DILAURYL THIODIPROPIONATE

(CAS #123-28-4)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 12, 2021

Expiration Date: November 12, 2026

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GreenScreen® Executive Summary for Dilauryl Thiodipropionate (CAS #123-28-4)

Dilauryl thiodipropionate (DLTDP) (IUPAC name: dodecyl 3-(3-dodecoxy-3-oxopropyl) sulfanyl propanoate) is the diester of lauryl alcohol and 3,3'-thiodipropionic acid, and it is part of the ester and thio compound chemical classes. Its primary use is as an antioxidant in cosmetics and food additives, a sequestering agent in cosmetic formulations, an additive for lubricants and greases, and a plasticizer and softening agent.

The United States Food and Drug Administration (U.S. FDA) recognizes dilauryl thiodipropionate as an acceptable direct food additive under 21 CFR §182.3280, for use in resinous and polymeric coatings under 21 CFR §175.300, in semi-rigid and rigid acrylic and modified acrylic plastics under 21 CFR §177.1010, and as an antioxidant employed in the manufacture of food-packaging materials under prior sanction 21 CFR §181.24.

Dilauryl thiodipropionate is a white crystalline-flake solid. Its estimated partition coefficient of approximately 11 indicate that it is not bioavailable and difficult to measure experimentally. Dilauryl thiodipropionate is insoluble in water and soluble in most organic solvents. Its vapor pressure, estimated to be 4.875 x 10^{-7} mmHg at 20°C, indicates that it is not a volatile organic compound.

Dilauryl thiodipropionate was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement" Due to Data Gaps). Prior to data gap analysis, it was assigned a preliminary Benchmark Score of 4. This score is based on the following hazard score combinations:

- Benchmark 4 (lowered to 3_{DG})
    - Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D)
    - Low Group II Human Toxicity (acute toxicity-AT, single exposure systemic toxicity-STs, single exposure neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE)
    - Low Group II* Human Toxicity (repeated exposure systemic toxicity-STr*, skin sensitization-SnS*, and respiratory sensitization-SnR*)
    - Low Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
    - Low Fate Hazards (persistence-P and bioaccumulation-B)
    - Low Physical Hazards (reactivity-R and flammability-F)

Data gaps (DG) exist for endocrine activity-E and neurotoxicity repeated dose-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), dilauryl thiodipropionate does not meet requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. However, it meets the requirements for a GreenScreen Benchmark™ Score of 3. In a worst-case scenario, if dilauryl thiodipropionate were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

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

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

Type I (input data) uncertainties in dilauryl thiodipropionate NAMs dataset include insufficient or lack of data for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity and bioaccumulation, and lack of validated test methods for respiratory sensitization. Dilauryl thiodipropionate's Type II (extrapolation output) uncertainties include lack of a defined applicability domain of Toxtree structural alerts and ToxCast models, inability of OncoLogic to evaluate the thio moiety of the compound, limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and of *in vitro* high throughput screening assays, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of dilauryl thiodipropionate'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 Dilauryl Thiodipropionate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	**M**	**R**	**D**	**E**	**AT**	**ST**		**N**		**SnS**	**SnR**	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
						s	r*	s	r*	*	*								
L	**L**	*L*	**L**	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	**L**	**L**	*L*	**L**	*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 Dilauryl Thiodipropionate (CAS #123-28-4)

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

Green Screen Assessment (v.1.0) Prepared By:
Name: Kristen Schaefer, M.F.S.
Title: Associate Toxicologist
Organization: ToxServices LLC

Date: September 29, 2011

Quality Control (v.1.0) Performed By:
Name: Margaret Whittaker, PhD., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: October 5, 2011

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Deb Remeikas, M.A.
Title: Research Scientist
Organization: ToxServices LLC
Date: August 16, 2021, November 8, 2021

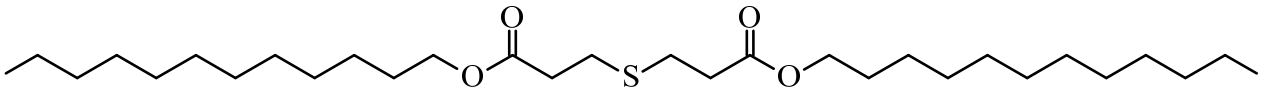
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 17, 2021; November 12, 2021

Expiration Date: November 12, 2026[2]

Chemical Name: Dilauryl thiodipropionate

CAS Number: 123-28-4

Chemical Structure(s):

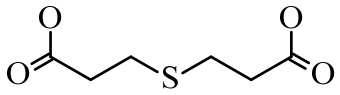


(ChemIDplus 2021a)

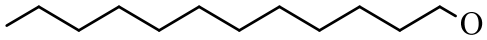
Also called:
3,3'-Thiobispropionic acid, didodecyl ester; Advastab 800; AI3-25277; Antioxidant AS; Antioxidant LTDP; Bis(dodecyloxycarbonylethyl) sulfide; BRN 1808848; Carstab dltdp; CCRIS 3936; Cyanox LTDP; D 1 (antioxidant); Didodecyl 3,3'-thiodipropionate; Dilauryl 3,3'-thiodipropionate; Dilauryl thiodipropionate; Dilauryl thiodipropionic acid; DLT; Dltdp; DLTP; Dmptp; EC 204-614-1; EINECS 204-614-1; HSDB 353; Ipognox 89; Irganox PS 800; Lauryl 3,3'-thiodipropionate; Lusmit; Milban F; Neganox DLTP; NSC 65494; Plastanox LTDP; Plastanox LTDP Antioxidant; Propanoic acid, 3,3'-thiobis-, didodecyl ester; Propionic acid, 3,3'-thiobis-, didodecyl ester; Propionic acid, 3,3'-thiodi-, didodecyl ester; Stabilizer DLT; Thiobis(dodecyl propionate); Thiodipropionic acid, dilauryl ester; Tyox B; UNII-V51YH1B080 (ChemIDplus 2021a).

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

Suitable surrogates or moieties of chemicals used in this assessment (CAS #s):
Limited data were identified for carcinogenicity, reproductive toxicity, and endocrine activity endpoints for dilauryl thiodipropionate. ToxServices used modeled and/or experimental data for the hydrolysis products lauryl alcohol (CAS #112-53-8) and thiodiproprionic acid (CAS #111-17-1) to support the evaluation of carcinogenicity, reproductive toxicity, and/or endocrine activity endpoints. Dilauryl thiodipropionate and thiodiproprionic acid have been evaluated together by the United States Environmental Protection Agency (U.S. EPA) (2011), Cosmetics Ingredient Review (CIR) (2010) Expert Panel, United States Food and Drug Administration (U.S. FDA) (1979), and the Joint WHO/FAO Expert Committee on Food Additives (JECFA) (1974) due to structural and toxicological similarities.



Surrogate: Thiodiproprionic acid (CAS #111-17-1) (ChemIDplus 2021b)



Surrogate: Lauryl alcohol (CAS #112-53-8) (ChemIDplus 2021c)

Identify Applications/Functional Uses: (CIR 2010, HSDB 2012, PubChem 2021)
1. Antioxidant
2. Sequestering agent
3. Additive for lubricants/greases
4. Plasticizer
5. Softening agent

Known Impurities[3]:
Cosmetic-grade dilauryl thiodipropionate may contain up to 0.3% free carboxylic acid as thiodipropionate acid (TDPA), a maximum of 0.1% sulfated ash, 3 ppm arsenic, and 20 ppm lead. The Food Chemical Codex (FCC) identifies a maximum allowed percentage of impurities in dilauryl thiodipropionate to be ≤ 10 ppm lead and ≤ 0.002% of heavy metals such as lead (Pb) (CIR 2010).

The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Dilauryl Thiodipropionate[4,5 6,7]: Dilauryl thiodipropionate was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement" Due to Data Gaps). Prior to data gap analysis, it was assigned a preliminary Benchmark Score of 4 (CPA 2018b). This score is based on the following hazard score combinations:
- Benchmark 4 (lowered to 3_{DG})

[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.

- Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D)
- Low Group II Human Toxicity (acute toxicity-AT, single exposure systemic toxicity-STs, single exposure neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE)
- Low Group II* Human Toxicity (repeated exposure systemic toxicity-STr*, skin sensitization-SnS*, and respiratory sensitization-SnR*)
- Low Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
- Low Fate Hazards (persistence-P and bioaccumulation-B)
- Low Physical Hazards (reactivity-R and flammability-F)

Data gaps (DG) exist for endocrine activity-E and neurotoxicity repeated dose-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), dilauryl thiodipropionate does not meet requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. However, it meets the requirements for a GreenScreen Benchmark™ Score of 3. In a worst-case scenario, if dilauryl thiodipropionate 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 Dilauryl Thiodipropionate

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As dilauryl thiodipropionate is rapidly biodegradable and has low solubility, hydrolysis is not expected to produce transformation products that persist in the environment (ECHA 2021a).

Introduction

Dilauryl thiodipropionate (DLTDP) (IUPAC name: dodecyl 3-(3-dodecoxy-3-oxopropyl) sulfanylpropanoate) is the diester of lauryl alcohol and 3,3'-thiodipropionic acid, and it is part of the ester and thio compound chemical classes. Its primary use is as an antioxidant in cosmetics and food additives (PubChem 2021), a sequestering agent in cosmetic formulations (CIR 1992, 2010), an additive for lubricants and greases, and plasticizer and softening agent (HSDB 2012, CIR 2010). Dilauryl thiodipropionate is manufactured by esterification reaction between thiodipropionitrile and lauryl alcohol using acid catalysts hydrochloric acid and sulfuric acid under vacuum. The reaction is conducted under vacuum to remove water, driving the reaction to completion. Once the reaction is complete, the products are filtered to remove impurities, and molten dilauryl thiodipropionate is

converted to solid products by flaking. The United States Food and Drug Administration (U.S. FDA) recognizes dilauryl thiodipropionate as an acceptable direct food additive under 21 CFR §182.3280, in resinous and polymeric coatings under 21 CFR §175.300, in semi-rigid and rigid acrylic and modified acrylic plastics under 21 CFR §177.1010, and as an antioxidant employed in the manufacture of food-packaging materials under prior sanction 21 CFR §181.24 (U.S. FDA 2021).

ToxServices assessed dilauryl thiodipropionate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). 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).

Dilauryl thiodipropionate is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) 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 dilauryl thiodipropionate can be found in Appendix C.

- Dilauryl thiodipropionate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Dilauryl thiodipropionate is not listed on the U.S. DOT list.
- Dilauryl thiodipropionate is on the following list for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters

Hazard Statement and Occupational Control

Dilauryl thiodipropionate does not have a harmonized EU GHS classification, no GHS H statements are listed in the ECHA Dossier, and largest aggregate of notifiers with a joint entry in the C&L inventory listed it as GHS Not Classified (ECHA 2021a,b). General personal protective equipment (PPE) recommendations are presented in Table 1, below.

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

Table 1: Occupational Exposure Limits and Recommended Personal Protective Equipment for Dilauryl Thiodipropionate (CAS #123-28-4)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Breathing equipment: Not necessary if room is well-ventilated.	Songwon 2020	PEL: 15* and 5** mg/m³ * total dust **respirable fraction	Songwon 2020
Protection of hands: Protective gloves and protective skin cream		REL: 10* and 5** mg/m³ * total dust **respirable fraction	
Eye protection: Safety glasses		TLV: 10 mg/m³ dust	
Body protection: Protective work clothing			
OEL: Occupational Exposure Limit PEL: Permissible Exposure Limit REL: Recommended Exposure Limits TLV: Threshold Limit Value			

Physicochemical Properties of Dilauryl Thiodipropionate

Dilauryl thiodipropionate is a white crystalline-flake solid. Its estimated partition coefficient of approximately 11 indicates that it is not bioavailable and difficult to measure experimentally (U.S. EPA 2013). Dilauryl thiodipropionate is insoluble in water and soluble in most organic solvents (CIR 2010), decreasing the potential for exposure via contaminated water, including drinking water. Its vapor pressure, estimated to be 4.875 x 10^{-7} mmHg at 20°C, indicates that it will exist in both the vapor and particulate phases in the atmosphere; however, it is likely to have minimal volatility and a low potential for inhalation exposure in the vapor phase (U.S. EPA 2013).

Table 2: Physical and Chemical Properties of Dilauryl Thiodipropionate (CAS #123-28-4)		
Property	**Value**	**Reference**
Molecular formula	$C_{30}H_{58}O_4S$	ChemIDplus 2021
SMILES Notation	CCCCCCCCCCCCOC(=O)CCSCCC(=O)OCCCCCCCCCCCC	ChemIDplus 2021
Molecular weight	514.85 g/mol	ChemIDplus 2021
Physical state	Solid	ECHA 2021a, CIR 2010
Appearance	White to off-white flakes	ECHA 2021a
Melting point	38-40°C (exp) 42.1°C (exp) by DSC	ECHA 2021a
Boiling point	Decomposition > 275°C, decomposes before boiling 495°C (exp)	ECHA 2021a U.S. EPA 2017a
Vapor pressure	4.875 x 10^{-7} mmHg (6.5 x 10^{-5} Pa) @ 20°C (est.); 2.1 x 10^{-6} mmHg @ 25°C (est)	ECHA 2021a; U.S. EPA 2021b
Water solubility	< 1 mg/L @ 20°C (similar to EU Method A.6) (exp); Insoluble in water	ECHA 2021a; CIR 2010
Dissociation constant	Not Applicable	ECHA 2021a
Density/specific gravity	1.04 g/cm^3 @ 20°C (exp); 0.975 g/cm^3	ECHA 2021a; CIR 2010
Partition coefficient	Log K_{ow} = 11 @ 25°C (calculated)	ECHA 2021a

Toxicokinetics

- *Absorption:* Data on the toxicokinetic activity of dilauryl thiodipropionate are available for oral and dermal routes of exposure. Inhalation exposure was not studied due to the physical state of the substance as a solid and the vapor pressure estimated to be 4.875 x 10^{-7} mmHg, indicating that absorption via inhalation is unlikely.
    - *Oral:* In a non-GLP-compliant toxicokinetic study conducted in a manner similar to OECD Guideline 417, male Sprague-Dawley rats were fed diets of 166 mg/kg/day carboxyl-[^{14}C] dilauryl thiodipropionate and orally exposed to 107, 166, and 208 mg/kg/day test substance in corn oil via gavage. Dilauryl thiodipropionate was almost entirely absorbed from the gastrointestinal tract at feed levels up to the highest dose (Klimisch 2, reliable with restrictions) (CIR 2010 as cited in ECHA 2021a).
    - *Dermal:* In an acute dermal toxicity study conducted according to OECD Guideline 402, the LD_{50} was > 2,000 mg/kg/day in rats (Klimisch 1, reliable with restrictions) (CIBA-Geigy 1992 as cited in ECHA 2021a). In Mauer optimization test, the test substance did not cause sensitization to guinea pigs (Klimisch 2, reliable with restrictions) (Unnamed Study 1976 as cited in ECHA 2021a). Based on the absence of effects in acute dermal and sensitization studies in rodents, low water solubility (<1 mg/L), high molecular mass > 500, and high log K_{ow} of 11, the REACH dossier authors assume the dermal absorption for dilauryl thiodipropionate to be low (ECHA 2021a).

- *Distribution:* Dilauryl thiodipropionate is rapidly distributed throughout the body as seen in an *in vivo* assay described above with Sprague-Dawley rats which received radio-labelled dilauryl thiodipropionate orally. Radioactivity was detected at near normal levels in all tissues except in adipose tissues where levels were elevated to 12 ppm after a single dose of 166 mg/kg/day; however, this was not considered significant as the dose was considerably higher than the maximum allowable daily intake of either dilauryl thiodipropionate or its metabolite thiodipropionic acid (TDPA) (Reynolds 1974 as cited in CIR 2010 as cited in ECHA 2021a).

- *Metabolism:* Dilauryl thiodipropionate may undergo hydrolysis via esterases to TDPA and lauryl alcohol (CIR 2010, U.S. FDA 1979).

- *Excretion:* Dilauryl thiodipropionate is very rapidly eliminated. Dilauryl thiodipropionate is predominantly excreted via urine (85 - 88%), as well as via feces (1.8 - 3.5%) and lastly as carbon dioxide (3 - 4%). Dilauryl thiodipropionate was excreted in urine as free TDPA or an acid-labile conjugate (CIR 2010, ECHA 2021a).

