hour after instillation; irritation resolved within 24 hours. No irritation was seen in the iris or cornea. Authors concluded that the 5% solution was mildly irritating.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M
Ethylhexylglycerin was assigned a score of Moderate for acute aquatic toxicity based on values of 60.2 mg/L in fish, 78.2 mg/L in daphnia, and 42.28 mg/L in algae. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity L/EC_{50} values are between 10 and 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on measured data for all three trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
    - 96-hour LC_{50} (*Danio rerio*, zebrafish) = 60.2 mg/L (OECD Guideline 203; GLP not specified).
    - 48-hour EC_{50} (*Daphnia magna*, water flea) = 78.3 mg/L (OECD Guideline 202; GLP not specified).
    - 72-hour EC_{50} (*Desmodesmus subspicatus*, green algae) = 42.28 mg/L (biomass), 84.3 mg/L (growth) (OECD Guideline 201; GLP not specified).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): M
Ethylhexylglycerin was assigned a score of Moderate for chronic aquatic toxicity based on a NOEC of 1.5 mg/L in fish. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when the most conservative chronic aquatic toxicity values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score is high as it is based on experimental data for all three trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Not present on any screening lists.
- ECHA 2023b
    - 35-day NOEC (*D. rerio*) = 1.5 mg/L (mortality, weight), 7.2 mg/L (length) (OECD Guideline 210; GLP not specified).
    - 21-day NOEC (*D. magna*) = 20 mg/L (reproduction, immobilization) (OECD Guideline 211; GLP not specified).
    - 21-day LOEC (*D. magna*) = 40 mg/L (reproduction) (OECD Guideline 211; GLP not specified).
    - 72-hour NOEC (*D. subspicatus*, green algae) = 22.178 mg/L (biomass, growth) (OECD Guideline 201; GLP not specified).

Environmental Fate (Fate)

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

Ethylhexylglycerin was assigned a score of Moderate for persistence based on a modeled half-life of 17.3 days in soil, which is predicted to be its dominant compartment, and experimental data demonstrating it will biodegrade but does not mee the ready or rapid biodegradability criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for persistence when the half-life in soil is between 16 and 60 days (CPA 2018b). The confidence in the score is low as it is based on modeled data and poorly reported studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - Ethylhexylglycerin was hydrolytically stable in a preliminary test (OECD Guideline 111 (Hydrolysis as a Function of pH); GLP not specified). No additional details were provided.
  - In a ready biodegradability test conducted according to OECD Guideline 301D (Closed Bottle Test) (GLP not specified), non-adapted domestic sewage was exposed to ethylhexylglycerin (concentration not specified) for 28 days under aerobic conditions. The level of degradation was 8.2% after 5 days, 0% after 14 days, 0% after 21 days, and 20.6% after 28 days. No additional details were provided.
  - In an inherent biodegradability test conducted according to OECD Guideline 302B (Zahn-Wellens/EMPA Test), domestic activated sludge (adaptation not specified) was exposed to 303.2 mg/L ethylhexylglycerin for 28 days under aerobic conditions. The level of degradation was 14% after 5 days, 40% after 12 days, 63% after 21 days, and 70% after 28 days (based on dissolved organic carbon (DOC)). No additional details were provided.
  - In a biodegradation in water/sewage treatment simulation test conducted according to OECD Guideline 303A (Simulation Test – Aerobic Sewage Treatment A: Activated Sludge Units), a mixture of sewage, soil and natural water was exposed to 25 mg/L ethylhexylglycerin (16 mg/L DOC) under aerobic conditions. Degradation of 45% was observed as DOC removal. No additional details were provided.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that ethylhexylglycerin is expected to be readily biodegradable. Level III Fugacity modeling (MCI method) predicts 62% will partition to soil with a half-life of 17.3 days, 36.9% will partition to water with a half-life of 8.67 days, and 0.983% will partition to air with a half-life of 5.79 hours (Appendix J).
- Based on the weight of evidence, a score of Moderate was assigned. Very limited details were available for the identified biodegradation studies, but the rates of 20.6% in 28 days for a ready biodegradability test and 70% in 28 days for an inherent biodegradability test indicate that ethylhexylglycerin does undergo biodegradation in the environment but is not readily or rapidly biodegradable. There is no evidence that it hydrolyzes in the environment. Modeling was performed in order to identify the predicted dominant compartment and estimated half-life for ethylhexylglycerin. EPI Suite™ predicts that ethylhexylglycerin will partition primarily to soil, with a half-life of 17.3 days in this compartment. This half-life corresponds to a score of Moderate, which is consistent with data demonstrating that ethylhexylglycerin will biodegrade but does not meet ready or rapid biodegradation criteria.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Ethylhexylglycerin was assigned a score of Very Low for bioaccumulation based on an experimental log K_{ow} of 2.53 with support from a modeled BCF of 15.73. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is less than 4 and the BCF is less than 100 (CPA 2018b). The confidence in the score is high as it is based on an experimental log K_{ow}.

- 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 2017
  - BCFBAF predicts a BCF of 21.69 using the regression based model based on a measured log K_{ow} of 2.53, and a BCF of 15.73 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix J).
- ECHA 2023b, Schulke Undated
  - Ethylhexylglycerin has an experimental log K_{ow} of 2.53 at 20°C from a test according to OECD Guideline 107.
- A score of Very Low was assigned based on the experimental log K_{ow} of 2.53, which indicates that the substance is hydrophilic and is not likely to bioaccumulate. This is consistent with the modeled BCF values of 21.69 and 15.73 which also corresponds to a Very Low.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Ethylhexylglycerin was assigned a score of Low for reactivity based on not being explosive and lack of alerts for an organic peroxide, self-reactive, or substances that upon contact with water emits flammable gases. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the chemical does not warrant GHS classification for any of the reactive subcategories, and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score was low as it is not based on experimental data for any of the reactivity subcategories.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- TCI America 2018
  - "No special reactivity has been reported" for ethylhexylglycerin and it has an instability rating of 0 from NFPA ("Normally stable. Not reactive with water.").
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of ethylhexylglycerin. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, ethylhexylglycerin is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix K).
  - Based on the structure of its components or moieties, Ethylhexylglycerin is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of ethylhexylglycerin has 3 oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.

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

Ethylhexylglycerin was assigned a score of Low for flammability based on its flash point of 152°C. GreenScreen® criteria classify chemicals as a Low hazard for flammability when available data indicate that the chemical does not warrant GHS classification as a flammable liquid (CPA 2018b). The confidence in the score was high as it is based on an experimental flash point.