In summary, dilauryl thiodipropionate is readily and extensively absorbed via oral and dermal exposures. Dilauryl thiodipropionate absorbs through the gastrointestinal tract, distributes throughout the body, and is rapidly hydrolyzed via esterase activity to TDPA and lauryl alcohol. Elimination of dilauryl thiodipropionate occurs rapidly and is predominantly via urine as free TDPA or an acid-labile conjugate.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Dilauryl thiodipropionate was assigned a score of Low for carcinogenicity based on the negative modeling results on dilauryl thiodipropionate by VEGA and Toxtree, supported by negative

experimental/modeled data on its hydrolysis products TDPA and lauryl alcohol. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is low as it is mainly based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Toxtree 2018
  - Dilauryl thiodipropionate does not have structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D).
  - *Surrogate: TDPA (CAS #111-17-1*): TDPA does not have structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D-1).
  - *Surrogate: Lauryl Alcohol (CAS #112-53-8*): Lauryl alcohol does not have structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D-2).
- VEGA 2021
  - ToxServices predicted the carcinogenicity potential of dilauryl thiodipropionate using the following six VEGA v1.2.8 models: CAESAR v2.1.9, ISS v.1.0.2, IRFMN/Antares v1.0.0, IRFMN/ISSCAN-CGX v1.0.0, IRFMN oral classification v1.0.0 models, and IRFMN inhalation classification v1.0.0 models. Dilauryl thiodipropionate was predicted to be non-carcinogenic in all six models, with 5 out of 6 having low reliability. The applicability domain (AD)[9] index was < 0.70 for five models: CAESAR v2.1.9 (AD = 0.643), ISS v.1.0.2 (AD index = 0), IRFMN/Antares v1.0.0 (AD index = 0), IRFMN/ISSCAN-CGX v1.0.0 (AD index = 0.594), and IRFMN oral classification v1.0.0 model (AD index = 0.633); therefore, the results of these models are not suitable for a weight of the evidence evaluation. The AD index was > 0.70 for one model: the IRFMN inhalation classification v1.0.0 model (AD index = 0.903); therefore, the result of this model is suitable for a weight of the evidence evaluation (VEGA 2021, Appendix E).
- U.S. EPA 2021c
  - ToxServices attempted to evaluate dilauryl thiodipropionate using OncoLogic (v9.0) and Oncologic (v.8.0) (U.S. EPA 2021c, 2019). However, OncoLogic 9.0 does not include aliphatic esters as one of the target chemical classes to be evaluated using this version, and OncoLogic 8.0 does not include a decision tree for aliphatic esters. Therefore, ToxServices was unable to evaluate the target chemical using Oncologic.
  - *Surrogate: TDPA (CAS #111-17-1*): ToxServices attempted to evaluate TDPA using OncoLogic (v9.0) and Oncologic (v.8.0) (U.S. EPA 2021c, 2019). However, OncoLogic 9.0 does not include aliphatic carboxylic acid as one of the target chemical classes to be evaluated using this version, whereas OncoLogic 8.0 does include a decision tree for aliphatic carboxylic acids. According to OncoLogic, medium molecular weight aliphatic carboxylic acids (C6 to C20) with terminal double bond or Cl/Br/I, α,β-unsaturation or monosubstitution with Cl/Br/I at α carbon have cancer concern due to genotoxic carcinogenicity. Additionally, the irritation potential of unsubstituted saturated fatty acids such as pentanoic acid may have marginal cancer concern by the dermal route due to its irritancy (Appendix F). As TDPA does not have these structural features and is not a

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

concern for irritation as a metabolite of dilauryl thiodipropionate in the body, TDPA has low cancer concern.
    - *Surrogate: Lauryl Alcohol (CAS #112-53-8)*: ToxServices attempted to evaluate lauryl alcohol using OncoLogic (v9.0) and Oncologic (v.8.0) (U.S. EPA 2021c, 2019). However, OncoLogic 9.0 does not include aliphatic alcohols as one of the target chemical classes to be evaluated using this version, whereas OncoLogic 8.0 does include a decision tree for aliphatic alcohols. According to OncoLogic 8.0, medium molecular weight alcohols (C6 to C20) are of carcinogenic concern because of possible oxidation to reactive metabolically persistent aliphatic carboxylic acids (e.g., perfluorinated fatty acids like perfluorooctanoic or ω – 1 branched fatty acids like 2-ethylhexanoic acid) that are potential nongenotoxic carcinogens, with the most potent ones peaking around 7 – 9 carbons. Lauryl alcohol has no structures of concern, and therefore the carcinogenicity concern is negligible (Appendix G).
- U.S. FDA 1979, 1992, 2021
    - Dilauryl thiodipropionate and metabolite TDPA are generally recognized as safe (GRAS) as food additives for use as antioxidants when the total content of antioxidants is not over 0.02 percent of fat or oil content, including the essential oil content of the food, provided good manufacturing practices are followed. TDPA and dilauryl thiodipropionate are also GRAS in the manufacturing of food packaging materials that result in less than 0.005% added to packaged food.
    - The U.S. FDA recognizes dilauryl thiodipropionate as an acceptable direct food additive under 21 CFR §182.3280, in resinous and polymeric coatings under 21 CFR §175.300, in semi-rigid and rigid acrylic and modified acrylic plastics under 21 CFR §177.1010, and as an antioxidant employed in the manufacture of food-packaging materials under prior sanction (21 CFR §181.24).
- JEFCA 1974
    - About 3 mg/kg/day of dilauryl thiodipropionate was determined to be an acceptable daily intake for man. JEFCA concluded that there was no current evidence that demonstrates or suggests a hazard to the public under the maximum use limits in food or food packaging and following current manufacturing practices.
- CIR 2010
    - Dilauryl thiodipropionate and metabolite TDPA are safe as used when formulated to be nonirritating.
- OECD 2006
    - *Surrogate: Lauryl Alcohol (CAS #112-53-8)*: Several members of the long chain aliphatic alcohol (LCAAs) group were not carcinogenic in studies conducted via various routes (dermal, oral, intraperitoneal) with test samples that were representative of the range of carbon chain lengths within the category of C6-C24. Based on this lauryl alcohol was not classified as carcinogenic (Category 1 or 2) in its ECHA dossier. In addition, these compounds do not contain structural elements of concern for potential interaction with DNA and have been shown to be without mutagenic activity, primarily on the basis of Ames assays and mouse micronucleus assays.
- Based on the weight of evidence, a score of Low was assigned. Dilauryl thiodipropionate does not contain any alerts for genotoxic or nongenotoxic carcinogenicity, but a lack of alerts is not sufficient to assign a Low. Dilauryl thiodipropionate is inside of the applicability domains for one of the VEGA models, and predicted to be a non-carcinogen. U.S. FDA, JEFCA, and CIR evaluated dilauryl thiodipropionate and its surrogate TDPA, identified that it has a long history of safe use in food and food packaging, and determined that it has a low concern for cancer. OncoLogic

predictions on both hydrolysis products indicate low cancer concerns. Based on these results and information, ToxServices concluded that dilauryl thiodipropionate is not likely to be carcinogenic.

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

Dilauryl thiodipropionate was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity in several bacterial mutagenicity assays and in an *in vitro* mammalian cell gene mutation assay, for clastogenicity in an *in vitro* chromosomal aberration assay, and an *in vivo* chromosomal aberration test and dominant lethal assay for the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both gene mutations and chromosomal aberrations (CPA 2018b). Confidence in the score is high because it is based on reliable data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant Ames test conducted according to OECD Guideline 471, EU Method B.13/14, and UKEMS. *Salmonella typhimurium* tester strains TA98, TA100, TA 102, TA1535, TA1537 were exposed to dilauryl thiodipropionate (purity not specified) in acetone at concentrations up to 1,000 µg/plate with and without metabolic activation (cofactor supplemented post-mitochondrial fraction (S9 mix), prepared from the livers of rats treated with Aroclor 1254) in two experiments, I and II. Negative and positive controls (sodium azide, 2-nitrofluorene, 9-aminoacridine, 2-aminoanthramine, and glutaraldehyde) were valid. Precipitation was observed at 1,000 µg/plate in experiment I, and at 500 µg/plate and above in experiment II. No cytotoxicity was observed in Experiment I, and cytotoxicity was observed in Experiment II which was presumed to be due to increased exposure due to pre-incubation (Klimisch 2, reliable with restrictions) (CCRIS 1992 as cited in ECHA Dossier).
  - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant Ames test conducted in a manner similar to OECD Guideline 471. *S. typhimurium* tester strains TA98, TA100, and TA1537 were exposed to dilauryl thiodipropionate (purity not specified) in acetone at concentrations at up to 5,000 µg/plate with and without metabolic activation (cofactor supplemented post-mitochondrial fraction (S9 mix), prepared from the livers of rats treated with Aroclor 1254). Negative and positive controls (daunorubicin-HCl, 4-nitroquinoline-N-oxide, 9(5)- aminoacridine hydrochloride monohydrate, and 2-aminoanthramine) were valid. Information on precipitation and cytotoxicity was not provided; however, the test substance was tested up to maximum concentration required by guideline (Klimisch 2, reliable with restrictions) (CIBA 894103, 1989 as cited in ECHA Dossier).
  - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant bacterial reverse mutation test conducted in a manner similar to OECD Guideline 471. *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* WP_2 *uvr* A were exposed to dilauryl thiodipropionate (purity not specified) in acetone at concentrations at up to 10,000 µg/plate with and without metabolic activation (cofactor supplemented post-mitochondrial fraction (S9 mix), prepared from the livers of rats treated with Aroclor 1254). Negative and positive controls (sodium azide, 2-nitrofluorene, 9-aminoacridine, and 2-aminoanthramine) were valid. Precipitation was observed at 6,666.7 µg/plate and above and no toxicity was observed; however, the test substance was tested up

to maximum concentration required by guideline (Klimisch 2, reliable with restrictions) (SRI intern.LSU-69 09 1979 as cited in ECHA Dossier).

- *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476. Mouse lymphoma L5178Y cells were exposed to dilauryl thiodipropionate (96.5% purity) at 31.25, 62.5, 125, and 250 µg/mL, with and without metabolic activation (cofactor supplemented post-mitochondrial fraction (S9 mix), prepared from the livers of rats treated with Aroclor 1254). The vehicle and positive controls (4-nitroquinoline-N-oxide and benzo(a)pyrene) were valid. In the range-finding study, no cytotoxicity was observed at any dose and the survival rate was 102.9% and 114.4% in the absence and presence of S-9, respectively. Precipitation was observed at the top two doses, 125 and 250 µg/mL, both in the absence and presence of S-9 but precipitation was not evident at the end of the 3-hour incubation period. In the screening study, the survival rate was 95.8% and 101.5% in the absence and presence of S-9, respectively. There was no evidence of induced mutant colonies over background (Klimisch 1, reliable without restriction1) (Hazleton 380/202 1993 as cited in ECHA Dossier).
- *In vitro*: Negative results for clastogenicity were obtained in a GLP-compliant chromosome aberration test conducted according to OECD Guideline 473 and EU Method B.10 with Chinese hamster ovary (CHO) cells exposed to dilauryl thiodipropionate (96.1% purity) in acetone at concentrations of 29.4, 42, and 60 µg/mL (experiment I) and 60, 92.3, and 142 µg/mL (experiment II) with and without metabolic activation (cofactor supplemented post-mitochondrial fraction (S9 mix), prepared from the livers of rats treated with Aroclor 1254). The vehicle and positive (4-nitroquinoline-N-oxide and cyclophosphamide) controls were valid. Precipitation occurred at 39 µg/mL and above and no cytotoxicity to the CHO cells was observed. No chromosomal changes were evident in this assay (Klimisch 1, reliable without restriction1) (Hazleton 380/203 1993, as cited in ECHA 2021a).
- *In vivo*: Negative results were obtained in a non-GLP-compliant dominant lethal assay conducted in a manner similar to OECD Guideline 478. Ten male rats (5/dose group) were exposed to dilauryl thiodipropionate (purity not specified) at 50, 500 or 5000 mg/kg in saline via gavage in both the acute study and the subacute study (dosed once/day for 5 days). The positive control, triethylene melamine, was administered intraperitoneally at a dose level of 0.3 mg/kg. Following treatment, the males were sequentially mated to 2 females a week for 8 weeks (7 weeks in the subacute study). Two virgin female rats were housed with a male for 5 days (Monday through Friday). These two females were removed and housed in a cage until sacrificed. The males were left alone for two days and two new females were housed with a male for the next 5 days (Monday through Friday). Females were killed using carbon dioxide at 14 days after separation from the male and at necropsy the uterus was examined for early deaths, late fetal deaths, and total implantations. There was no clear pattern of either increases or decreases between the control and test groups in any of the parameters studied. Thus, dilauryl thiodipropionate was considered to be non-genotoxic in rats in the dominant lethal assay when using the dosages employed in this study (Klimisch 2, reliable with restrictions) (USFDA71-268 1973 as cited in ECHA Dossier).
- *In vivo*: Negative results were obtained in GLP-unspecified bone marrow chromosomal aberration study conducted in a manner similar to OECD Guideline 475. In the acute phase, male albino rats (5/group) were sacrificed 6, 24 or 48 hours after dosing by oral gavage with 50, 500 or 5000 mg/kg dilauryl thiodipropionate. In the subacute phase, animals receive five consecutive daily doses at the same levels. Two hours prior to sacrifice, each animal received 4 mg/kg of colcemid intraperitoneally. Animals were sacrificed with carbon dioxide. The epiphysis of one femur was removed and evaluated for chromosomal aberration. Fifty metaphase spreads were scored per animal. Mitotic indices were obtained

by counting at least 500 cells and the ratio of the number of cells in mitosis to the number of cells observed was expressed as the mitotic index. The compound produced no detectable significant aberration of the bone marrow metaphase chromosomes of rats when administered orally at the dosage levels employed in this study following acute or short term exposure (Klimisch 2, reliable with restrictions) (USFDA71-268 1973 as cited in ECHA Dossier).

- *In vivo*: In a hot-mediated assay, groups of 10 ICR random-bred male mice were used in the acute and subacute studies. Dilauryl thiodipropionate was administered orally via gavage at doses of 50, 500 or 5000 mg/kg once (acute studies) or on 5 consecutive days (subacute studies). The positive control group received either 100 mg/kg dimethyl nitrosamine in the case of *S. typhimurium* or 350 mg/kg ethylmethane sulfonate in the case of *Saccharomyces cerevisiae*. All animals received 2 ml of the indicator organism intraperitoneally. Each ml contained 3.0 x 10^8 cells of *Salmonella* (his G-46 and TA-1530) and 5.0 x 10^8 cells of *Saccharomyces* (D-3). Three hours later each animal was sacrificed and 2 ml sterile saline introduced intraperitoneally. As much fluid as possible was then aseptically removed from the peritoneal cavity. The exudates were diluted and plated. All plates were incubated at 37°C, for 18 hours (yeast) or 40 hours (bacteria) to determine mutation frequency. Dilauryl thiodipropionate produced no significant reversion or recombinant increases in *Salmonella* strain TA1530 or yeast. However, in *Salmonella* strain G-46, this compound induced reversion in both the acute and subacute trials. A slight dose response was observed in the acute trials (0.54, 2.11, 4.51, and 5.36 in the control, 50, 500, and 5000 mg/kg groups, respectively) but not in the subacute trials (0.62, 5.62, 6.03 and 6.33 in the control, 50, 500 and 5000 mg/kg group, respectively) (Klimisch 2, reliable with restrictions) (Unnamed Study 1973 as cited in ECHA Dossier). *ToxServices notes that the host-mediated assay* is not a validated assay under OECD.

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

Dilauryl thiodipropionate was assigned a score of Low for reproductive toxicity based on a male and female reproductive NOAEL of 1,000 mg/kg/day, the highest dose tested, in a subchronic 90-day repeat dose oral toxicity in rats for the target compound, supported by screening reproductive/developmental toxicity studies on its hydrolysis products TDPA and lauryl alcohol. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). Confidence in this classification is low as limited evidence of reproductive toxicity was observed with the surrogate TDPA.

- 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 2021a
  - *Oral:* In a subchronic GLP-compliant 90-day repeat dose oral toxicity study conducted according to OECD Guideline 408, male and female Sprague-Dawley rats (10/sex/dose) were given doses of dilauryl thiodipropionate (96.1% purity) at 0, 125, 350, or 1,000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups

after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organs examined histologically included the epididymides, mammary glands, ovaries, prostate, seminal vesicles, testes, and uterus (horn + cervix). There were no unscheduled deaths and no treatment related clinical signs. No microscopic changes were found in reproductive organs examined. *ToxServices identified a reproductive toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on no histopathology finding observed in reproductive organs* (Klimisch 1, reliable without restriction) (Pharmakon 380/573 1993 as cited in ECHA Dossier).

- ECHA 2021c
    - *Oral: Surrogate: TDPA (CAS #111-17-1*): In a one generation GLP-unspecified reproduction/developmental toxicity screening test conducted in a manner similar to OECD Guideline 421, male and female Sprague-Dawley rats (12/sex/dose) were administered the TDPA (99.4% purity) in carboxymethyl cellulose (CMC) daily by gavage at doses of 0, 100, 300 or 1,000 mg/kg/day. Animals were exposed 2 weeks before pairing and continuously thereafter, up to the day 52, or day 3 post-partum. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, copulation rate, organ weights, estrous cycle, sperm measures, reproductive performance, gross pathology, and histopathology. Offspring were evaluated for clinicals signs of toxicity, survival, mean litter size, sex ratio, body weight, and gross examination of organs and tissues. There were no treatment-related effects on any of the reproductive parameters measured. There were no treatment-related effects on number of live and dead pups, sex ratio, body weight, or external macroscopic examination, either. Infertility was observed in 2 pairs and 1 pair in the control and 300 mg/kg/day groups, respectively. In males of the 300 mg/kg/day group, particularly of those with observed infertility, atrophy of the testes and epididymis and lung white mottling/zones were observed. For the 300 mg/kg/day males only, in the testes, seminiferous epithelia vacuolation was found, and multinucleated giant cell formation was found in the this and higher groups. For the epididymis, epididymis lumen cell debris was found in the 1,000 mg/kg group. In addition, testes seminiferous tubule atrophy, epididymis lumen cell debris, and prostate gland dilatation were found in the cases of death in the 1,000 mg/kg group. Testes seminiferous tubule atrophy, seminiferous epithelia vacuolation, and epididymis lumen cell debris were found in 1 male from the 300 mg/kg group that did not induce pregnancy. These findings indicate that test material administration has an effect on fertility. No effect on the females from test material administration was observed. Authors assigned a male reproductive NOAEL of 100 mg/kg/day for males, based on treatment related histopathological findings in the testis noted in males at 300 mg/kg/day and higher, and a female reproductive and developmental NOAEL of 1,000 mg/kg/day, the highest dose tested, for females and based on no adverse effects (Klimisch 2, reliable with restrictions) (Unnamed Study 2004 as cited in ECHA Dossier).
- ECHA 2021d
    - *Oral: Surrogate: Lauryl Alcohol (CAS #112-53-8*): In a GLP-compliant repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to a draft version of OECD Guideline 422, male and female Wistar rats (12/sex/dose) were administered lauryl alcohol (99% purity) in the diet at concentrations of 0, 1,500, 7,500, or 30,000 ppm (reported in the REACH dossier to be approximately 100, 500, or 2,000 mg/kg/day). Doses were selected based on results of a preliminary test, but no additional details were provided. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 41-44 days, while females were treated for a

14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 5 for a total of up to 54 days. Female parameters evaluated included a histopathological evaluation of the ovaries, and male parameters evaluated included testis weight and epididymis weight and histopathology. Offspring were evaluated for the number of pups on days 1, 4, and 5, mortality and weight gain on postnatal days 1-4, mean pup body weight on postnatal day 5, and presence of gross abnormalities (external abnormalities including the head, and abdomen and thoracic cavity) on day 5. There were no statistically significant treatment-related effects on pregnancy rate, gestation length, or numbers of corpora lutea, implantations, resorptions, or pups at birth. While the pregnancy rate was slightly reduced in treated groups (to 83% at the low and mid dose and 75% at the high dose, compared to 92% in controls), this effect was not statistically significant and fell within the range of normal historical controls. There were no effects on offspring viability or gross pathology, or any of the male and female reproductive parameters evaluated. Organ weights and histopathology were not affected by treatment. The study authors identified a NOAEL of 30,000 ppm (approximately 2,000 mg/kg/day) for reproductive and developmental toxicity based on a lack of effects at the highest dose tested (Klimisch 2, reliable with restrictions) (Hansen 1992, as cited in ECHA 2021d).