- 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 2023b
  - Ethylhexylglycerin has a flash point of 152°C (EU Method A.9).
- Based on the weight of evidence, a score of Low was assigned as chemicals with a flash point > 93°C do not warrant GHS classification as a flammable liquid (UN 2021).

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, persistence, and bioaccumulation, and *in vitro* assays for genotoxicity. 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 ethylhexylglycerin's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Ethylhexylglycerin's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to evaluate ethylhexylglycerin's carcinogenic potential, the uncertain *in vivo* relevance of *in silico* prediction of endocrine receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of ethylhexylglycerin's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: Insufficient experimental data are available. **Endocrine activity:** No *in vivo* data are available on circulating hormones on the target substance. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (Sas), and no applicability domain can be defined (Toxtree 2018). OncoLogic could not evaluate the structure of the compound. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in

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

	non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[12] The mammalian cell gene mutation assay (as defined in OECD Guideline 490) cannot reliably detect aneugens, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells)[13]. **Endocrine activity:** The *in vivo* relevance of *in silico* modeling of receptor binding activities is uncertain due to lack of toxicokinetic considerations. **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/OECD Toolbox/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: Danish QSAR/VEGA
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	

[11] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[12] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[13] https://www.oecd-ilibrary.org/docserver/9789264264908-en.pdf?expires=1622037214&id=id&accname=guest&checksum=F0669770FC98B49A32E3AFBA1A4D86F5

Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301D, 302B, 303A Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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Youssef, J., and M. Badr. 2011. Peroxisome proliferator-activated receptors and cancer: challenges and opportunities. *Br J Pharmacol*. 164(1):68-82. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171861/#b46

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 Ethylhexylglycerin (CAS #70445-33-9)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Ethylhexylglycerin / 70445-33-9	*L*	**L**	*M*	*L*	DG	**M**	**M**	*M*	*L*	**L**	*M*	DG	**L**	vH	**M**	**M**	*M*	**vL**	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Ethylhexylglycerin	2

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

Table 6

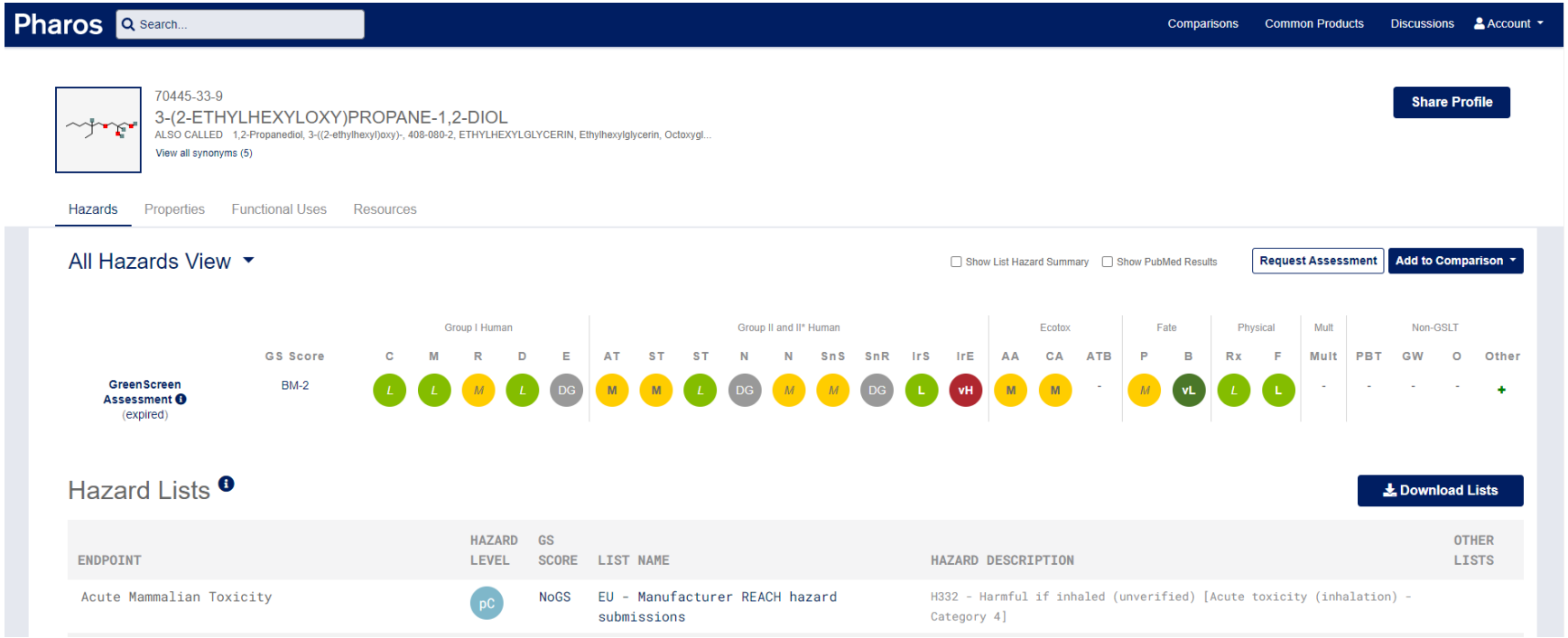
Chemical Name	Final GreenScreen® Benchmark Score
Ethylhexylglycerin	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Ethylhexylglycerin (CAS #70445-33-9)