- Based on the weight of evidence, a conservative score of Low was assigned. No evidence of histopathological effects in reproductive organs were observed in a subchronic repeated dose oral toxicity study on the target chemical; however, this study did not examine reproductive functions of the animals. TDPA is a metabolite of the target chemical and effects on histopathology of male reproductive organs were observed in a reproductive and developmental screening study in rats, with a LOAEL of 300 mg/kg/day, although reproductive function did not appear to have been affected. According to GHS criteria, a Category 2 classification is warranted when there is some evidence from humans or experimental animals of an adverse effect on development in the absence of other toxic effects (UN 2019). However, no effects on the histopathological examination of male reproductive organs were observed in the subchronic study for the parent compound at up to 1,000 mg/kg/day, which is equivalent to 1,000 mg/kg/day x MW (TDPA) / MW (dilauryl thiodipropionate) (as one mol of the parent compound is hydrolyzed to one mol of TDPA) = 1,000 mg/kg/day x 178/515 = 346 mg/kg/day TDPA. This is a dose level leading to an internal level of TDPA higher than the LOAEL of 300 mg/kg/day for reproductive toxicity conducted on TDPA. Therefore, weight of evidence indicates that dilauryl thiodipropionate is unlikely to be a reproductive toxicant.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Dilauryl thiodipropionate was assigned a score of Low for developmental toxicity based on maternal and developmental NOAELs of 1,000 mg/kg/day in rabbits and 1,600 mg/kg/day in rats, mice, and hamsters, the highest dose tested, in four prenatal developmental toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as based on reliable data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *Oral:* In a non-GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, twenty-one female Wistar rats received doses of dilauryl thiodipropionate (purity unspecified) at 16, 74, 350, or 1,600 mg/kg in corn oil orally via

gavage on days 6 through 15 of gestation. On day 20 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects. No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1,600 mg/kg dilauryl thiodipropionate on days 6 through l5 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses. The study authors identified a maternal and developmental NOAEL as 1,600 mg/kg/day, the highest dose tested, based on no effects observed (Klimisch 2, reliable with restrictions) (FDA 1992, Liebert 1992 as cited in ECHA Dossier).

- *Oral:* In a non-GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, twenty female CD-1 mice were administered doses of dilauryl thiodipropionate (purity unspecified) at 16, 74, 350, or 1,600 mg/kg/day in corn oil via gavage on days 6 through 15 of gestation. The mice were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 17 of gestation. On day 17 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects. No adverse effects were found with respect to implantations and maternal and fetal survival after oral administration to mice of up to 1600 mg/kg dilauryl thiodipropionic acid on days 6-15 of gestation. The number of abnormalities seen in the soft or skeletal tissues of the treated fetuses was comparable to that seen in the sham control fetuses. The study authors identified a maternal and developmental NOAEL as 1,600 mg/kg/day, the highest dose tested, based on no effects observed (Klimisch 2, reliable with restrictions) (FDA 1992, Liebert 1992 as cited in ECHA Dossier).
- *Oral:* In a non-GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, twenty pregnant Golden hamsters were administered doses of dilauryl thiodipropionate (purity unspecified) at 16, 74, 350, or 1,600 mg/kg in corn oil via gavage on days 6 through 10 of gestation orally via gavage. On day 14 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects. The numbers of implantations and maternal and fetal survival were not adversely affected. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses. The study authors identified a maternal and developmental NOAEL as 1,600 mg/kg/day, the highest dose tested, based on no effects observed (Klimisch 2, reliable with restrictions) (FDA 1992, Liebert 1992 as cited in ECHA Dossier).
- *Oral:* In a non-GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414, artificially inseminated Dutch rabbits (15-29/group) were administered doses of dilauryl thiodipropionate (purity unspecified) at 2.5, 10, 45, 216, or

1,000 mg/kg in corn oil via gavage on days 6 through 18 of gestation. On day 29, all does were subjected to c-section. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. The body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities by dissection. All fetuses were then cleared in potassium hydroxide, stained with alizarin red S dye, and examined for skeletal defects. Eight to thirteen pregnant dams survived to term in each dose group. There was no clearly discernible effect on nidation or on maternal or fetal survival at doses as high as 1,000 mg/kg. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control. The maternal and fetal NOAEL for this study was determined to be 1,000 mg/kg/day (Klimisch 3, not reliable) (FDA 1992, Liebert 1992 as cited in ECHA Dossier). *ToxServices identified that this study was marked as Klimisch 3 in the ECHA dossier; however, the study was cited as reliable evidence for evaluation of this endpoint by authoritative bodies such as U.S. FDA and CIR (U.S. FDA 2010, CIR 2012). Therefore, this study was included as weight of evidence.*

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2021d
  - Dilauryl thiodipropionate was not evaluated by and did not have ToxCast model information.
  - *Surrogate: TDPA (CAS #111-17-1*): TDPA was active in 1/13 estrogen receptor (ER) assays, 0/9 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/8 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix H).
  - *Surrogate: TDPA (CAS #111-17-1*): TDPA was predicted to be inactive for estrogen receptor agonism, antagonism and binding using the CERAPP Potency Level (Consensus and from literature) models. It was also predicted to be inactive for androgen receptor agonism, antagonism and binding using the COMPARA (Consensus) model in ToxCast (Appendix I).
- VEGA 2021
  - Dilauryl thiodipropionate was predicted to be inactive in the Estrogen Receptor Relative Binding Affinity model (IRFMN) with strong reliability (Global AD Index = 0.907) (see Appendix J).
  - Dilauryl thiodipropionate was predicted to be possibly non-active in the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with strong reliability (Global AD Index = 0.938 (see Appendix J).
  - Dilauryl thiodipropionate was predicted to be non-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with strong reliability (Global AD Index = 0.942) (see Appendix J).
- DTU 2021 (only in domain predictions are summarized below)

  - Dilauryl thiodipropionate, its predicted metabolites from *in vivo* rat metabolism simulator, and predicted metabolites from the rat liver S9 metabolism simulator, contain no structural alerts for estrogen receptor binding (Appendix K).
  - Dilauryl thiodipropionate was predicted to be negative for the model battery for estrogen receptor α-binding with full training sets consisting of negative and in domain results by Case Ultra and SciQSAR models (Appendix K).
  - Dilauryl thiodipropionate was positive and in the applicability domain for the Leadscope model, negative and in the applicability domain for the SciQSAR model for estrogen receptor α-binding with balanced training set (Human *in vitro*) (Appendix K).
  - Dilauryl thiodipropionate was predicted to be negative for estrogen receptor activation (CERAPP data *in vitro*) by the Leadscope model.
  - Dilauryl thiodipropionate was predicted to be negative for androgen receptor activation (CoMPARA data *in vitro*) by the Leadscope model (Appendix K).
  - Dilauryl thiodipropionate was predicted to be negative by the model battery for androgen receptor inhibition (human *in vitro*) consisting of negative and in domain results by Case Ultra, Leadscope and SciQSAR models (Appendix K).
  - Dilauryl thiodipropionate was predicted to be negative for thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*) and QSAR2 (Rat *in vitro*) by Leadscope model (Appendix K).
- Based on the weight of evidence, a score of Data Gap was assigned. Dilauryl thiodipropionate was reported to be inactive in several *in vitro* mechanistic assays for androgen receptor activity (binding, inhibition, and activation), estrogen receptor activation, thyroperoxidase (TPO) inhibition and steroidogenesis. Additional modeling indicated that TDPA was negative for the agonism and antagonism of estrogen and androgen receptors. However, no *in vivo* assays for the three receptors (estrogen, androgen, and thyroid) were identified, and *in silico* predictions along with *in vitro* data are not sufficient to assign a score of Low for this endpoint.

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

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

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

Dilauryl thiodipropionate was assigned a score of Low based on oral values greater than 2,000 mg/kg and dermal values greater and 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when acute oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2018b). Confidence in the score was high because it was based on a well-conducted studies on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 401, male and female Tif:RAIf(SPF), F3-crosses of RII 1/Tif X RII 2/Tif rats (5/sex/group) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in CMPS80 via gavage. Clinical signs and body weights were measured over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. Clinical signs observed were dyspnea on days 1 through 10, ruffled fur on days 1 through 9, curved body position on days 1 through 6, and all animals

recovered within 11 days. No compound related gross organ changes were observed. The study authors identified an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 1, reliable without restriction) (Unnamed Study 1982 as cited in ECHA 2021a).

- *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, rats (1-5/sex/group, sex, and species unspecified) were orally administered single doses of 2,000, 4,000, 8,000, and 16,000 mg/kg dilauryl thiodipropionate (purity unspecified) in oil via gavage. Clinical signs were observed over 14 days post-dose and all animals were then subjected to a necropsy. Mortalities occurred in top doses; at 16,000 mg/kg/day, 5/5 animals died within 3-5 days post treatment and at 8,000 mg/kg/day, 1/5 animals died within 5 days post treatment, and at 4,000 mg/kg/day and below no animals died. Clinical signs observed in animals that died were apathy, loss of appetite, hunched posture, ruffled fur in animals that died. There were no clinical findings in animals that survived. The study authors identified an LD_{50} to be > 8,000 mg/kg, based on >50% mortality observed at top dose (Klimisch 2, reliable with restrictions) (Unnamed Study 1954 as cited in ECHA 2021a).
- *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, male rats (2/sex/group, species unspecified) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in physiological saline via gavage. Clinical signs were observed over 5 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. There were no clinical findings in animals that survived. Necropsies of these animals on day six revealed no gross morphological change in the organs examined. The study authors identified an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 2, reliable with restrictions) (Unnamed Study 1973 as cited in ECHA 2021a).
- *Dermal*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 402 and EU Method B.3, male and female Tif:RAIf(SPF) (5/sex/group) were administered a single dose of 2,000 mg/kg dilauryl thiodipropionate (purity unspecified) in arachis oil via semi occlusive patches to 10% of the body surface (trunk). Washing was performed at the end of the 24-hour exposure period followed by a 14-day observation period. Clinical signs were recorded over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred and all rats gained weight as expected during the study period. Piloerection was seen, being a common symptom in acute dermal tests. The animals recovered within 2 days. The study authors identified a dermal LD_{50} of > 2,000 mg/kg (Klimisch 1, reliable without restriction) (Unnamed Study 1992 as cited in ECHA 2021a).

- U.S. EPA 2021b
  - *Oral*: A group of 12 male rats was dosed with 5,000 mg/kg while groups of 10 male rats were dosed with either 50 or 500 mg/kg dilauryl thiodipropionate (97% pure); all animals were then necropsied on day 6 (species not reported). All animals survived to the scheduled necropsy and appeared normal during the 5-day observation period. No gross morphological changes were observed. ToxServices has assigned an LD_{50} of > 5,000 mg/kg for this study.
- U.S. EPA 2021b, ECHA 2021a
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 19, 10, 20, or 20 mice were dosed orally with 300, 500, 1,000, or 2,000 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively (strain not provided). Animals were observed for 1 week following treatment. There were 4, 0, 0, and 1 death observed at 300, 500, 1,000, and 2,000 mg/kg, respectively. The LD_{50} was

determined to be > 2,000 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1941 as cited in ECHA 2021a).

- *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 5 or 10 rats (species/sex not provided) were dosed orally with 2,000 or 2,500 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively. Animals were observed for 7 days following treatment. No deaths occurred at either dose level. The oral LD_{50} was determined to be > 2,500 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1947 as cited in ECHA 2021a).

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

Dilauryl thiodipropionate was assigned a score of Low for systemic toxicity (single dose) based on no signs of systemic toxicity up to 2,000 mg/kg/day in oral and dermal acute studies in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). Confidence in the score was high because it was based on a well-conducted studies on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 401, male and female Tif:RAIf(SPF), F3-crosses of RII 1/Tif X RII 2/Tif rats (5/sex/group) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in CMPS80 via gavage. Clinical signs and body weights were measured over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. Clinical signs observed were dyspnea on days 1 through 10, ruffled fur on days 1 through 9, curved body position on days 1 through 6, and all animals recovered within 11 days. No compound related gross organ changes were observed. The study authors identified an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 1, reliable without restriction) (Unnamed Study 1982 as cited in ECHA 2021a).
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, rats (1-5/sex/group, sex, and species unspecified) were orally administered single doses of 2,000, 4,000, 8,000, and 16,000 mg/kg dilauryl thiodipropionate (purity unspecified) in oil via gavage. Clinical signs were observed over 14 days post-dose and all animals were then subjected to a necropsy. Mortalities occurred in top doses; at 16,000 mg/kg/day, 5/5 animals died within 3-5 days post treatment and at 8,000 mg/kg/day, 1/5 animals died within 5 days post treatment, and at 4,000 mg/kg/day and below no animals died. Clinical signs observed in animals that died were apathy, loss of appetite, hunched posture, ruffled fur in animals that died. There were no clinical findings in animals that survived. The study authors identified an LD_{50} to be > 8,000 mg/kg, based on >50% mortality observed at top dose (Klimisch 2, reliable with restrictions) (Unnamed Study 1954 as cited in ECHA 2021a).
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, male rats (2/sex/group, species unspecified) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in physiological saline via gavage. Clinical signs were observed over 5 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. There were no clinical findings in animals that survived. Necropsies of these animals on day six revealed no gross

morphological change in the organs examined. The study authors an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 2, reliable with restrictions) (Unnamed Study 1973 as cited in ECHA 2021a).
    - *Dermal*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 402 and EU Method B.3, male and female Tif:RAIf(SPF) (5/sex/group) were administered a single dose of 2,000 mg/kg dilauryl thiodipropionate (purity unspecified) in arachis oil via semi occlusive patches to 10% of the body surface (trunk). Washing was performed at the end of the 24-hour exposure period followed by a 14-day observation period. Clinical signs were recorded over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred and all rats gained weight as expected during the study period. Piloerection was seen, being a common symptom in acute dermal tests. The animals recovered within 2 days. The study authors identified a dermal LD_{50} of > 2,000 mg/kg (Klimisch 1, reliable without restriction) (Unnamed Study 1992 as cited in ECHA 2021a).
- U.S. EPA 2021b
    - *Oral*: A group of 12 male rats was dosed with 5,000 mg/kg while groups of 10 male rats were dosed with either 50 or 500 mg/kg dilauryl thiodipropionate (97% pure); all animals were then necropsied on day 6 (species not reported). All animals survived to the scheduled necropsy and appeared normal during the 5 day observation period. No gross morphological changes were observed. ToxServices has assigned an LD_{50} of > 5,000 mg/kg for this study.
- U.S. EPA 2021b, ECHA 2021a
    - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 19, 10, 20, or 20 mice were dosed orally with 300, 500, 1,000, or 2,000 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively (strain not provided). Animals were observed for 1 week following treatment. There were 4, 0, 0, and 1 death observed at 300, 500, 1,000, and 2,000 mg/kg, respectively. The LD_{50} was determined to be > 2,000 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1941 as cited in ECHA 2021a).
    - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 5 or 10 rats (species/sex not provided) were dosed orally with 2,000 or 2,500 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively. Animals were observed for 7 days following treatment. No deaths occurred at either dose level. The oral LD_{50} was determined to be > 2,500 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1947 as cited in ECHA 2021a).

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

Dilauryl thiodipropionate was assigned a score of Low for systemic toxicity (repeated dose) based on male and female oral systemic toxicity NOAELs ≥ 350 mg/kg/day following subchronic and chronic exposures. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when subchronic oral NOAELs are greater than 100 mg/kg/day (CPA 2018b). Confidence in the score was high because it was based on a well-conducted study on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a, U.S. EPA 2021b
    - *Oral:* In a GLP-compliant 90-day repeated dose oral toxicity study conducted according to OECD Guideline 408, male and female Sprague Dawley Ico:OFA-SD (lOPS Caw) rats

(10/sex/dose, 5/control group) were given doses of 0, 125, 350, or 1,000 mg/kg/day dilauryl thiodipropionate (96.1% purity) in 1% carboxymethylcellulose (CMC) in water by gavage, using a metal cannula for approximately 13 weeks. Groups of 5 animals/sex were included at the control and high dose level for a 28-day recovery period before sacrifice. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. Rats were fed *ad lib*, but fasted approximately 16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided *ad lib*, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed in control and high dose groups at week 4, in all groups at week 13, and in recovery group at week 17. Parameters included hematology, clinical chemistry. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on selected organs/tissues for all animals. The hearts from all animals was examined after PTAH staining. There were no unscheduled deaths and no treatment related clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to treatment. Urine parameters were unaffected other than being slightly acidic in the high dose animals as compared to the controls. This was reversible after the 4-week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. The treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions. The study authors determined a systemic toxicity NOAEL to be 350 mg/kg/day based on signs of early or ongoing myocarditis at the highest dose of 1,000 mg/kg/day. A NOEL was determined to be 125 mg/kg/day based on non-adverse changes in hematology and biochemistry at 350 mg/kg/day (Klimisch 1, reliable without restriction) (CIBA CB93/48 1993 as cited in ECHA 2021a).

- *Oral*: In a chronic non-GLP-compliant repeated dose oral toxicity study, groups of 10 male albino rats were fed 0, 0.5 or 3.0% dilauryl thiodipropionate (purity unspecified) in the diet for approximately 6 months. The control group consisted of 11 males. Weekly records were kept of average body weights, feed consumption, moralities, general appearance, and gross pathology over a period of 292 days. Subsequently, decision was made to extend exposure period to 2 years. No additional information was provided. Two controls and three males from the 3.0% dose group died during the first 6 months. Approximately 4 months into the study, some animals ingesting similar materials succumbed to Salmonellosis (described by authors as possible 'paratyphoid' infection). At the end of the two years, 9 of 11 controls, 9 of 10 from the 0.5% group and 10 of 10 from the 3.0% group had died. Mortality in the controls occurred during the final months of the experiment; in contrast, mortality in the treated groups occurred from 6 months to a year earlier. Ingestion of dilauryl

thiodipropionate did not seriously affect weight development or general appearance (Klimisch 3, not reliable) (Unnamed Study 1947, Diamante et al. 2011, Liebert 1992, as cited in ECHA 2021a).

- *Oral*: In a subchronic non-GLP-compliant repeated dose oral toxicity study, groups consisting of one mongrel dog were fed a 10:1 mixture of dilauryl thiodipropionate and TDPA (purity unspecified) at 0.1, 1.0 or 3.0% in the diet for 100 days. Material was heated to 190˚C for 30 minutes. This corresponded to approximately 25, 250 or 750 mg/kg/day in the diet. Excess food was given once a day, allowing ample time for maximum voluntary consumption. Daily records of food consumption were maintained, and the weights of the dogs were recorded weekly. Urinalysis and blood counts were repeated after a period of one month and again at the termination of the experiment. At the termination of the study, the dogs were sacrificed and histological sections were made of the kidneys, livers, spleens, and pancreas. The dog receiving 1% in the diet became sick on the eighth day and died on the tenth day of the experiment, apparently from distemper. "No untoward effects" were observed on the survivors and no further information was provided (Klimisch 3, not reliable) (Unnamed Study 1947 as cited in ECHA 2021a).

- ECHA 2021a
  - *Oral*: A follow-up analysis of the above subchronic repeated dose study was performed. In the 90-day repeated dose oral toxicity study, male Sprague Dawley Ico:OFA-SD (lOPS Caw) rats (3/dose) were given doses of 0, 125, 350, or 1000 mg/kg/day dilauryl thiodipropionate (96.1% purity) in 1% carboxymethylcellulose (CMC) in water by gavage, using a metal cannula for approximately 13 weeks. Groups of 5 animals/sex were included at the control and high dose level for a 28-day recovery period before sacrifice. Formalin-fixed liver tissues from 5 males in the control and high dose groups as well as recovery groups were further processed for electromicroscopical investigations. There were no treatment related effects on the organelle distribution in hepatocytes, and the study authors concluded that there was no peroxisome proliferating effects (Klimisch 1, reliable without restriction) (CIBA 1994 as cited in ECHA 2021a).
  - *Oral*: In a GLP-compliant 28-day repeated dose oral toxicity study conducted in a manner similar to OECD Guideline 407, male and female Sprague Dawley rats (5/sex/dose) were given doses of 0, 125, 250, 500 or 1,000 mg/kg/day dilauryl thiodipropionate (96.1% purity) in 1% carboxymethylcellulose (CMC) in water by gavage for 4 weeks. Cage side observations, clinical observations, body weight measurements, food consumption, hematology, clinical chemistry, gross pathology, histopathology, and organ weights were measured at autopsy. No effects were observed in clinicals signs, body weights, food consumption, hematology, clinical chemistry, or gross pathological, and there were no mortalities related to test substance. Males in the 1,000 mg/kg/day group, the highest dose, had slightly lower mean absolute and relative kidney weights than controls; however, the toxicological significant was not considered significant. The study authors determined a systemic toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, based on no mortality, abnormalities, or signs of systemic toxicity observed (Klimisch 2, reliable with restrictions) (Unnamed Study 1993 as cited in ECHA 2021a).

- U.S. EPA 2021b
  - Groups of 20 male rats/dose were fed 0.5, 1.0 or 3.0% in the diet for two years. Feed consumption was obtained weekly and body weights were obtained at appropriate intervals. Gross and histopathologic examinations were conducted. No further details provided. Body weights were decreased slightly in rats receiving 1.0 and 3.0% in the diet for the first 6 months of the 2 year study. Body weights were unaffected in rats receiving 0.5% in the diet

over the same time period. Mortality was unaffected during the first 9 months of the study. Mortality was higher in high dose group with 10, 7 and 16 animals ingesting 0.5, 1.0 or 3.0%, respectively, dead at the end of the study. There were no significant differences in average body weights or histopathologic changes in the rats exposed to 3.0% dilauryl thiodipropionate in the diet for up to 2 years.

- Based on the weight of evidence, a score of Low was assigned. Dilauryl thiodipropionate was reported to cause possible heart effects at 1,000 mg/kg/day, the highest dose tested, in 90-day oral repeated-dose toxicity study in rats. From the same study, was the NOAEL was reported at 350 mg/kg/day. These heart effects were not consistently seen across studies. 5 out of 6 studies showed no effects observed with NOAELs between 750-1,000 mg/kg/day, the highest doses tested. GHS Category 2 classification would require significant effects observed in animal studies following repeat oral doses of 10 to 100 mg/kg (UN 2019). Given effects were seen at much higher doses, ToxServices did not classify dilauryl thiodipropionate under GHS.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Dilauryl thiodipropionate was assigned a score of Low for neurotoxicity (single dose) based on lack of clinical signs or gross pathology findings indicative of neurotoxicity at sublethal doses. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and they are not classified under GHS for neurotoxic effects (CPA 2018b). The confidence in the score is low as comprehensive neurotoxicity examinations were not performed in acute toxicity studies identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 401, male and female Tif:RAIf(SPF), F3-crosses of RII 1/Tif X RII 2/Tif rats (5/sex/group) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in CMPS80 via gavage. Clinical signs and body weights were measured over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. Clinical signs observed were dyspnea on days 1 through 10, ruffled fur on days 1 through 9, curved body position on days 1 through 6, and all animals recovered within 11 days. No compound related gross organ changes were observed. The study authors identified an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 1, reliable without restriction) (Unnamed Study 1982 as cited in ECHA 2021a).
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, rats (1-5/sex/group, sex, and species unspecified) were orally administered single doses of 2,000, 4,000, 8,000, and 16,000 mg/kg dilauryl thiodipropionate (purity unspecified) in oil via gavage. Clinical signs were observed over 14 days post-dose and all animals were then subjected to a necropsy. Mortalities occurred in top doses; at 16,000 mg/kg/day, 5/5 animals died within 3-5 days post treatment and at 8,000 mg/kg/day, 1/5 animals died within 5 days post treatment, and at 4,000 mg/kg/day and below no animals died. Clinical signs observed in animals that died were apathy, loss of appetite, hunched posture, ruffled fur in animals that died. There were no clinical findings in animals that survived. The study authors identified an LD_{50} to be > 8,000 mg/kg, based on >50% mortality observed at top dose (Klimisch 2, reliable with restrictions) (Unnamed Study 1954 as cited in ECHA 2021a).

- *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, male rats (2/sex/group, species unspecified) were orally administered a single dose of 5,000 mg/kg dilauryl thiodipropionate (purity unspecified) in physiological saline via gavage. Clinical signs were observed over 5 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred in any dose group. There were no clinical findings in animals that survived. Necropsies of these animals on day six revealed no gross morphological change in the organs examined. The study authors an LD_{50} to be > 5,000 mg/kg, based on no mortality observed (Klimisch 2, reliable with restrictions) (Unnamed Study 1973 as cited in ECHA 2021a).
- *Dermal*: In a non-GLP-compliant acute toxicity study conducted according to OECD Guideline 402 and EU Method B.3, male and female Tif:RAIf(SPF) (5/sex/group) were administered a single dose of 2,000 mg/kg dilauryl thiodipropionate (purity unspecified) in arachis oil via semi occlusive patches to 10% of the body surface (trunk). Washing was performed at the end of the 24-hour exposure period followed by a 14-day observation period. Clinical signs were recorded over 14 days post-dose and all animals were then subjected to a necropsy. No mortalities occurred and all rats gained weight as expected during the study period. Piloerection was seen, being a common symptom in acute dermal tests. The animals recovered within 2 days. The study authors identified a dermal LD_{50} of > 2,000 mg/kg (Klimisch 1, reliable without restriction) (Unnamed Study 1992 as cited in ECHA 2021a).

- U.S. EPA 2021b
  - *Oral*: A group of 12 male rats was dosed with 5,000 mg/kg while groups of 10 male rats were dosed with either 50 or 500 mg/kg dilauryl thiodipropionate (97% pure); all animals were then necropsied on day 6 (species not reported). All animals survived to the scheduled necropsy and appeared normal during the 5 day observation period. No gross morphological changes were observed. ToxServices has assigned an LD_{50} of > 5,000 mg/kg for this study.
- U.S. EPA 2021b, ECHA 2021a
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 19, 10, 20, or 20 mice were dosed orally with 300, 500, 1,000, or 2,000 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively (strain not provided). Animals were observed for 1 week following treatment. There were 4, 0, 0, and 1 death observed at 300, 500, 1,000, and 2,000 mg/kg, respectively. The LD_{50} was determined to be > 2,000 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1941 as cited in ECHA 2021a).
  - *Oral*: In a non-GLP-compliant acute toxicity study conducted in a manner similar to OECD Guideline 401, groups of 5 or 10 rats (species/sex not provided) were dosed orally with 2,000 or 2,500 mg/kg dilauryl thiodipropionate (97% pure) dissolved in olive oil, respectively. Animals were observed for 7 days following treatment. No deaths occurred at either dose level. The oral LD_{50} was determined to be > 2,500 mg/kg (Klimisch 4, not assignable) (Unnamed Study 1947 as cited in ECHA 2021a).

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

Dilauryl thiodipropionate was assigned a score of Data Gap for neurotoxicity (repeated dose) based on lack of adequate data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a, U.S. EPA 2021b

  - In the subchronic oral toxicity studies in rats described in the repeated dose toxicity section, gross pathology and histopathology were performed on brain, sciatic nerve, bone (femur) and articulation; bone (sternum) with bone marrow; bone marrow smears; spinal cord (cervical, thoracic, lumbar), and no adverse effects were noted.
- Based on the weight of evidence, a Data Gap was assigned for this endpoint. Although gross pathological and histopathological examinations on some neuronal tissues and organs did not reveal any adverse effects at dilauryl thiodipropionate doses of up to 1,000 mg/kg/day in rodents, neurobehavioral endpoints were not monitored in the repeated dose toxicity studies. Therefore, there are insufficient data to assign a score of Low, and a Data Gap was assigned.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Dilauryl thiodipropionate was assigned a score of Low for skin sensitization based on negative results for sensitization in a Maurer optimization study. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when they have negative data and 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.
- ECHA 2021a
  - A guinea pig Maurer optimization test conducted in a manner similar to "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959), of the US Association of Food and Drug Officials (AFDO) was performed with male and female Pirbright white guinea pigs (10/sex/dose) induced with intradermal injections of 0.1 mL of test substance in polyethylene glycol and saline (70:30) and 0.1 mL of test substance in 0.1% in polyethylene glycol / saline (70:30) without adjuvant. There were 9 exposures during the induction phase, 3 in the first week, 3 in the second week, and 3 in the third week. On day 33, The challenge dose was 0.1 mL of test substance in 0.1 % in polyethylene glycol / saline (70:30) without adjuvant injected intradermally. When adjuvant was present (second induction), the test substance was mixed with adjuvant in a 1:1 ratio. The dermal reactions were scored 24 hours after the challenge and the animals were re-challenged on day 28. Positive reactions were observed in 1/20 animals in the negative control group and in 2/20 animals receiving 0.1% dilauryl thiodipropionate at 24 hours with no clinical observations reported. All 20 of the animals in the positive control group exhibited positive reactions. No further information was provided. The study authors concluded that dilauryl thiodipropionate is not sensitizing to skin (Klimisch 2, reliable with restriction) (CIBA-Geigy (Siss4733) 1976 as cited in ECHA 2021a).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Dilauryl thiodipropionate was assigned a score of Low for respiratory sensitization based on negative skin sensitization data and a lack of structural alerts for respiratory sensitization. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020a

  - Dilauryl thiodipropionate does not contain any structural alerts for respiratory sensitization (Appendix L)
- DTU 2021
  - Dilauryl thiodipropionate was predicted to be negative and in domain by the model battery consisting negative and in domain predictions by Case Ultra, Leadscope, and SciQSAR models for respiratory sensitization in humans (Appendix M).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As dilauryl thiodipropionate was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by dilauryl thiodipropionate, and as dilauryl thiodipropionate does not contain any structural alerts for respiratory sensitization (OECD 2020a), dilauryl thiodipropionate is not expected to be a respiratory sensitizer.

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

Dilauryl thiodipropionate was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation observed in rabbit studies. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when they have negative data and 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.
- ECHA 2021a
  - A non-GLP-compliant skin irritation study similar to OECD Guideline 404 was performed with New Zealand White rabbits (3/sex) administered a dermal application of 1 mL of 50% dilauryl thiodipropionate (purity not specified) in polyethylene glycol (w/v) to abraded and intact skin under occlusive dressing for 24 hours. An observation period of 7 days followed the exposure period. Results were provided for the intact skin sites. The mean erythema score was 0.09/4 and the edema score was 0.6/4. All effects were fully reversible within 72 hours. The study authors concluded that dilauryl thiodipropionate is not irritating to the skin (Klimisch 2, reliable with restrictions) (CIBA-Geigy (No. 46275SL) 1975 as cited in ECHA 2021a).
    - *The effects observed in this study are not sufficient to classify dilauryl thiodipropionate as a GHS Category 3 skin irritant. The criteria for a GHS Category 3 skin irritant are as follows: mean score of ≥ 1.5 and < 2.3 for erythema/eschar or for edema in at least 2 of 3 tested animals (UN 2019).*
  - In an acute toxicity study previously described in Tif: RAI f (SPF) rats that reported an LD_{50} > 2,000 mg/kg, animals (5/sex) were exposed to the test substance on the skin under occlusion at 2,000 mg/kg for 24 hours, and then observed for 14 days. No skin irritation was observed after the patch removal (Klimisch 1, reliable without restriction).
- U.S. EPA 2021b
  - Dilauryl thiodipropionate was found to not be irritating in 16 male volunteers in an occlusive human patch test.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): L
Dilauryl thiodipropionate was assigned a score of Low for eye irritation/corrosivity based on the minimal ocular irritation effects that were insufficient for classification as a GHS eye irritant that were observed in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when they have negative data and 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:* New Zealand - GHS - 6.4A - Irritating to the eye (GHS Category 2A/2B).
- ECHA 2021a
  - A non-GLP-compliant skin irritation study similar to OECD 405 was performed with New Zealand rabbits (3 without rinsing, 3 with rinsing; sex not specified) administered eye instillations of 0.1 g dilauryl thiodipropionate (purity not specified) for 1 second. Half of the animals had their eyes rinsed with warm water while the other half did not. The animals were observed for 72 hours following installation with reactions scored at 1, 6, 48, and 72 hours. Results were the same between rinsed and non-rinsed eyes. For rinsed eyes, the mean cornea score (1h, 24h, 48h, 72h) was 0/4 (six animals). For rinsed eyes, the mean iris score (1h, 24h, 48h, 72h) was 0/2 (six animals). For rinsed eyes, the mean conjunctiva score (1h) was 0.66/4, fully reversible within 6 hours, and no further discharge was observed at later time points. For rinsed eyes, the mean conjunctiva score (6h, 24h) was 0.33/3, fully reversible within 48 hours, and no redness was observed at later time points. For rinsed eyes, the chemosis score (1h only) was 1.6/4, fully reversible within 6h, and no chemosis was observed at later timepoints. For unrinsed eyes, the mean conjunctiva score (1h) was 1/3, and fully reversible within 24 hours; and the mean conjunctiva score (24h, 48h, 72h) was 0/3. All other effects were reversible within 7 days. The study authors concluded that dilauryl thiodipropionate is not irritating to the eyes (Klimisch 2, reliable with restrictions) (CIBA-Geigy (No. 46775SL) 1975 as cited in ECHA 2021a).
    - *The effects observed in this study are not sufficient to classify dilauryl thiodipropionate as a GHS Category 2 eye irritant. The criteria for a GHS Category 2 eye irritant are as follows: corneal opacity ≥ 1, and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or chemosis ≥ 2 (UN 2019).*
- U.S. EPA 2021b
  - Dilauryl thiodipropionate produced no signs of irritation when one drop of a solution containing 0.8 mg/mL was placed into the right conjunctival sacs of two rabbits.
  - Mild irritation was observed following the instillation of 500 mg neat material in the eyes of rabbits (number of animals not reported).
- NZ EPA 2021
  - New Zealand classified dilauryl thiodipropionate to Classification 6.4A (equivalent to GHS Category 2A/2B) based on irritation observed in the rabbit eyes. No additional details were provided.
    - *As specific scores were not reported in this study, ToxServices discounted this classification.*

<u>Ecotoxicity (Ecotox)</u>

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Dilauryl thiodipropionate was assigned a score of Low for acute aquatic toxicity based on a lack of adverse effects expected at saturation. GreenScreen® criteria classify chemicals as a Low hazard for

acute aquatic toxicity when acute aquatic toxicity values are greater than 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental 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 2021a, U.S. EPA 2021b
  - 96-hour LC_{50} (*Danio rerio*, zebrafish) > 71 mg/L (non-GLP-compliant, OECD 203) (Klimisch 2, reliable with restrictions); alkylphenol-polyglycoether and tetrahydrofuran were used as solvents to increase water solubility of the test compound.
  - 72-hour biomass EC_{50} (*Desmodesmus subspicatus*, green algae) = 33.9 mg/L (non-GLP-compliant, 87/302/EEC) (Klimisch 2, reliable with restrictions); alkylphenol-polyglycoether and N,N-dimethylformamide were used as solvents to increase water solubility of the test compound.
- ECHA 2021a
  - 24-hour mobility EC_{50} (*Daphnia magna*) = 11 mg/L (non-GLP-compliant, OECD 202) (Klimisch 2, reliable with restrictions); alkylphenol-polyglycoether and tetrahydrofuran were used as solvents to increase water solubility of the test compound.
- U.S. EPA 2021b
  - 48-hour mobility EC_{50} (*D. magna*) = 10 mg/L; alkylphenol-polyglycolether and tetrahydrofuran were used as solvents to increase water solubility of the test compound.
- Based on a water solubility of < 1 mg/L at 20°C as determined in a test similar to EU Method A.6 (ECHA 2021a), no adverse effects are expected on aquatic biota at saturation. The effect concentrations above would classify as GHS Category 2; however, they represent the worst case assumption where water solubility is achieved by excessive use of solvents, which is not likely in the environment. Therefore, dilauryl thiodipropionate is classified as Low for this endpoint.