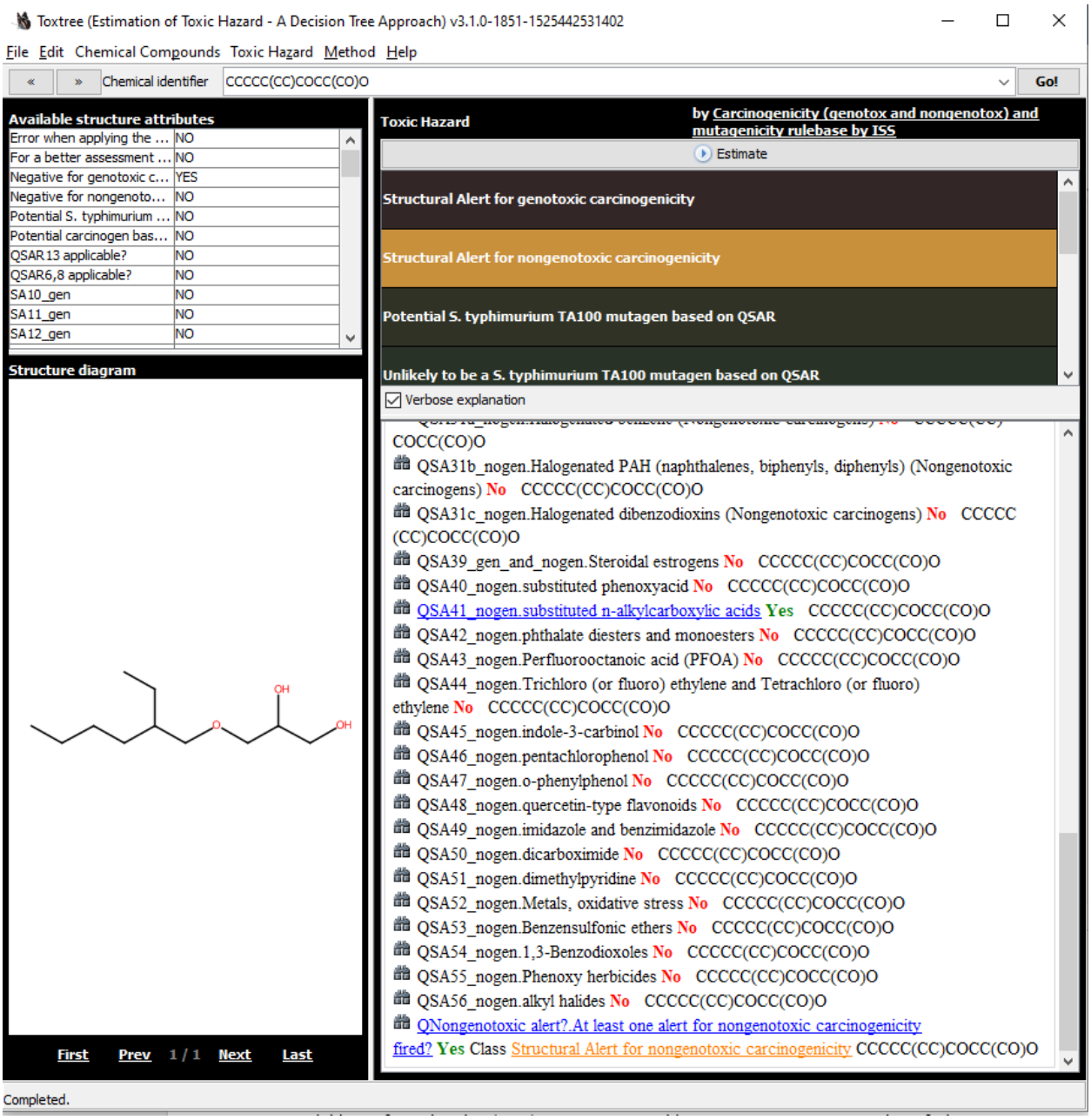


Eye Irritation/Corrosivity	vH	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H318 - Causes serious eye damage [Serious eye damage/eye irritation - Category 1]	+2
	vH	LT-UNK	GHS - Australia	H318 - Causes serious eye damage [Serious eye damage/eye irritation - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified) [Serious eye damage/eye irritation - Category 1]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	M	LT-UNK	GHS - Australia	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]	+2
	U	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

Positive Lists (2)

- Cosmetic Ingredient Review (CIR): Safe as Used
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients

APPENDIX D: Toxtree Carcinogenicity Results for Ethylhexylglycerin (CAS #70445-33-9)



APPENDIX E: Danish (Q)SAR Database Carcinogenicity Modeling for Ethylhexylglycerin (CAS #70445-33-9)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	POS_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_IN
FDA RCA Cancer Female Mouse	NEG_IN	POS_IN
FDA RCA Cancer Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Rodent	NEG_IN	INC_OUT

Commercial models from CASE Ultra and Leadscope

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

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	Structural alert for nongenotoxic carcinogenicity; Substituted n-alkylcarboxylic acids (Nongenotox)
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

OECD QSAR Toolbox v.4.2 profilers

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

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

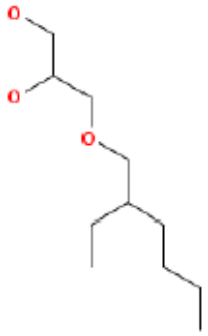
DTU-developed models

APPENDIX F: VEGA Carcinogenicity Modeling Output for Ethylhexylglycerin (CAS #70445-33-9)

VEGA Carcinogenicity model (CAESAR) 2.1.9 page 1

1. Prediction Summary

Prediction for compound Molecule 0

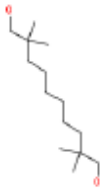


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.134
P(NON-Carcinogen): 0.867
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

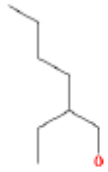
CAS: 35449-36-6
Dataset id: 345 (Training set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.804

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

Compound #2

CAS: 2432-99-7
Dataset id: 50 (Test set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.776

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #3

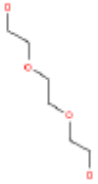
CAS: 104-76-7
Dataset id: 314 (Training set)
SMILES: OCC(CC)CCCC
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Compound #4

CAS: 103-23-1
Dataset id: 315 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

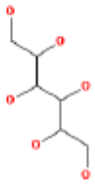
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 112-27-6
Dataset id: 773 (Training set)
SMILES: OCCOCCOCCO
Similarity: 0.755

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 69-65-8
Dataset id: 421 (Training set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.749

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.635 Explanation: the predicted compound could be out of the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.789 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.512 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
⚠	**Concordance for similar molecules** Concordance index = 0.512 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**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 = 0.733 Explanation: model class assignment is well defined.
✓	**Neural map neurons concordance** Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

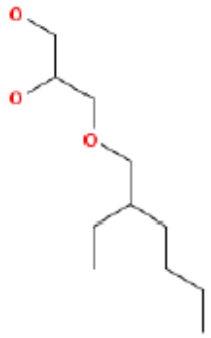
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

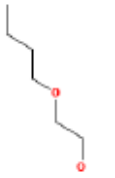


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not adequate
The following alerts have been found: SA41 Substituted n-alkylcarboxylic acids

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
Structural alerts: SA41 Substituted n-alkylcarboxylic acids
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

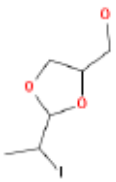
CAS: 111-76-2
Dataset id: 596 (Training set)
SMILES: OCCOCCCC
Similarity: 0.806

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

Compound #2

CAS: 2432-99-7
Dataset id: 36 (Training set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.776