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

Dilauryl thiodipropionate was assigned a score of Low for chronic aquatic toxicity based on a lack of adverse effects expected at saturation. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2018b). The confidence in the score is low as no data are available for fish and crustacea, and modeling includes all trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - 72-hour biomass NOEC (*D. subspicatus*, green algae) = 11 mg/L (non-GLP-compliant, 87/302/EEC) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2017b
  - Dilauryl thiodipropionate belongs to the Esters ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 4.3×10^{-6} mg/L in fish, 1.6×10^{-5} mg/L in daphnia, and 1.5×10^{-4} mg/L in green algae (Appendix N), which are more than 10X below the estimated solubility limit of 2.16×10^{-7} mg/L. Therefore, no effects are expected at saturation in water.
- Based on a water solubility of < 1 mg/L at 20°C as determined in a test similar to EU Method A.6 (ECHA 2021a), no adverse effects are expected on aquatic biota at saturation.

Environmental Fate (Fate)

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

Dilauryl thiodipropionate was assigned a score of Low for persistence based on dilauryl thiodipropionate being readily biodegradable without information on the 10-day window, meeting the GHS rapid degradation criteria (>70% degradation in 28 days). GreenScreen® criteria classify chemicals as a Low hazard for persistence when they meet the rapid degradation criteria under GHS, and they primarily partition to soil, water, or sediment (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - A non-GLP-compliant ready biodegradability test conducted according to OECD 301C was performed with non-specified medium exposed to dilauryl thiodipropionate (purity not specified) at 100 mg/L for 28 days. At the end of the exposure period, the level of biodegradation was 82% based on O_2 consumption and 97% based on test material analysis. Dilauryl thiodipropionate was considered to be readily biodegradable in this test (Klimisch 2, reliable with restrictions). *As the pass level (70%) was not reached within 10 days after reaching 10%, ToxServices concluded that the test substance is readily biodegradable but not meeting the 10-day window. It meets the GHS rapid degradability criteria (reaching > 70% degradation in 28 days).*
  - A non-GLP-compliant ready biodegradability test conducted according to OECD 301B: CO2 Evolution Test (1981) was performed with aerobic, domestic, non-adapted, activated sludge exposed to dilauryl thiodipropionate (purity not specified) at 10.9 and 19.9 mg/L for 28 days. At the end of the exposure period, the biodegradation was determined as: 10.87 mg/L = 25% in 28 days and 19.93 mg/L = 57% in 28 days. The measured CO2 evolution in 28 days was: 10.6 mg (concentration 10.9 mg/L) and 43.9 mg (concentration 19.9 mg/L). Dilauryl thiodipropionate was not considered to be readily biodegradable in this test (Klimisch 2, reliable with restrictions).
- Songwon 2020
  - A non-GLP-compliant ready biodegradability test conducted according to OECD 301D was performed with non-specified medium exposed to dilauryl thiodipropionate (purity not specified) at unknown starting concentrations for 28 days. At the end of the exposure period, the level of biodegradation was 71% and dilauryl thiodipropionate was considered to be readily biodegradable in this test.
- U.S. EPA 2017a
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that dilauryl thiodipropionate is expected to be readily biodegradable. Fugacity modeling (EQC default method) predicts 65.8% will partition to sediment with a half-life of 135 days, 30.4% will partition to soil with a half-life of 30 days, and 3.62% will partition to water with a half-life of 15 days (Appendix O).
- Based on the weight of evidence, a score of Low was assigned. Dilauryl thiodipropionate was claimed to be readily biodegradable in two ready biodegradability tests, but no data were provided on the 10-day window. However, it reached >70% degradation in these studies, and thereby meeting the GHS criteria for "rapid degradability". This corresponds to a score of Low. One additional OECD 301B study reported it to be not rapidly degradable. However, per OECD guidance, when conflicting data are available from multiple biodegradability tests, the positive tests

(i.e., readily biodegradable) of acceptable reliability could be considered valid regardless of the negative studies (OECD 2001).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Dilauryl thiodipropionate was assigned a score of Very Low for bioaccumulation based on an estimated BAF of 1.078. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF or BAF values are < 100 (CPA 2018b). The confidence in the score is low as it is based on modeled/calculated log K_{ow} values and modeled BCFs.

- 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 2017a
  - BCFBAF predicts a BAF of 1.078 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration, based on a calculated log K_{ow} of 11 (Appendix O).
- Songwon 2020
  - The data sheet for dilauryl thiodipropionate stated that for bioaccumulation it is "not worth-mentioning accumulation in organisms" and BCF values range between 7.43-15.2 (QSAR).
  - The data sheet for dilauryl thiodipropionate also stated a log K_{ow} value of 11.79 (QSAR).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Dilauryl thiodipropionate was assigned a score of Low for reactivity based on an SDS stating that it is not explosive and on lack of structural alerts for oxidizing and explosive properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score is low due to lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of dilauryl thiodipropionate. These procedures are listed in the GHS (UN 2019).
  - Based on the structure of its components or moieties, dilauryl thiodipropionate is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix P).
  - Based on the structure of its components or moieties, dilauryl thiodipropionate 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.
- ECHA 2021a
  - Dilauryl thiodipropionate does not contain structural alerts for explosive or oxidizing properties.
  - Based on the chemical structure and experience handling the chemical, dilauryl thiodipropionate is not pyrophoric and is not expected to be flammable in contact with water.
- Songwon 2020

  - The data sheet for dilauryl thiodipropionate stated that the product is not explosive. However, formation of explosive air/dust mixtures are possible. Also, dilauryl thiodipropionate does not have oxidizing properties.
- Based on this data, ToxServices did not classify dilauryl thiodipropionate as a reactive chemical based on GHS criteria (UN 2019).

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

Dilauryl thiodipropionate was assigned a score of Low for flammability based on it not being classified as a flammable solid under GHS criteria (UN 2019). GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is assigned for this endpoint (CPA 2018b). The confidence in the score was high as it is based on 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.
- ECHA 2021a, Songwon 2020
  - In a GLP-compliant flammability test similar to EU Method A.10 (flammability (solids)), dilauryl thiodipropionate could not be ignited. Therefore, it is not flammable.
  - The substance is a solid and has a melting point ≤ 160°C; therefore, auto flammability is not applicable.
- Based on this data, ToxServices did not classify dilauryl thiodipropionate as a flammable chemical based on GHS criteria (UN 2019).

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® comprise *in silico* modeling for carcinogenicity, endocrine activity, and respiratory sensitization, chronic aquatic toxicity and bioaccumulation, and *in vitro* testing for genotoxicity and endocrine activity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020b). 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 2020b):

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

As shown in Table 3, Type I (input data) uncertainties in dilauryl thiodipropionate NAMs dataset include insufficient or lack of data for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity and bioaccumulation, and lack of validated test methods for respiratory sensitization. Dilauryl thiodipropionate Type II (extrapolation output) uncertainties include lack of a defined applicability domain of Toxtree structural alerts and ToxCast models, inability of OncoLogic to evaluate the thio moiety of the compound, limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and of *in vitro* high throughput screening assays, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of dilauryl thiodipropionate type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 3: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** No *in vivo* data on hormone levels are available. **Respiratory sensitization:** No experimental data or human data are available and there are no validated test methods. **Chronic aquatic toxicity:** Measured data are only available for one trophic level **Bioaccumulation:** No experimental data are available and log K_{ow} suggests a very high bioaccumulation potential.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). OncoLogic could only evaluate partial structures of the chemical and could not evaluate the thio moiety (U.S. EPA 2019, 2021c).

[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).

	Genotoxicity: The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e. the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[12] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[13]. **Endocrine activity:** ToxCast models don't define applicability domain; the *in vivo* relevance of EDSP Tox 21 screening assays and the ToxCast and Danish QSAR modeling is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **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
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays; *In silico* modeling: Danish QSAR/ToxCast
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/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/Danish QSAR
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	N	
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Dilauryl Thiodipropionate (CAS #123-28-4)

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**
Yes	Dilauryl thiodipropionate	**123-28-4**	*L*	**L**	*L*	**L**	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	**L**	**L**	*L*	**L**	*vL*	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Dilauryl thiodipropionate	4

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Dilauryl thiodipropionate	3DG

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

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3												
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	3DG

APPENDIX C: Pharos Output for Dilauryl Thiodipropionate (CAS #123-28-4)

123-28-4
Dilauryl thiodipropionate
ALSO CALLED 115628-90-5, 1185856-54-5, 1555920-79-0, 3, didodecyl ester, 3,3'-Thiobis[propionic acid], didodecyl...
View all synonyms (74)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

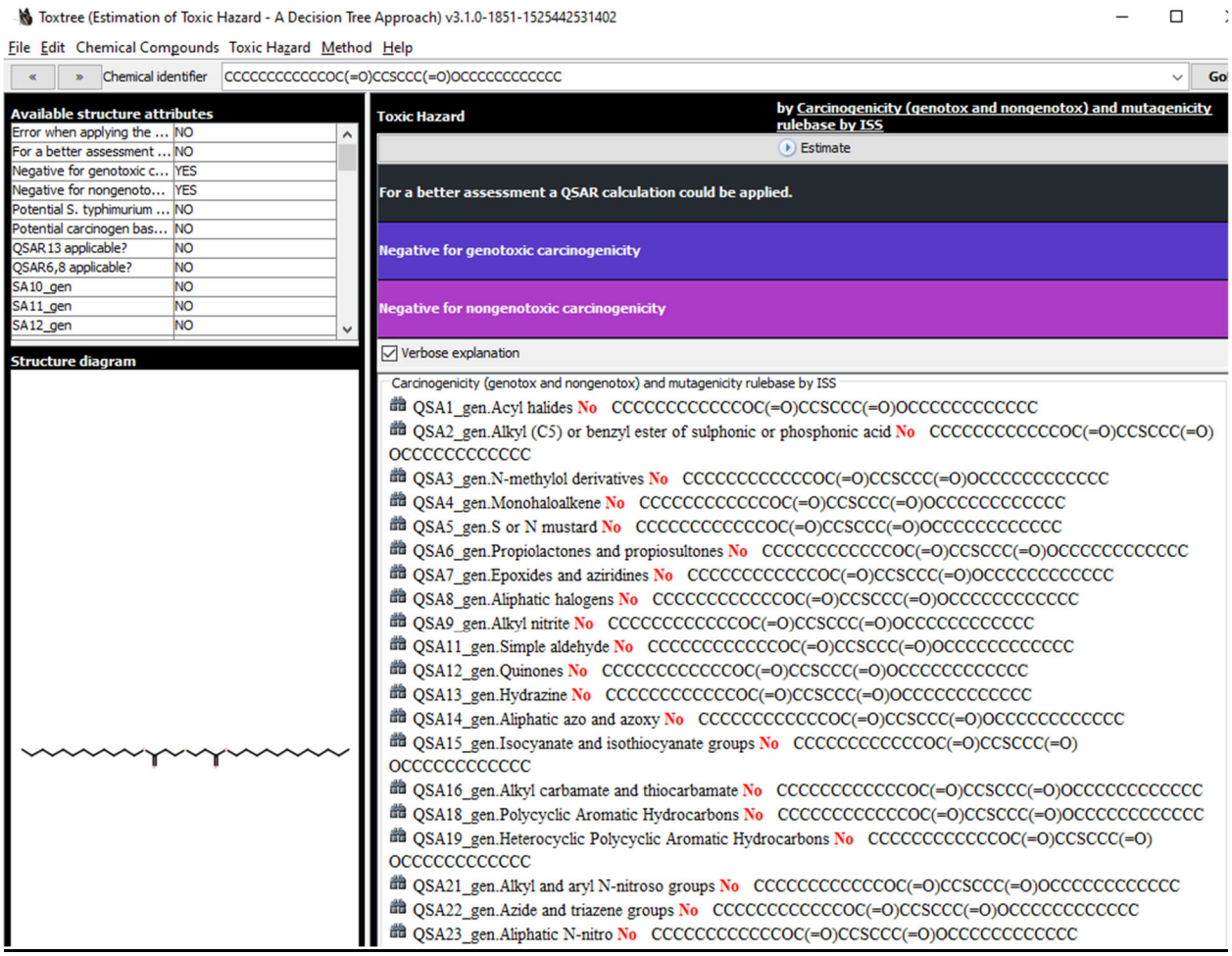
		Group I Human					Group II and II* Human									Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-UNK	-	-	-	-	-	-	-	-	-	-	-	-	-	H	-	-	-	-	-	-	-	pC	-	-	-	R

Hazard Lists

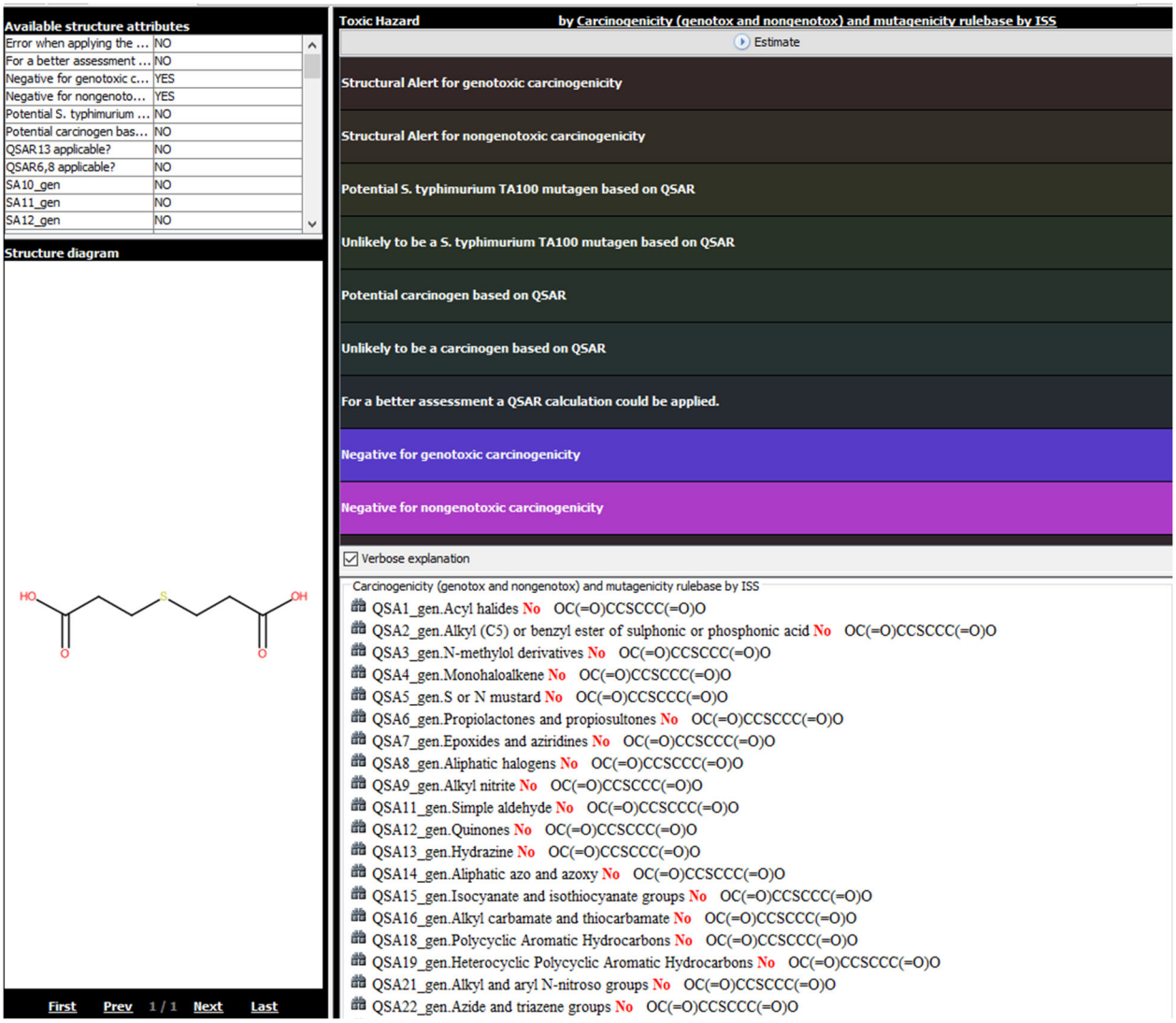
Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	
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	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 1]	+2
	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]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H413 - May cause long lasting harmful effects to aquatic life (unverified) [Hazardous to the aquatic environment (chronic) - Category 4]	

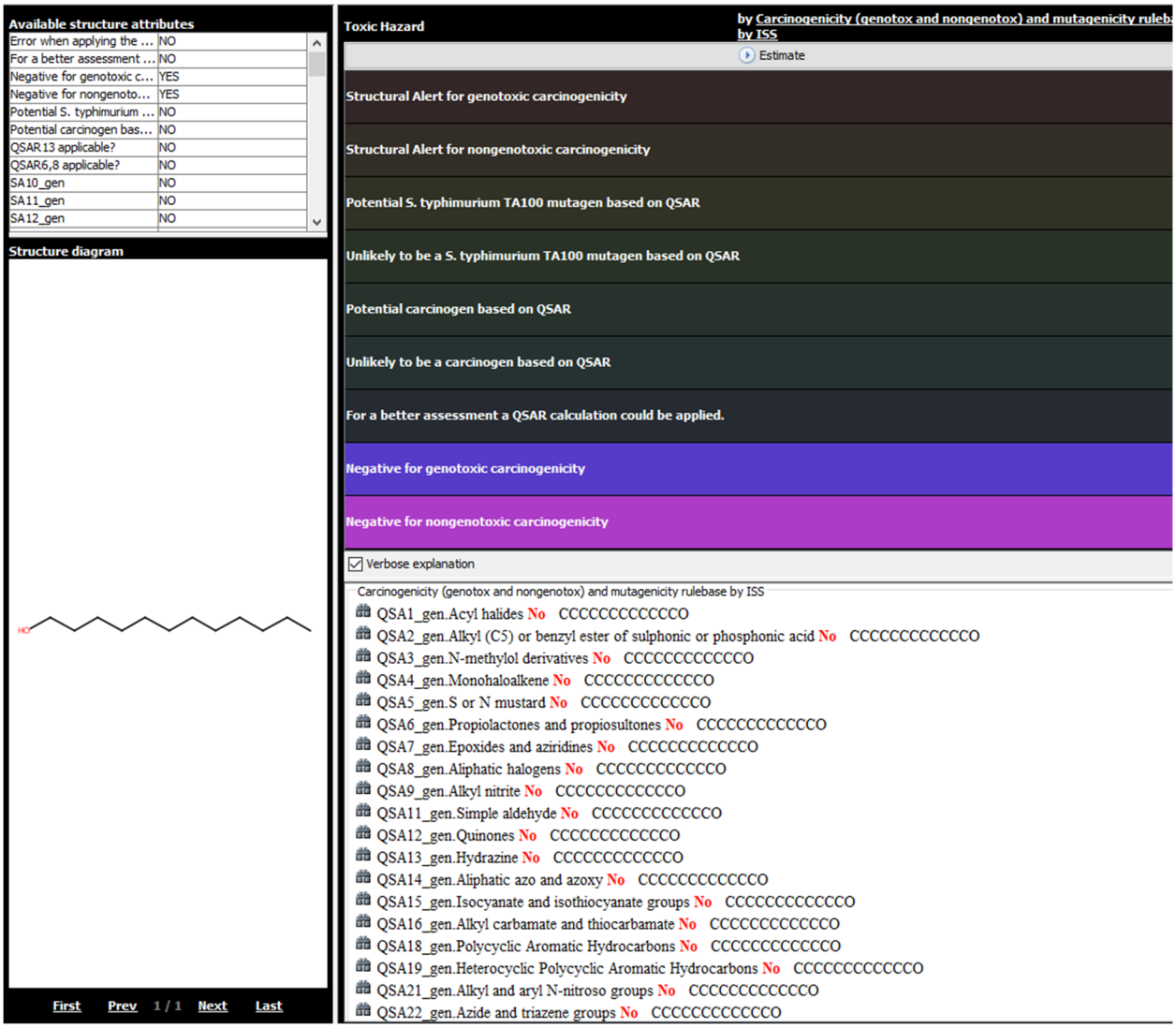
APPENDIX D: Toxtree Carcinogenicity Results for Dilauryl Thiodipropionate (CAS #123-28-4)



APPENDIX D-1: Toxtree Carcinogenicity Results for Surrogate TDPA (CAS #111-17-1)



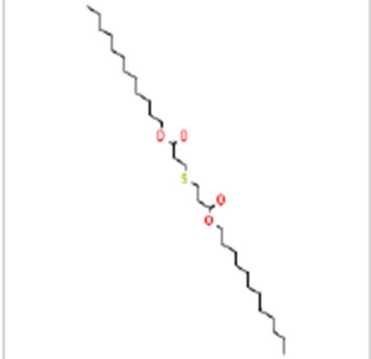
APPENDIX D-2: Toxtree Carcinogenicity Results for Surrogate Lauryl Alcohol (CAS #112-53-8)



APPENDIX E: VEGA Carcinogenicity Results for Dilauryl Thiodipropionate (CAS #123-28-4)

1. Prediction Summary

Prediction for compound Molecule 0

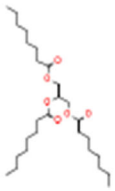


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCC)CCSCCC(=O)OCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.13
P(NON-Carcinogen): 0.87
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

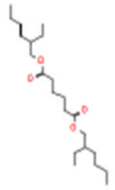
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 538-23-8
Dataset id: 759 (Test set)
SMILES: O=C(OCC(OC(=O)CCCCCCC)COC(=O)CCCCCCC)CCCCCCC
Similarity: 0.846

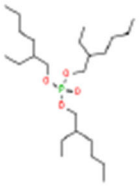
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 103-23-1
Dataset id: 315 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

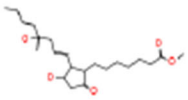
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 78-42-2
Dataset id: 784 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

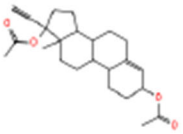
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 59122-46-2
Dataset id: 485 (Training set)
SMILES: O=C(OC)CCCCCCC1C(=O)CC(O)C1(C=CCC(O)(C)CCCC)
Similarity: 0.747

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



Compound #5

CAS: 297-76-7
Dataset id: 321 (Training set)
SMILES: O=C(OC4C=C3CCC2C(CCC1(C)(C2(CCC1(C#C)(OC(=O)C))))C3CC4)C
Similarity: 0.731

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

Compound #6

CAS: 27323-65-5
Dataset id: 450 (Training set)
SMILES: O=C(OC)CCCCCCCC=CC=CC(OO)CCCCC
Similarity: 0.731

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.643 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.837 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✗	**Accuracy of prediction for similar molecules** Accuracy index = 0.494 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✗	**Concordance for similar molecules** Concordance index = 0.494 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.
✓	**Model class assignment reliability** Pos/Non-Pos difference = 0.739 Explanation: model class assignment is well defined.
✓	**Neural map neurons concordance** Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

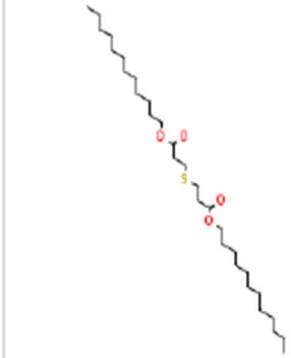
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

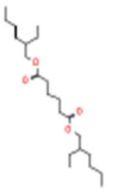


Prediction: Reliability:

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

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

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

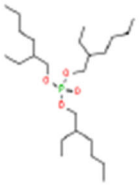


Compound #1

CAS: 103-23-1
Dataset id: 52 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA41 Substituted n-alkylcarboxylic acids; SA42 Phthalate diesters and monoesters

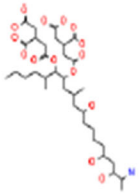


Compound #2

CAS: 78-42-2
Dataset id: 69 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA41 Substituted n-alkylcarboxylic acids

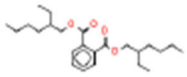


Compound #3

CAS: 116355-83-0
Dataset id: 764 (Training set)
SMILES:
O=C(O)CC(CC(=O)OC(CC(C)CC(O)CCCCC(O)CC(O)C(C)N)C(OC(=O)CC(C(=O)O)CC(=O)O)C(C)CCCC)C(=O)O
Similarity: 0.717

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA41 Substituted n-alkylcarboxylic acids

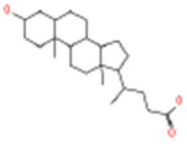


Compound #4

CAS: 117-81-7
Dataset id: 53 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA41 Substituted n-alkylcarboxylic acids; SA42 Phthalate diesters and monoesters

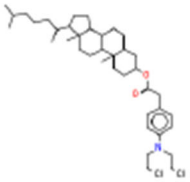


Compound #5

CAS: 434-13-9
Dataset id: 117 (Training set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.705

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

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



Compound #6

CAS: 3546-10-9
Dataset id: 216 (Training set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CCCl)CCCl
Similarity: 0.688

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA5 S or N mustard

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 = 0.789
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

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

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

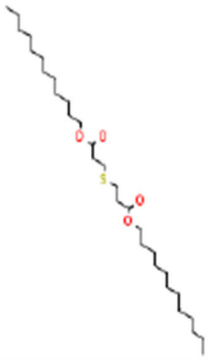
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

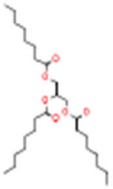


Prediction: Reliability:

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

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

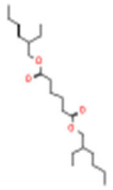
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 769 (Training set)
SMILES: O=C(OCC(OC(=O)CCCCCCC)COC(=O)CCCCCCC)CCCCCCC
Similarity: 0.846

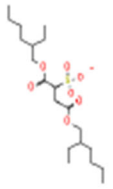
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 315 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

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

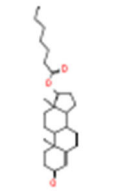


Compound #3

CAS: N.A.
Dataset id: 1222 (Training set)
SMILES: O=C(OCC(CC)CCCC)CC(C(=O)OCC(CC)CCCC)S(=O)(=O)[O-]
Similarity: 0.776

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

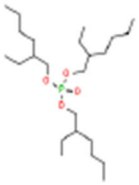
Alerts (not found in the target): Carcinogenity alert no. 107



Compound #4

CAS: N.A.
Dataset id: 939 (Training set)
SMILES: O=C(OC2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CCCCCC
Similarity: 0.76

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

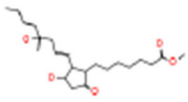


Compound #5

CAS: N.A.
Dataset id: 782 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 98



Compound #6

CAS: N.A.
Dataset id: 484 (Training set)
SMILES: O=C(OC)CCCCCCC1C(=O)CC(O)C1(C=CCC(O)(C)CCCC)
Similarity: 0.747

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.619 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.813 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.34 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
⚠	**Concordance for similar molecules** Concordance index = 0.652 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

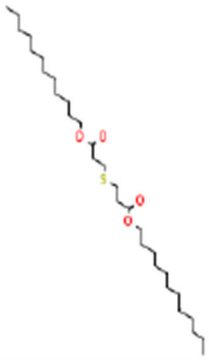
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

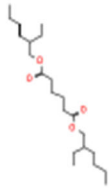


Prediction: Reliability:

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

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

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

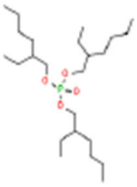


Compound #1

CAS: 103-23-1
Dataset id: 43 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

Experimental value: Carcinogen
Predicted value: Carcinogen

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

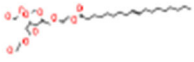


Compound #2

CAS: 78-42-2
Dataset id: 59 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 15

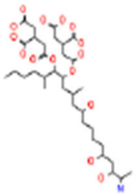


Compound #3

CAS: 9005-65-6
Dataset id: 975 (Training set)
SMILES: O=C(OCCOCC(OCCO)C1OC(OCCO)CC1(OCCO))CCCCCCCCC=CCCCCCCCC
Similarity: 0.73

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 39

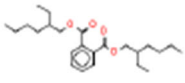


Compound #4

CAS: 116355-83-0
Dataset id: 597 (Training set)
SMILES:
O=C(O)CC(C(=O)O)CC(=O)OC(CC(C)CC(O)CCCCC(O)CC(O)C(N)C)C(OC(=O)CC(C(=O)O
)CC(=O)O)C(C)CCCC
Similarity: 0.717

Experimental value: Carcinogen
Predicted value: Carcinogen

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



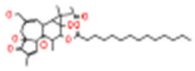
Compound #5

CAS: 117-81-7
Dataset id: 44 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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



Compound #6

CAS: 16561-29-8
Dataset id: 909 (Training set)
SMILES:
O=C(OC34(C(OC(=O)CCCCCCCCCCCCCC)C(C)C2(O)(C(C=C(CO)CC1(O)(C(=O)C(=CC12)C))C3C4(C)(C))))C
Similarity: 0.707

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 29; Carcinogenity alert no. 39

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.594
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.765
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.691
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.309
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

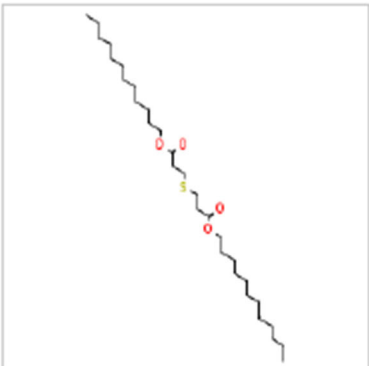
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

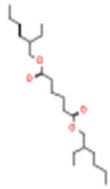


Prediction: Reliability:

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

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

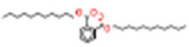
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 103-23-1
Dataset id: 94 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

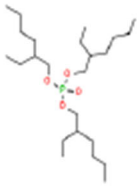
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 3648-20-2
Dataset id: 488 (Training set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.804

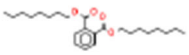
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 78-42-2
Dataset id: 313 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

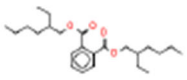
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 117-84-0
Dataset id: 614 (Training set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.751

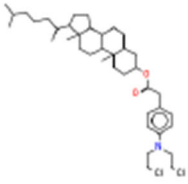
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 117-81-7
Dataset id: 44 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 3546-10-9
Dataset id: 256 (Training set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)(C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CC
Cl)CCCl
Similarity: 0.688

Experimental value: Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.633 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.816 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✗	**Accuracy of prediction for similar molecules** Accuracy index = 0.49 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✗	**Concordance for similar molecules** Concordance index = 0.49 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

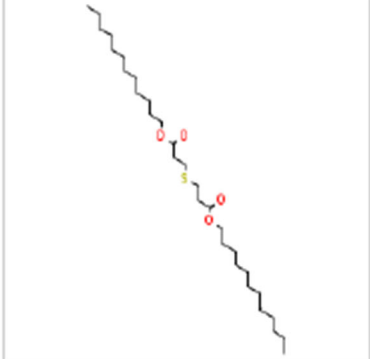
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

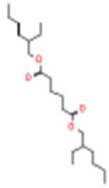


Prediction: Reliability:

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

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

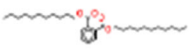
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 103-23-1
Dataset id: 391 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

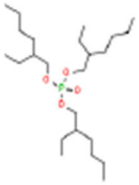
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 3648-20-2
Dataset id: 460 (Test set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.804

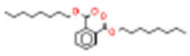
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 78-42-2
Dataset id: 741 (Training set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.758

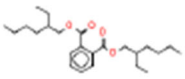
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 117-84-0
Dataset id: 597 (Training set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.751

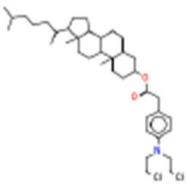
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 117-81-7
Dataset id: 38 (Training set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 3546-10-9
Dataset id: 219 (Training set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CCCl)CCCl
Similarity: 0.688

Experimental value: Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.903
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.816
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

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

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

Symbols explanation:

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

APPENDIX F: OncoLogic Modeling Results for the Surrogate TDPA (CAS #111-17-1)

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : 64197

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Carboxylic Acids*

Aliphatic carboxylic acids (R-COOH) may be loosely divided into (a) high M.W.fatty acids (C > 20), (b) medium size carboxylic acids (C = 6 to 20), and (c) low M.W. carboxylic acids (C < 6). In general, aliphatic carboxylic acids (especially group (a)) have low potential to be significant carcinogens. However, a number of metabolically persistent aliphatic carboxylic acids (e.g., perflourinated fatty acid like perfluoroooctanoic acid; ω – 1 branched fatty acids like 2-ethylhexanoic acid) have been shown to be nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Among low M.W. carboxyxlic acids, those with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens whereas some unsubstituted saturated fatty acids (e.g., pentanoic acid) may be of marginal concern via dermal route due to their irritancy.