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

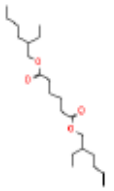


Compound #3

CAS: 5634-39-9
Dataset id: 619 (Training set)
SMILES: OCC1OC(OC1)C(C)I
Similarity: 0.761

Experimental value: Carcinogen
Predicted value: Carcinogen

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



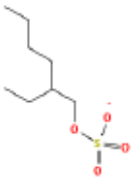
Compound #4

CAS: 103-23-1
Dataset id: 52 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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



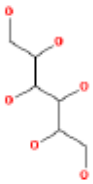
Compound #5

CAS: 126-92-1
Dataset id: 77 (Training set)
SMILES: O=S(=O)([O-])OCC(CC)CCCC
Similarity: 0.752

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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



Compound #6

CAS: 69-65-8
Dataset id: 86 (Training set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.749

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 = 0.79 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✔	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

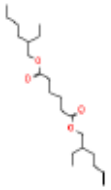
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: SA41 Substituted n-alkylcarboxylic acids

Substituted n-alkylcarboxylic acids

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

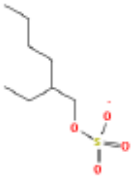


CAS: 103-23-1
Dataset id: 52 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Carcinogen

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

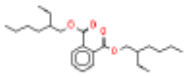
Alerts (not found in the target): SA42 Phthalate diesters and monoesters



CAS: 126-92-1
Dataset id: 77 (Training set)
SMILES: O=S(=O)([O-])OCC(CC)CCCC
Similarity: 0.752

Experimental value: Carcinogen
Predicted value: Carcinogen

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



CAS: 117-81-7
Dataset id: 53 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.678

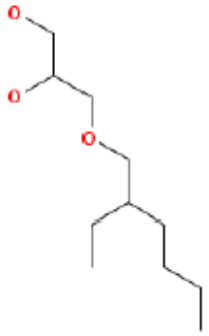
Experimental value: Carcinogen
Predicted value: Carcinogen

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

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

1. Prediction Summary

Prediction for compound Molecule 0

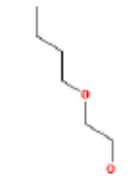


Prediction: Reliability:

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)COCC(CC)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

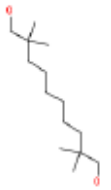
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 1364 (Training set)
SMILES: OCCOCCCC
Similarity: 0.806

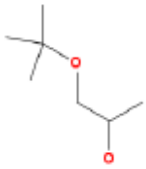
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 345 (Training set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.804

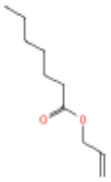
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: N.A.
Dataset id: 913 (Training set)
SMILES: OC(C)COC(C)(C)C
Similarity: 0.794

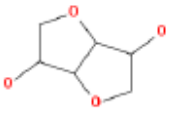
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: N.A.
Dataset id: 1275 (Training set)
SMILES: O=C(OCC=C)CCCCCC
Similarity: 0.788

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



Compound #5

CAS: N.A.
Dataset id: 1422 (Training set)
SMILES: OC1COC2C(O)COC12
Similarity: 0.782

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

Compound #6

CAS: N.A.
Dataset id: 50 (Training set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.776

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.895
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.801
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

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

Symbols explanation:

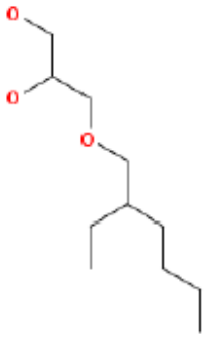
The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

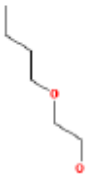


Prediction: Reliability:

Prediction is 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:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not adequate
The following relevant fragments have been found: Carcinogenity alert no. 29

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural alerts: Carcinogenity alert no. 29
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

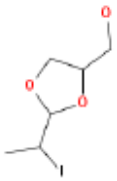
CAS: 111-76-2
Dataset id: 498 (Training set)
SMILES: OCCOCCCC
Similarity: 0.806

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #2

CAS: 2432-99-7
Dataset id: 29 (Training set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.776

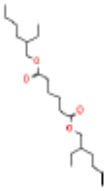
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: 5634-39-9
Dataset id: 511 (Training set)
SMILES: OCC1OC(OC1)C(C)I
Similarity: 0.761

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

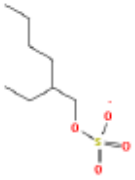


Compound #4

CAS: 103-23-1
Dataset id: 43 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 29

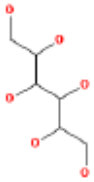


Compound #5

CAS: 126-92-1
Dataset id: 648 (Training set)
SMILES: O=S(=O)([O-])OCC(CC)CCCC
Similarity: 0.752

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 8



Compound #6

CAS: 69-65-8
Dataset id: 69 (Training set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.749

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.779 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✔	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

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

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

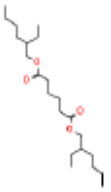
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: Carcinogenity alert no. 29

Structural alert for carcinogenity defined by the SMARTS: C(OC)C(C)C

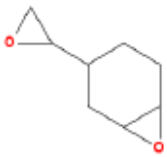
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 103-23-1
Dataset id: 43 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 29

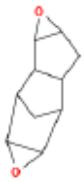


CAS: 106-87-6
Dataset id: 685 (Training set)
SMILES: O1CC1C2CCC3OC3(C2)
Similarity: 0.748

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 29

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



CAS: 81-21-0
Dataset id: 766 (Training set)
SMILES: O3C4CC5C2CC(C1OC12)C5(C34)
Similarity: 0.729

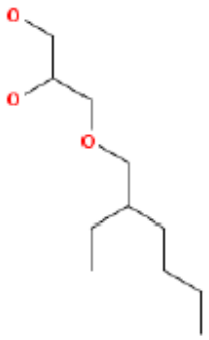
Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 29

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

1. Prediction Summary

Prediction for compound Molecule 0

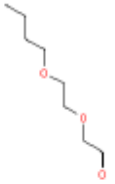


Prediction: Reliability:

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)COCC(CC)CCCC
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

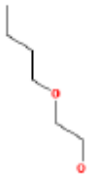
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 112-34-5
Dataset id: 453 (Test set)
SMILES: OCCOCCOCCCC
Similarity: 0.843

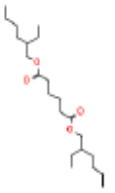
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id: 509 (Training set)
SMILES: OCCOCCCC
Similarity: 0.806

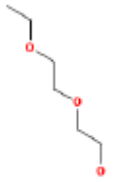
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 103-23-1
Dataset id: 94 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

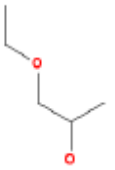
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 111-90-0
Dataset id: 454 (Training set)
SMILES: OCCOCCOCC
Similarity: 0.758

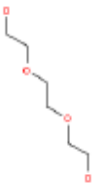
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 1569-02-4
Dataset id: 663 (Training set)
SMILES: OC(C)COCC
Similarity: 0.755

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



Compound #6

CAS: 112-27-6
Dataset id: 727 (Test set)
SMILES: OCCOCCOCCO
Similarity: 0.755

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.907
Explanation: the predicted compound is into 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 found.

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

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

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

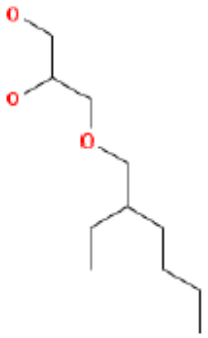
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

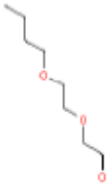


Prediction: Reliability:

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

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

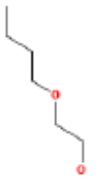
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 112-34-5
Dataset id: 420 (Test set)
SMILES: OCCOCCOCCCC
Similarity: 0.843

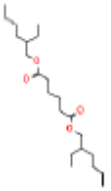
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id: 482 (Training set)
SMILES: OCCOCCCC
Similarity: 0.806

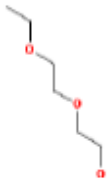
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 103-23-1
Dataset id: 391 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

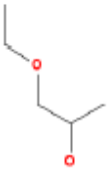
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 111-90-0
Dataset id: 421 (Training set)
SMILES: OCCOCCOCC
Similarity: 0.758

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



Compound #5

CAS: 1569-02-4
Dataset id: 652 (Training set)
SMILES: OC(C)COCC
Similarity: 0.755

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

Compound #6

CAS: 112-27-6
Dataset id: 727 (Training set)
SMILES: OCCOCCOCCO
Similarity: 0.755

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.907
Explanation: the predicted compound is into 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 found.

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

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

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

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

Symbols explanation:

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

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

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

APPENDIX G: Danish (Q)SAR Database Endocrine and Molecular Endpoints for Ethylhexylglycerin (CAS #70445-33-9)

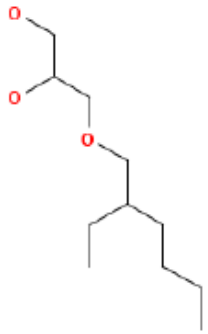
Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_OUT	NEG_IN	NEG_OUT	NEG_OUT
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		INC_OUT	NEG_IN	NEG_OUT	POS_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA		N/A	N/A	NEG_IN	N/A
data (*in vitro*)					
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			32680.57	4855.562	
- μM			159955.8	23765.66	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			6611.345	265.3198	
- μM			32359.38	1298.614	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 μM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 μM (*in vitro*)		N/A	N/A	NEG_IN	N/A

APPENDIX H: VEGA Endocrine Activity Modeling Results for Ethylhexylglycerin (CAS #70445-33-9)

1. Prediction Summary

Prediction for compound Molecule 0

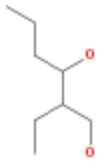


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 4
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

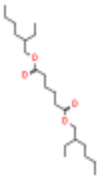
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 94-96-2
Dataset id: 17 (Training set)
SMILES: OCC(CC)C(O)CCC
Similarity: 0.836

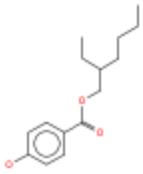
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 103-23-1
Dataset id: 9 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.76

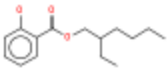
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 5153-25-3
Dataset id: 221 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccc(O)cc1
Similarity: 0.755

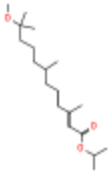
Experimental value: Active
Predicted value: Inactive



Compound #4

CAS: 118-60-5
Dataset id: 184 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(O)
Similarity: 0.752

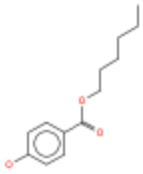
Experimental value: Inactive
Predicted value: Active



Compound #5

CAS: 40596-69-8
Dataset id: 5 (Training set)
SMILES: O=C(OC(C)C)C=C(C=CCC(C)CCCC(OC)(C)C)C
Similarity: 0.738

Experimental value: Inactive
Predicted value: Active



Compound #6

CAS: 1083-27-8
Dataset id: 219 (Training set)
SMILES: O=C(OCCCCCC)c1ccc(O)cc1
Similarity: 0.735

Experimental value: Active
Predicted value: Active

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.891
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.793
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

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

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

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

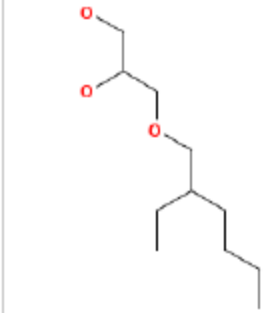
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

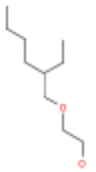


Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted ER-mediated effect: NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 1
No. alerts for possible non-activity: 2
Structural alerts: ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

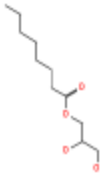


Compound #1

CAS: N.A.
Dataset id: 910 (Training set)
SMILES: OCCOCC(CC)CCCC
Similarity: 0.914

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3



Compound #2

CAS: N.A.
Dataset id: 751 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCC
Similarity: 0.907

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

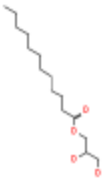
Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

Compound #3

CAS: N.A.
Dataset id: 504 (Training set)
SMILES: OCCOCCCCCC
Similarity: 0.878

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3



Compound #4

CAS: N.A.
Dataset id: 678 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCCCCCC
Similarity: 0.867

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

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

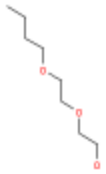
Compound #5

CAS: N.A.
Dataset id: 794 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCCCCCCCC
Similarity: 0.846

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9



Compound #6

CAS: N.A.
Dataset id: 508 (Training set)
SMILES: OCCOCCOCCCC
Similarity: 0.843

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

3.2 Applicability Domain:
Measured Applicability Domain Scores

✔	**Global AD Index** AD index = 0.948 Explanation: the predicted compound is into the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.899 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✔	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