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

APPENDIX G: OncoLogic Modeling Results for the Surrogate Lauryl Alcohol (CAS #112-53-8)

SUMMARY :
CODE NUMBER : lauryl alcohol
SUBSTANCE ID :
JUSTIFICATION:

Aliphatic Alcohols*

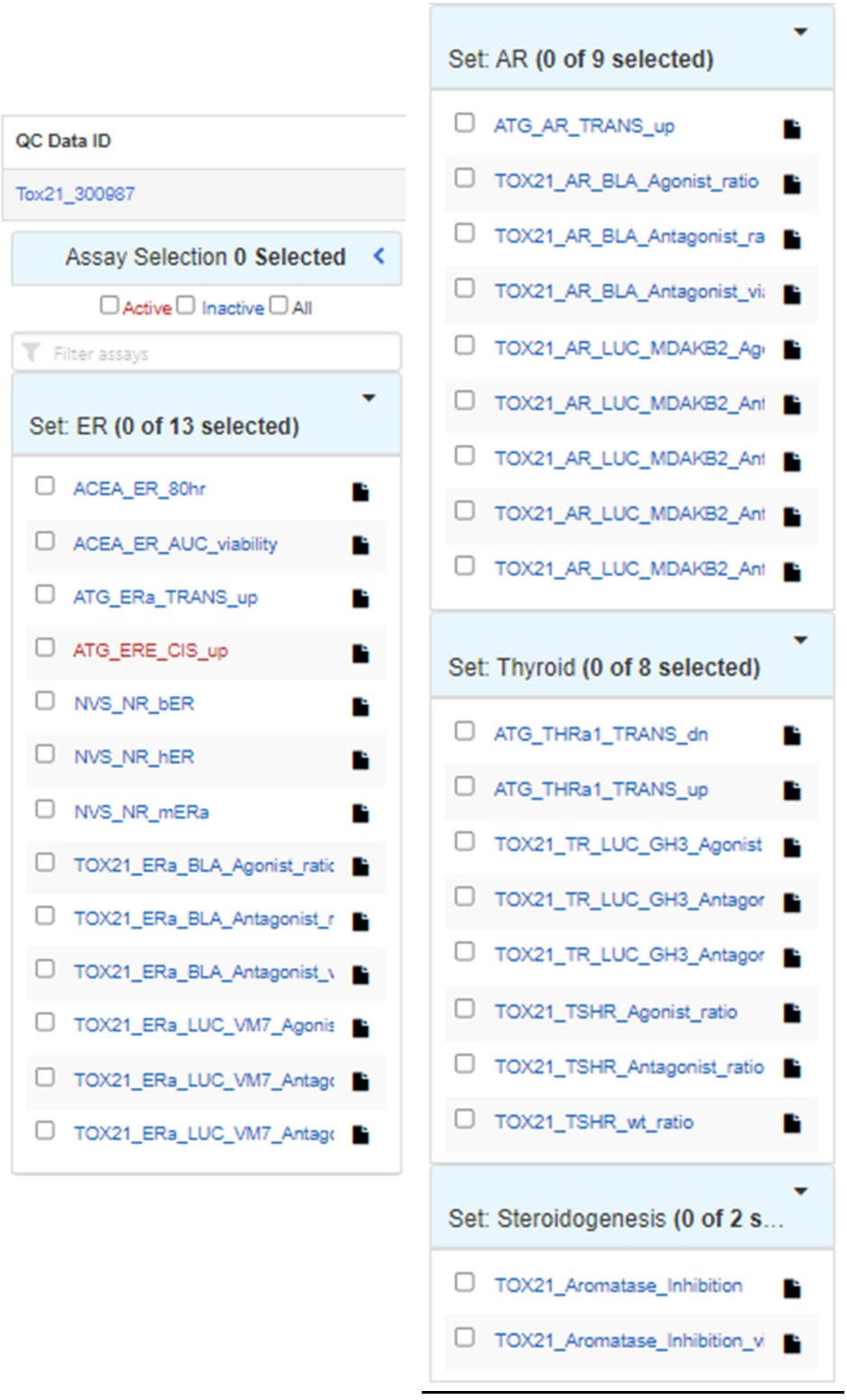
Aliphatic alcohols (R-OH) may be loosely divided into (a) high M.W.alcohols (C > 20), (b) medium size alcohols (C = 6 to 20), and (c) low M.W. alcohols (C < 6). In general, high M.W. aliphatic alcohols have low potential to be significant carcinogens. A number of medium size alcohols (e.g., CF3(CF2)6CH2OH;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

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

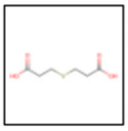
---

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

APPENDIX H: CompTox EDSP21 Results for Surrogate TDPA (CAS #111-17-1)



APPENDIX I: ToxCast Model Predictions for Surrogate TDPA (CAS #111-17-1)



3,3'-Thiodipropionic acid

111-17-1 | DTXSID8044200

Searched by CAS-RN.

ToxCast: Models

ToxCast Model Predictions

Download ToxCast Model Predictions

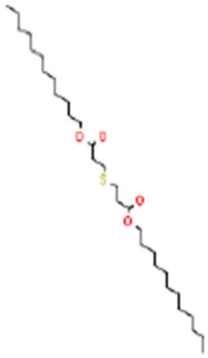
Model	Receptor	Agonist	Antagonist	Binding
ToxCast Pathway Model (AUC)	Androgen	-	-	-
ToxCast Pathway Model (AUC)	Estrogen	-	-	-
COMPARA (Consensus)	Androgen	Inactive	Inactive	Inactive
CERAPP Potency Level (From Literature)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)
CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)

APPENDIX J: VEGA Endocrine Endpoint for Dilauryl Thiodipropionate (CAS #123-28-4)

VEGA Estrogen Receptor Relative Binding Affinity model (IRFMN) page 1

1. Prediction Summary

Prediction for compound Molecule 0

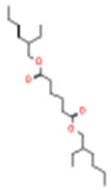


Prediction: Reliability:

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: O=C(OCCCCCCCCCCCC)CCSCCC(=O)OCCCCCCCCCCCC
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 19
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

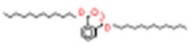
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 103-23-1
Dataset id: 9 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.829

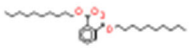
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 2432-90-8
Dataset id: 328 (Training set)
SMILES: O=C(OCCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCCC)
Similarity: 0.816

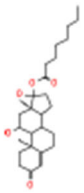
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 84-77-5
Dataset id: 327 (Test set)
SMILES: O=C(OCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCC)
Similarity: 0.789

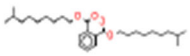
Experimental value: Inactive
Predicted value: Active



Compound #4

CAS: 6678-14-4
Dataset id: 140 (Training set)
SMILES: O=C(OC3(O)(CCC2C4CCC1=CC(=O)CCC1(C)C4(C(O)CC23(C)))CCCCCCC
Similarity: 0.765

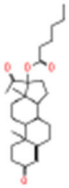
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 26761-40-0
Dataset id: 334 (Test set)
SMILES: O=C(OCCCCCCCC(C)C)c1ccccc1(C(=O)OCCCCCCCC(C)C)
Similarity: 0.765

Experimental value: Active
Predicted value: Active



Compound #6

CAS: 630-56-8
Dataset id: 112 (Training set)
SMILES: O=C(OC3(C(=O)C)(CCC2C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CCCCC
Similarity: 0.762

Experimental value: Inactive
Predicted value: Inactive

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 = 0.822 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:

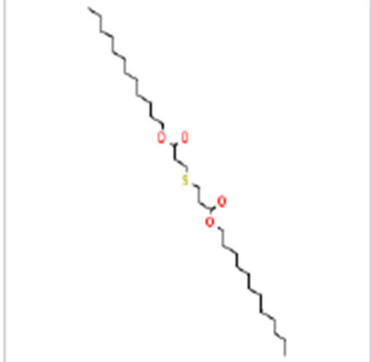
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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 Possible 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 possible non-activity alert no. 1; ER possible non-activity alert no. 5; ER possible non-activity alert no. 9

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCC)CCSCCC(=O)OCCCCCCCCCCCC
Experimental value: -
Predicted ER-mediated effect: Possible NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 0
No. alerts for possible non-activity: 3
Structural alerts: ER possible non-activity alert no. 1; ER possible non-activity alert no. 5; ER possible non-activity alert no. 9
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: 981 (Training set)
SMILES: O=C(OCCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCCC
Similarity: 0.898

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

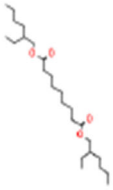
Compound #2

CAS: N.A.
Dataset id: 1204 (Training set)
SMILES: O=C(OCCCCCCCC(C)C)CCCCC(=O)OCCCCCCCC(C)C
Similarity: 0.876

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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



Compound #3

CAS: N.A.
Dataset id: 373 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCC(=O)OCC(CC)CCCC
Similarity: 0.869

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

Compound #4

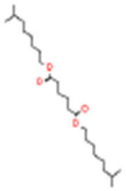
CAS: N.A.
Dataset id: 1306 (Training set)
SMILES: O=C(OCCCCCCC)CCCCC(=O)OCCCCCCCCC
Similarity: 0.864

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

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



Compound #5

CAS: N.A.
Dataset id: 1230 (Training set)
SMILES: O=C(OCCCCCCC(C)C)CCCCC(=O)OCCCCCCC(C)C
Similarity: 0.857

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

Compound #6

CAS: N.A.
Dataset id: 1160 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCCCCCCCCCCCC
Similarity: 0.842

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	**Global AD Index** AD index = 0.938 Explanation: the predicted compound is into the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.88 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 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: 981 (Training set)
SMILES: O=C(OCCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCCC
Similarity: 0.898

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

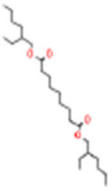
Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

CAS: N.A.
Dataset id: 1204 (Training set)
SMILES: O=C(OCCCCCCCCC(C)C)CCCCC(=O)OCCCCCCCCC(C)C
Similarity: 0.876

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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



CAS: N.A.
Dataset id: 373 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCC(=O)OCC(CC)CCCC
Similarity: 0.869

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

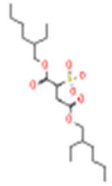
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: ER possible non-activity alert no. 5

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

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

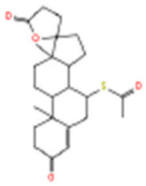


CAS: N.A.
Dataset id: 629 (Training set)
SMILES: O=C(OCC(CC)CCCC)CC(C(=O)OCC(CC)CCCC)S(=O)(=O)O
Similarity: 0.773

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. 5; ER possible non-activity alert no. 9

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

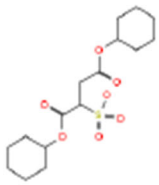


CAS: N.A.
Dataset id: 21 (Training set)
SMILES: O=C1OC3(CC1)(CCC2C5C(CCC23(C))C4(C(=CC(=O)CC4)CC5SC(=O)C)(C))
Similarity: 0.735

Experimental value: NON-active
Predicted value: Possible active

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 5; ER possible non-activity alert no. 9

Alerts (not found in the target): ER possible activity alert no. 4; ER non-activity alert no. 1; ER possible non-activity alert no. 2



CAS: N.A.
Dataset id: 1171 (Training set)
SMILES: O=C(OC1CCCCC1)CC(C(=O)OC2CCCCC2)S(=O)(=O)O
Similarity: 0.734

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. 5; ER possible non-activity alert no. 9

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

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. 9

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

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

CAS: N.A.
Dataset id: 981 (Training set)
SMILES: O=C(OCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCC
Similarity: 0.898

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

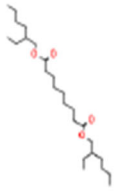
Alerts (not found in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

CAS: N.A.
Dataset id: 1204 (Training set)
SMILES: O=C(OCCCCCCCC(C)C)CCCCC(=O)OCCCCCCCC(C)C
Similarity: 0.876

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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



CAS: N.A.
Dataset id: 373 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCC(=O)OCC(CC)CCCC
Similarity: 0.869

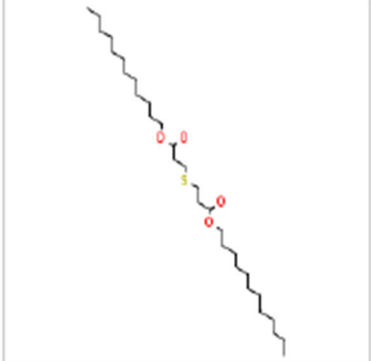
Experimental value: NON-active
Predicted value: NON-active

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

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

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER alert no. 117, inactive

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCC)CCSCCC(=O)OCCCCCCCCCCCC
Experimental value: -
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 1
Structural alerts: ER alert no. 117, inactive
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

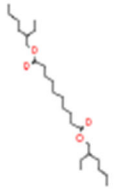
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 2432-87-3
Dataset id: 1465 (Training set)
SMILES: CCCCCCCCOC(=O)CCCCCCCCC(=O)OCCCCCCCC
Similarity: 0.898

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

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

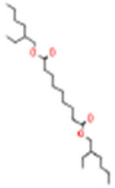


Compound #2

CAS: 122-62-3
Dataset id: 790 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.878

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

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



Compound #3

CAS: 103-24-2
Dataset id: 896 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.869

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

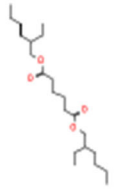
Alerts (not found in the target): ER alert no. 91, inactive

Compound #4

CAS: 22047-49-0
Dataset id: 1393 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCCCCCCCCCCC)CC
Similarity: 0.842

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

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



Compound #5

CAS: 103-23-1
Dataset id: 349 (Training set)
SMILES: CCCCC(COC(=O)CCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.829

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

Alerts (not found in the target): ER alert no. 25, inactive; ER alert no. 49, inactive

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

Compound #6

CAS: 109-43-3
Dataset id: 1296 (Training set)
SMILES: CCCCOC(=O)CCCCCCCCC(=O)OCCCC
Similarity: 0.821

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

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.942
Explanation: the predicted compound is into the Applicability Domain of the model.

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

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

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

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

Symbols explanation:

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

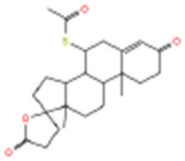
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: ER alert no. 117, inactive

Fragment related to ER inactivity (moderate reliability), defined by the SMARTS: CCSC

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

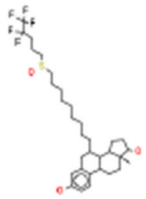


CAS: 52-01-7
Dataset id: 210 (Training set)
SMILES: CC(=O)SC1CC2=CC(=O)CCC2(C)C2CCC3(C)C(CCC43CCC(=O)O4)C21
Similarity: 0.735

Experimental value: NON-active
Predicted value: Active

Alerts (found also in the target): ER alert no. 117, inactive

Alerts (not found in the target): ER alert no. 10, active; ER alert no. 11, active; ER alert no. 118, inactive; ER alert no. 126, active; ER alert no. 130, active; ER alert no. 137, active

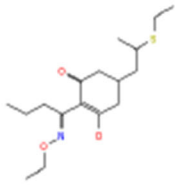


CAS: 129453-61-8
Dataset id: 5 (Training set)
SMILES:
CC12CCC3C(C1CCC2O)C(Cc1cc(O)ccc13)CCCCCCCCCS(=O)CCCC(F)(F)C(F)(F)F
Similarity: 0.681

Experimental value: Active
Predicted value: Active

Alerts (found also in the target): ER alert no. 117, inactive

Alerts (not found in the target): ER alert no. 1, active; ER alert no. 11, active; ER alert no. 114, inactive; ER alert no. 123, active; ER alert no. 137, active; ER alert no. 143, active



CAS: 74051-80-2
Dataset id: 734 (Training set)
SMILES: CC(CC1CC(O)=C(C(=O)C1)C(CCC)=NOCC)SCC
Similarity: 0.659

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

Alerts (found also in the target): ER alert no. 117, inactive

Alerts (not found in the target): ER alert no. 34, inactive; ER alert no. 112, inactive

APPENDIX K: Danish (Q)SAR Endocrine and Molecular Endpoints for Dilauryl Thiodipropionate (CAS #123-28-4)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	INC_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	NEG_OUT	POS_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_OUT	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
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			82353.24	1689.393	82543.07
- µM			159955.8	3281.332	160324.5
- 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			16660.23	12.04483	169.0366
- µM			32359.38	23.39483	328.322
- Positive for IC_{50} ≤ 10 µM					

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- 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	POS_IN	NEG_IN	POS_IN	POS_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	POS_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	POS_OUT	N/A
Pregnane X Receptor (PXR) Activation (Rat *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
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	POS_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

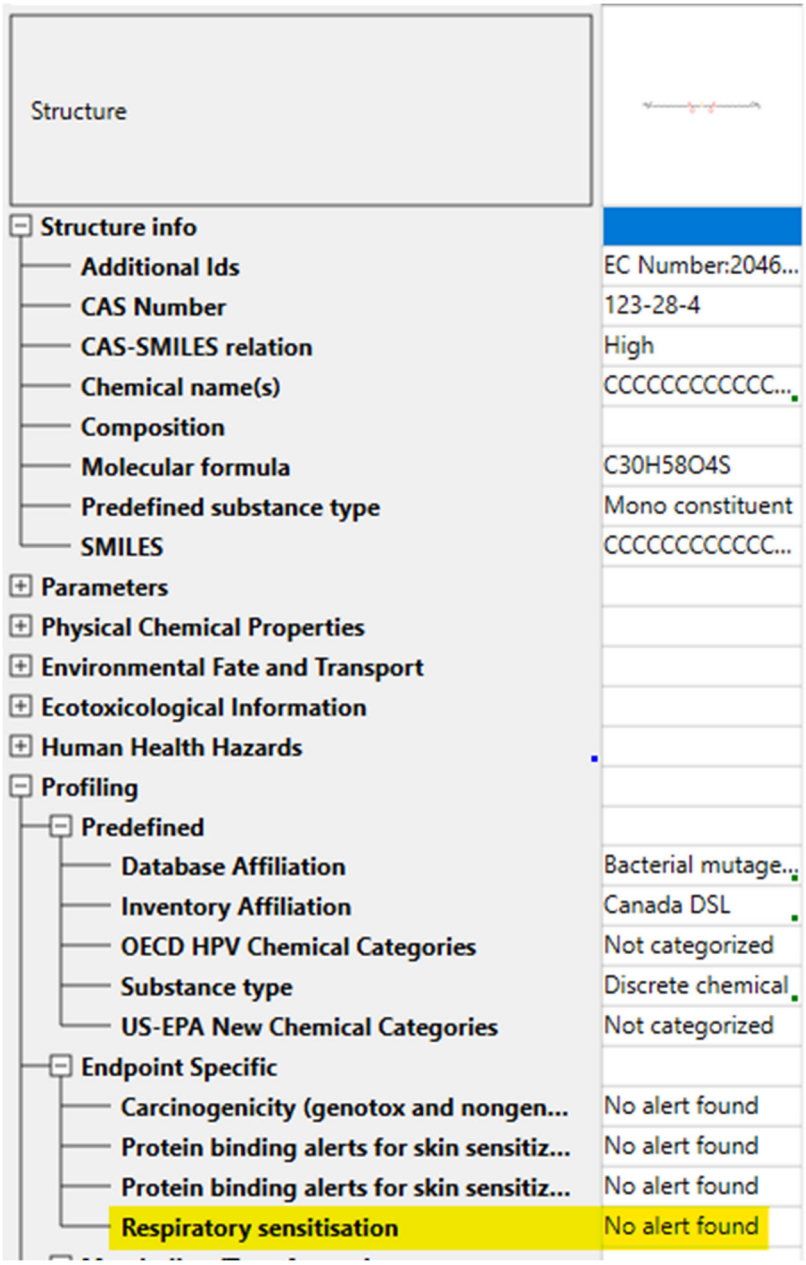
DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, MW>500
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, MW>500; Non binder, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	Non binder, MW>500; Non binder, non cyclic structure
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