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

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

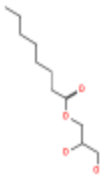
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 1 of 3:

Fragment found: ER non-activity alert no. 29

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

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

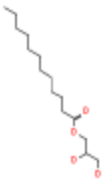


CAS: N.A.
Dataset id: 751 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCC
Similarity: 0.907

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9



CAS: N.A.
Dataset id: 678 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCCCCCC
Similarity: 0.867

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

CAS: N.A.
Dataset id: 794 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCCCCCCCC
Similarity: 0.846

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

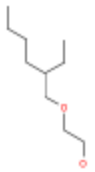
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 2 of 3:

Fragment found: ER possible non-activity alert no. 1

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

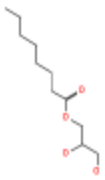
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 910 (Training set)
SMILES: OCCOCC(CC)CCCC
Similarity: 0.914

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3



CAS: N.A.
Dataset id: 751 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCC
Similarity: 0.907

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

CAS: N.A.
Dataset id: 504 (Training set)
SMILES: OCCOCCCCCC
Similarity: 0.878

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

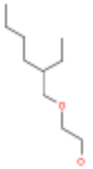
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 3 of 3:

Fragment found: ER possible non-activity alert no. 3

Fragment related to possible non-activity for ER-mediated effect, defined by the SMARTS: C(O)CO

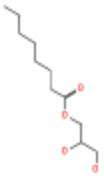
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 910 (Training set)
SMILES: OCCOCC(CC)CCCC
Similarity: 0.914

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3



CAS: N.A.
Dataset id: 751 (Training set)
SMILES: O=C(OCC(O)CO)CCCCCCC
Similarity: 0.907

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 9

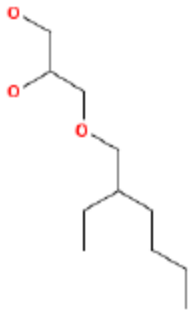
CAS: N.A.
Dataset id: 504 (Training set)
SMILES: OCCOCCCCCC
Similarity: 0.878

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 3

1. Prediction Summary

Prediction for compound Molecule 0

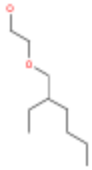


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: OCC(O)COCC(CC)CCCC
Experimental value: -
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 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

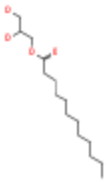
CAS: 1559-35-9
Dataset id: 1301 (Training set)
SMILES: CCCCC(COCCO)CC
Similarity: 0.914

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

Compound #2

CAS: 112-25-4
Dataset id: 916 (Training set)
SMILES: CCCCCCOCCO
Similarity: 0.878

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

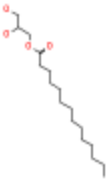


Compound #3

CAS: 142-18-7
Dataset id: 1247 (Training set)
SMILES: CCCCCCCCCCC(=O)OCC(O)CO
Similarity: 0.867

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

Alerts (not found in the target): ER alert no. 118, inactive



Compound #4

CAS: 589-68-4
Dataset id: 1308 (Training set)
SMILES: CCCCCCCCCCCCC(=O)OCC(O)CO
Similarity: 0.846

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

Alerts (not found in the target): ER alert no. 118, inactive

Compound #5

CAS: 112-34-5
Dataset id: 485 (Training set)
SMILES: CCCCOCCOCCO
Similarity: 0.843

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

Alerts (not found in the target): ER alert no. 18, inactive

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

Compound #6

CAS: 143-22-6
Dataset id: 486 (Training set)
SMILES: CCCCOCCOCCOCCO
Similarity: 0.842

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

Alerts (not found in the target): ER alert no. 18, inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.946
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.895
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

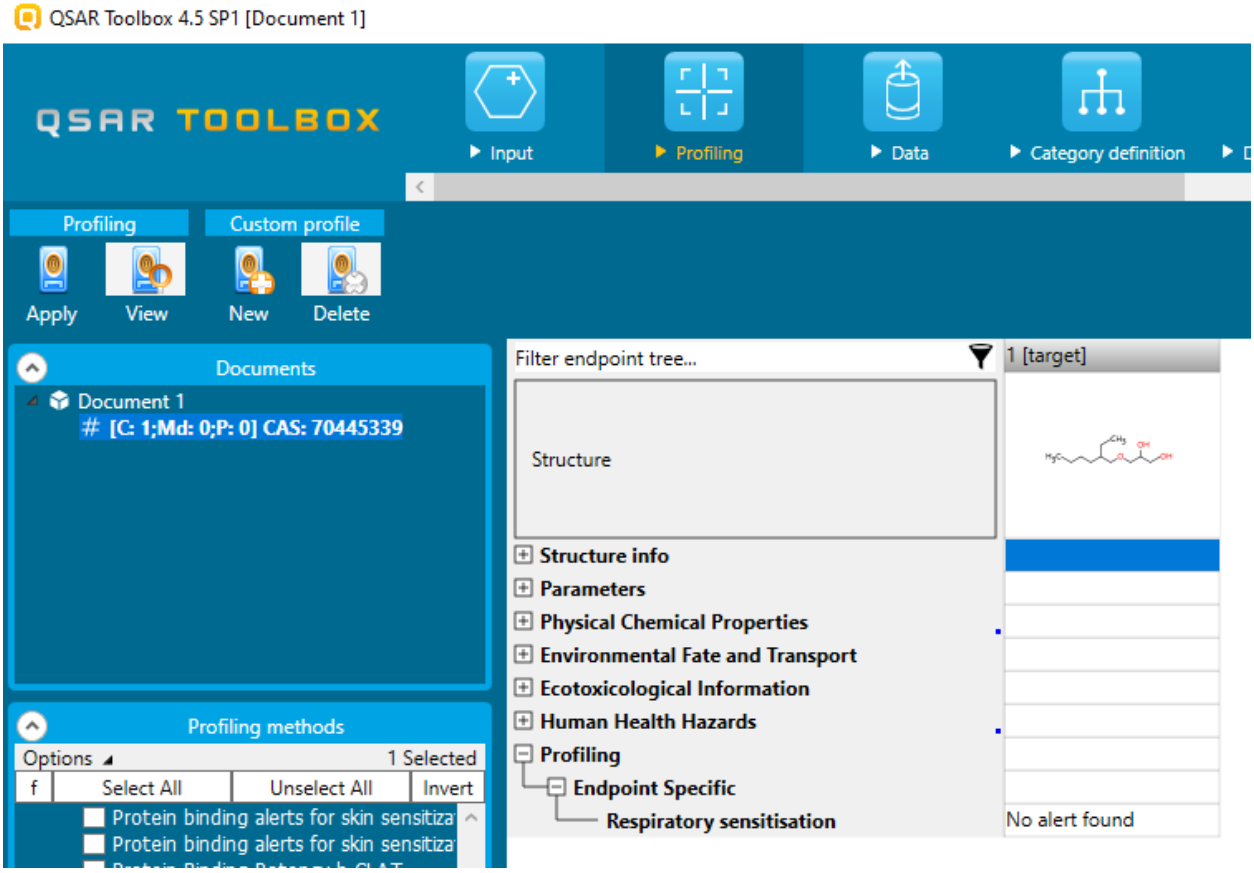
Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

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

Symbols explanation:

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

APPENDIX I: OECD Toolbox for Respiratory Sensitization Results for Ethylhexylglycerin (CAS #70445-33-9)



APPENDIX J: EPI Suite™ Modeling Results for Ethylhexylglycerin (CAS #70445-33-9)

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

CAS Number: 70445-33-9
SMILES : CCCCC(CC)COCC(CO)O
CHEM : Ethylhexylglycerin
MOL FOR: C11 H24 O3
MOL WT : 204.31
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.53
Boiling Point (deg C): 285.00
Melting Point (deg C): -76.00
Vapor Pressure (mm Hg): 0.0023
Water Solubility (mg/L): 1800
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 2.22

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 307.33 (Adapted Stein & Brown method)
Melting Pt (deg C): 60.12 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.000199 (Modified Grain method)
VP (Pa, 25 deg C) : 0.0265 (Modified Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 856.9
log Kow used: 2.53 (user entered)
melt pt used: -76.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 37833 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.48E-008 atm-m3/mole (1.50E-003 Pa-m3/mole)
Group Method: 2.68E-012 atm-m3/mole (2.72E-007 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 3.435E-007 atm-m3/mole (3.481E-002 Pa-m3/mole)
VP: 0.0023 mm Hg (source: User-Entered)
WS: 1.8E+003 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.53 (user entered)
Log Kaw used: -6.218 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 8.748
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7288
Biowin2 (Non-Linear Model) : 0.6808
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.3573 (days-weeks)
Biowin4 (Primary Survey Model) : 4.0712 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.6222
Biowin6 (MITI Non-Linear Model): 0.7049
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.2177
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): 0.307 Pa (0.0023 mm Hg)
Log Koa (Koawin est): 8.748
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 9.78E-006
Octanol/air (Koa) model: 0.000137
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000353
Mackay model : 0.000782
Octanol/air (Koa) model: 0.0109

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 44.3200 E-12 cm3/molecule-sec
Half-Life = 0.241 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 2.896 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000568 (Junge-Pankow, Mackay avg)
0.0100 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 10 L/kg (MCI method)
Log Koc: 1.000 (MCI method)
Koc : 25.77 L/kg (Kow method)

Log Koc: 1.411 (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 = 1.336 (BCF = 21.69 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.1186 days (HL = 0.0761 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.197 (BCF = 15.73)
Log BAF Arnot-Gobas method (upper trophic) = 1.197 (BAF = 15.73)
log Kow used: 2.53 (user entered)

Volatilization from Water:
Henry LC: 3.44E-007 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 2438 hours (101.6 days)
Half-Life from Model Lake : 2.671E+004 hours (1113 days)

Removal In Wastewater Treatment:
Total removal: 3.20 percent
Total biodegradation: 0.10 percent
Total sludge adsorption: 3.08 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	**0.983**	**5.79**	**1000**
Water	**36.9**	**208**	**1000**
Soil	**62**	**416**	**1000**
Sediment	**0.0778**	**1.87e+003**	**0**

Persistence Time: 256 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.983	5.79	1000
Water	36.9	208	1000
water	(36.9)		
biota	(0.000626)		
suspended sediment	(0.000554)		
Soil	62	416	1000
Sediment	0.0778	1.87e+003	0

Persistence Time: 256 hr

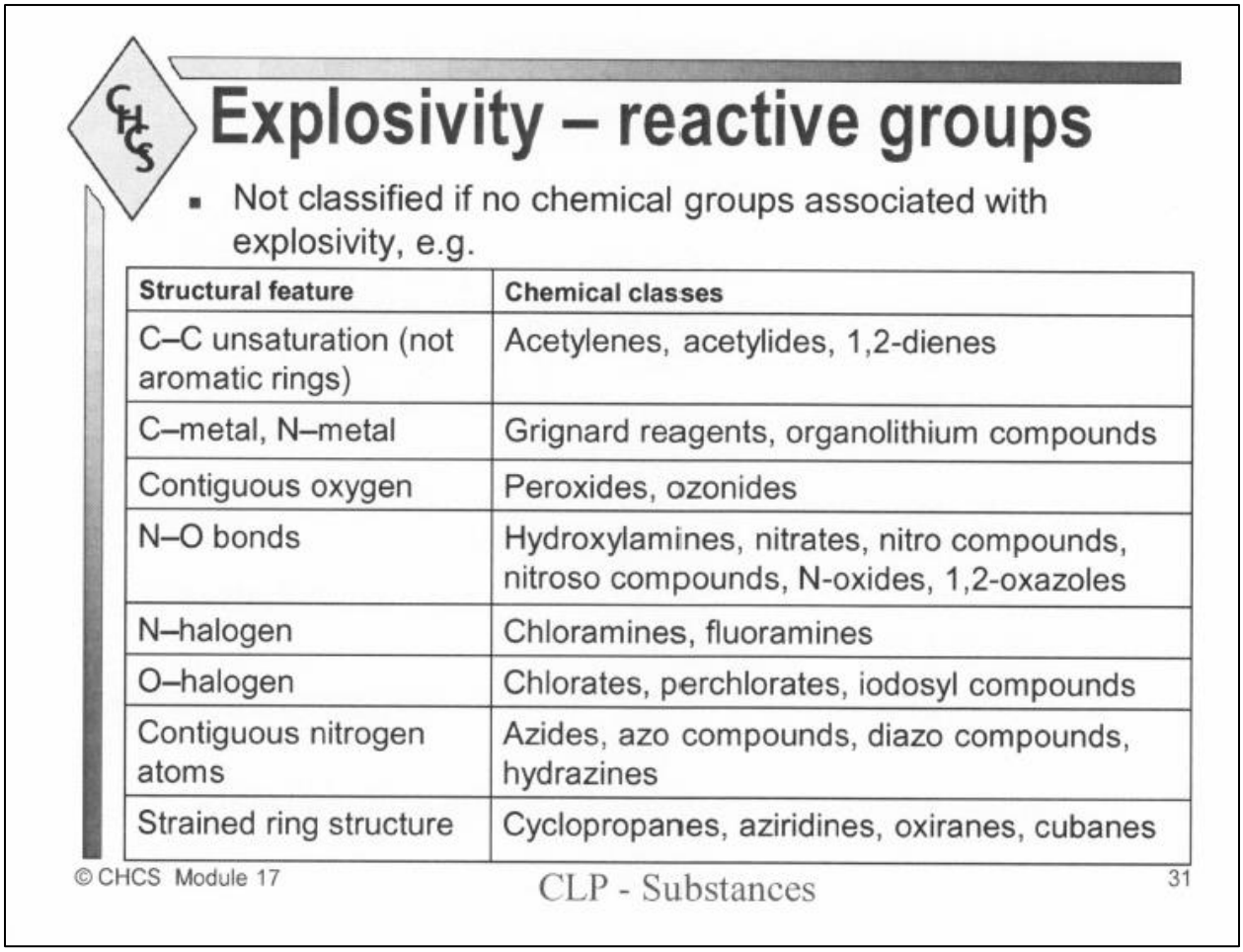
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.858	5.79	1000