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

APPENDIX L: OECD Toolbox Respiratory Sensitization Results for Dilauryl Thiodipropionate (CAS #123-28-4)



APPENDIX M: Danish (Q)SAR Respiratory Sensitization Endpoints for Dilauryl Thiodipropionate (CAS #123-28-4)

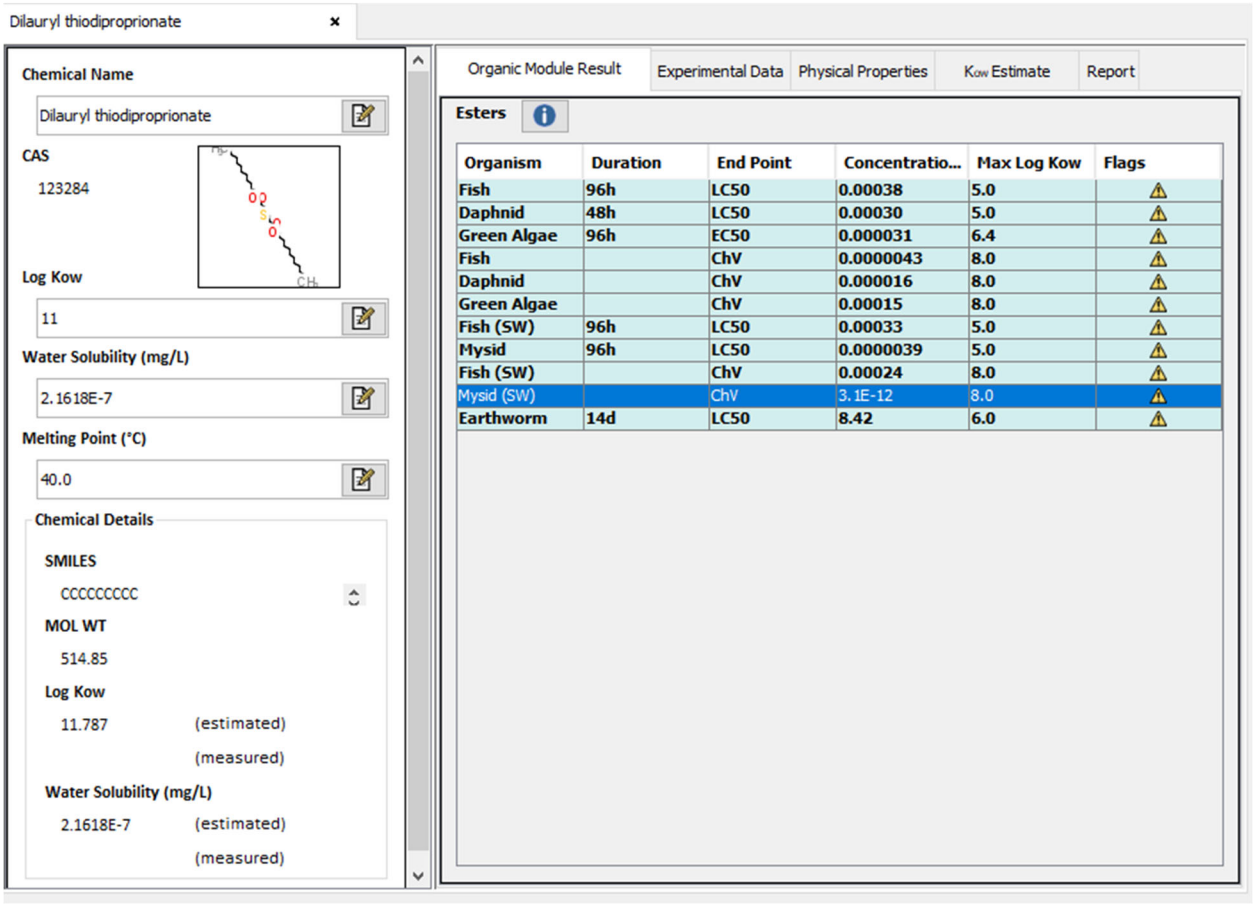
Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Respiratory Sensitisation in Humans		NEG_IN	NEG_IN	NEG_IN	NEG_IN

DTU-developed models

**Based on commercial training set*

APPENDIX N: ECOSAR Modeling Results for Dilauryl Thiodipropionate (CAS #123-28-4)



Organism	Duration	End Point	Concentratio...	Max Log Kow	Flags
Fish	96h	LC50	0.00038	5.0	⚠
Daphnid	48h	LC50	0.00030	5.0	⚠
Green Algae	96h	EC50	0.000031	6.4	⚠
Fish		ChV	0.0000043	8.0	⚠
Daphnid		ChV	0.000016	8.0	⚠
Green Algae		ChV	0.00015	8.0	⚠
Fish (SW)	96h	LC50	0.00033	5.0	⚠
Mysid	96h	LC50	0.0000039	5.0	⚠
Fish (SW)		ChV	0.00024	8.0	⚠
Mysid (SW)		ChV	3.1E-12	8.0	⚠
Earthworm	14d	LC50	8.42	6.0	⚠

APPENDIX O: EPI Suite™ Modeling Results for Dilauryl Thiodipropionate (CAS #123-28-4)

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

CAS Number: 000123-28-4
SMILES : O=C(OCCCCCCCCCCCC)CCSCCC(=O)OCCCCCCCCCCCC
CHEM : Propanoic acid 3,3'-thiobis(didodecyl) ester
MOL FOR: C30 H58 O4 S1
MOL WT : 514.85
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 11.00
Boiling Point (deg C) : 495.00
Melting Point (deg C) : 40.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 11.79

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 519.29 (Adapted Stein & Brown method)
Melting Pt (deg C): 155.21 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.69E-008 (Modified Grain method)
VP (Pa, 25 deg C) : 3.58E-006 (Modified Grain method)
MP (exp database): 40 deg C
BP (exp database): 495 deg C
Subcooled liquid VP: 3.67E-008 mm Hg (25 deg C, Mod-Grain method)
: 4.9E-006 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1.23e-006
log Kow used: 11.00 (user entered)
melt pt used: 40.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 5.1485e-007 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 4.00E-006 atm-m3/mole (4.05E-001 Pa-m3/mole)
Group Method: 5.73E-007 atm-m3/mole (5.81E-002 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: 1.482E-002 atm-m3/mole (1.501E+003 Pa-m3/mole)
VP: 2.69E-008 mm Hg (source: MPBPVP)
WS: 1.23E-006 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 11.00 (user entered)
Log Kaw used: -3.786 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 14.786
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.0677
Biowin2 (Non-Linear Model) : 0.9995
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.9385 (weeks)
Biowin4 (Primary Survey Model) : 4.1010 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.9499
Biowin6 (MITI Non-Linear Model): 0.9234
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 1.0609
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): 4.89E-006 Pa (3.67E-008 mm Hg)
Log Koa (Koawin est): 14.786
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.613
Octanol/air (Koa) model: 150
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.957
Mackay model : 0.98
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 52.0771 E-12 cm3/molecule-sec
Half-Life = 0.205 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 2.465 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.968 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 9.402E+006 L/kg (MCI method)
Log Koc: 6.973 (MCI method)
Koc : 7.557E+006 L/kg (Kow method)
Log Koc: 6.878 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 7.711E-002 L/mol-sec
Kb Half-Life at pH 8: 104.028 days
Kb Half-Life at pH 7: 2.848 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.568 (BCF = 36.94 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.1897 days (HL = 1.548 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.034 (BCF = 0.9237)
Log BAF Arnot-Gobas method (upper trophic) = 0.033 (BAF = 1.078)
log Kow used: 11.00 (user entered)

Volatilization from Water:
Henry LC: 5.73E-007 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 2321 hours (96.7 days)
Half-Life from Model Lake : 2.551E+004 hours (1063 days)

Removal In Wastewater Treatment:
Total removal: 94.04 percent
Total biodegradation: 0.78 percent
Total sludge adsorption: 93.26 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)
**** Note: When the Log Kow is > 7, the model may be underestimating the mass of material in sediment and overestimating the mass of material in the water column (biota). Consider using the results of the default EQC model. ****

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.357	4.93	1000
Water	22.2	360	1000
Soil	76.2	720	1000
Sediment	1.23	3.24e+003	0

Persistence Time: 520 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)

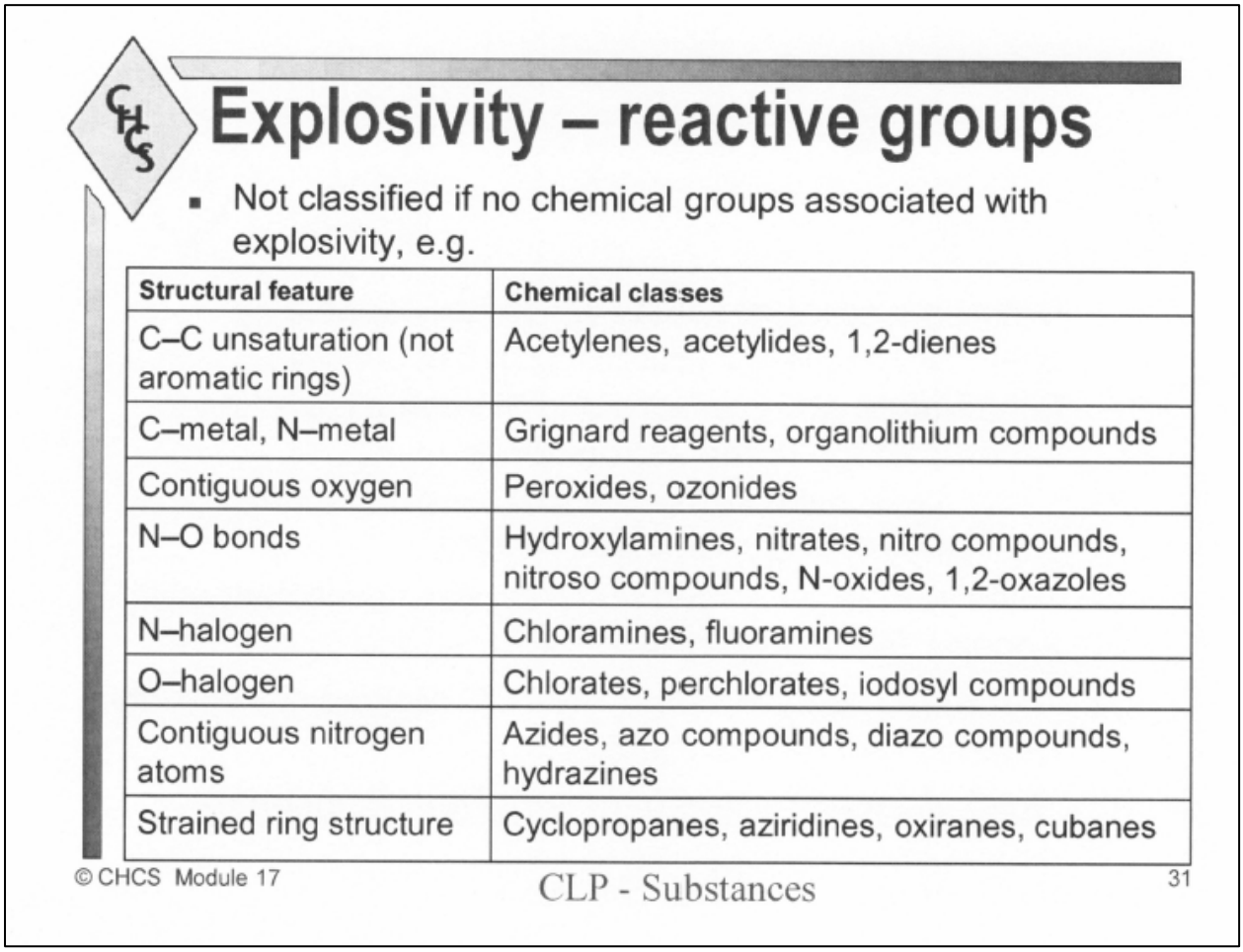
Air	0.357	4.93	1000
Water	22.2	360	1000
water	(0.00442)		
biota	(22.1)		
suspended sediment	(0.0623)		
Soil	76.2	720	1000
Sediment	1.23	3.24e+003	0
Persistence Time: 520 hr			

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	**0.142**	**4.93**	**1000**
Water	**3.62**	**360**	**1000**
water	**(5.44e-005)**		
biota	**(0.272)**		
suspended sediment	**(3.34)**		
Soil	**30.4**	**720**	**1000**
Sediment	**65.8**	**3.24e+003**	**0**
Persistence Time: 1.3e+003 hr			

APPENDIX P: 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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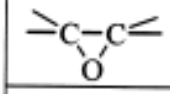
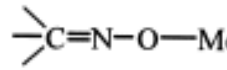
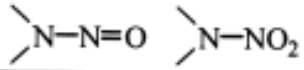
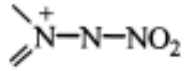
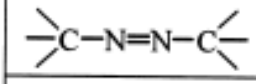
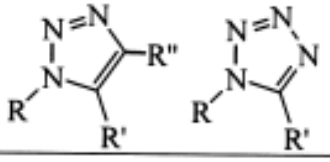
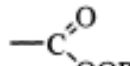
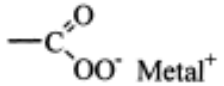
Explosivity – Full List

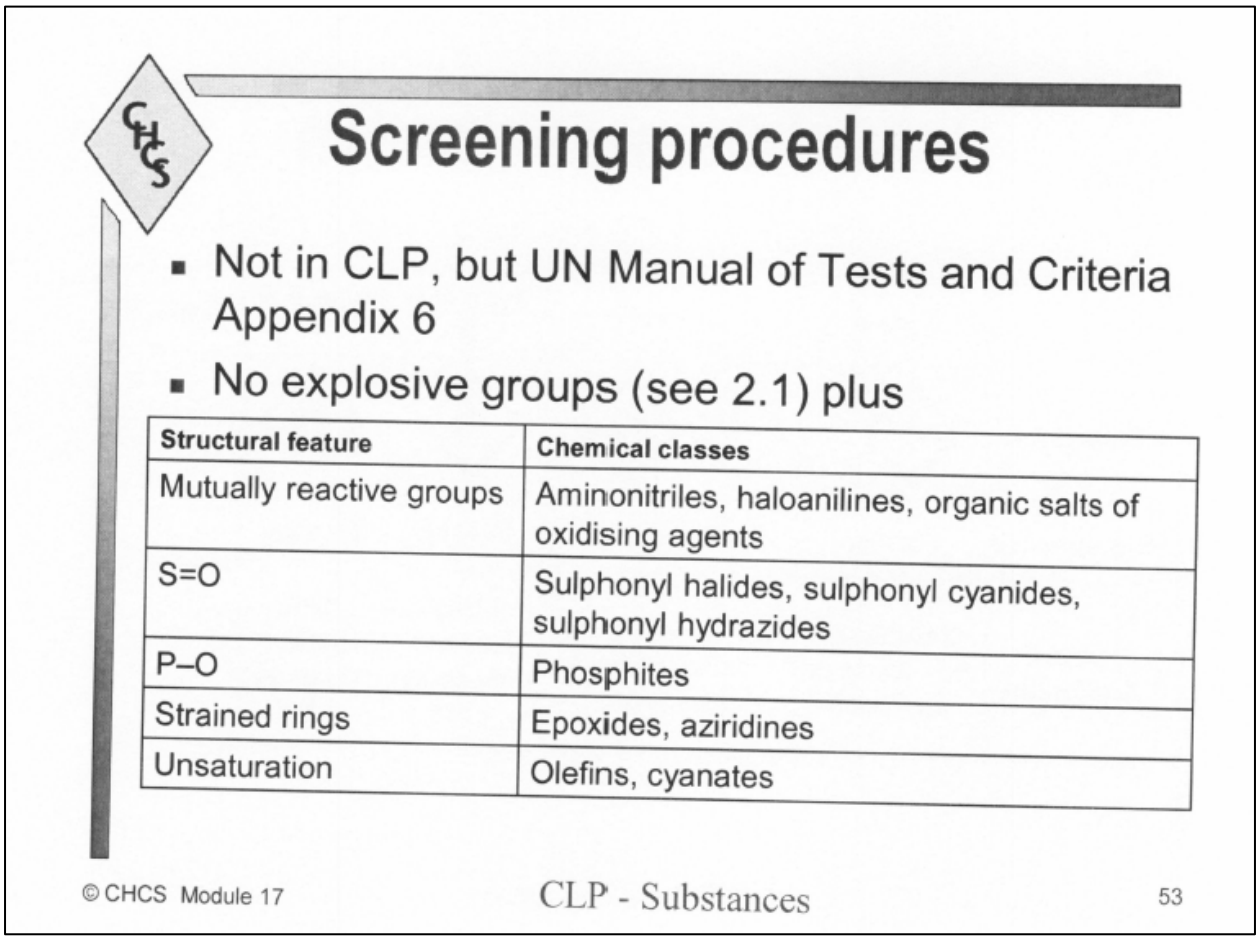
Table R.7.1-28 Chemical groups associated with explosive properties

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



Screening procedures

- Not in CLP, but UN Manual of Tests and Criteria Appendix 6
- No explosive groups (see 2.1) plus

Structural feature	Chemical classes
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising agents
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P–O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

APPENDIX Q: Change in Benchmark Score

Table 4 provides a summary of changes to the GreenScreen® Benchmark™ for dilauryl thiodipropionate. This GreenScreen® has undergone two rounds of update and the benchmark score changed from 3 to 3_{DG}.

Table 4: Change in GreenScreen® Benchmark™ for Dilauryl Thiodipropionate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 5, 2021	BM-3	v. 1.0	New assessment
August 16, 2021	BM-3_{DG}	v. 1.4	Updated assessment to version 1.4 Criteria
November 12, 2021	BM-3_{DG}	v. 1.4	Minor updates without changing any hazard scores

Licensed GreenScreen® Profilers

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