Water 28.4 208 1000
water (28.4)
biota (0.000481)
suspended sediment (0.00592)
Soil 70.6 416 1000
Sediment 0.175 1.87e+003 0
Persistence Time: 284 hr

APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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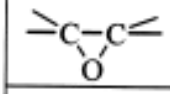
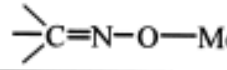
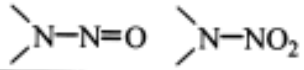
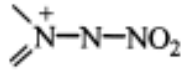
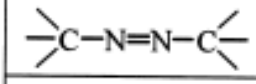
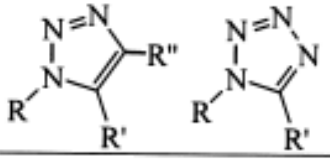
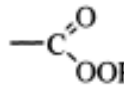
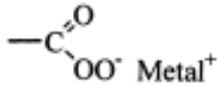
Explosivity – Full List

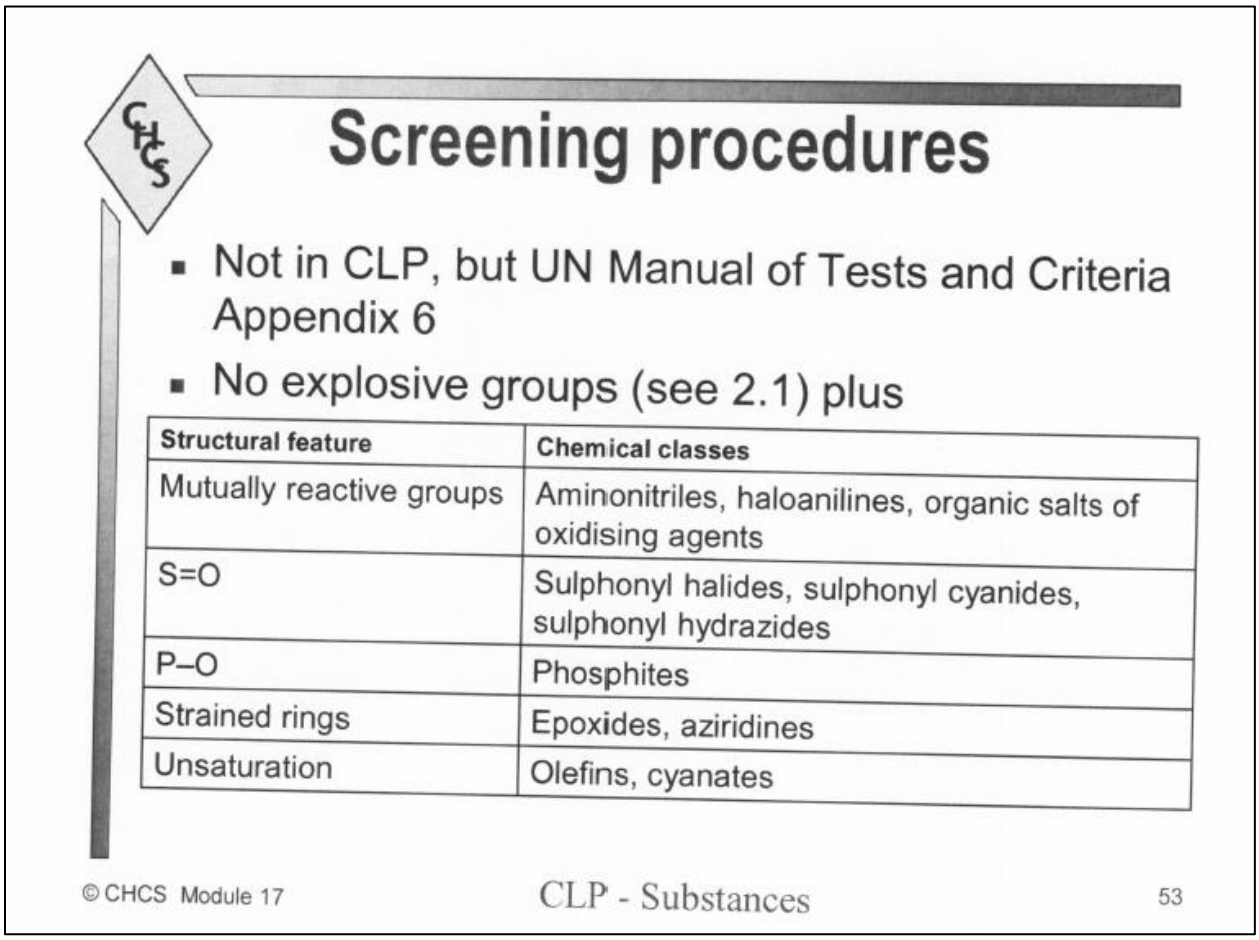
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



APPENDIX L: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for ethylhexylglycerin. The original GreenScreen® assessment was performed in 2016 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.4 update in the current GreenScreen® assessment.

Table 5: Change in GreenScreen® Benchmark™ for Ethylhexylglycerin

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
January 29, 2016	BM-2	v. 1.2	New assessment
March 30, 2023	BM-2	v. 1.4	BM-2 score maintained.

Licensed GreenScreen® Profilers

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