OCTADECYL 3-(3,5-DI-TERT-BUTYL-4-HYDROXYPHENYL)PROPIONATE

(CAS #2082-79-3)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 16, 2021

Expiration Date: November 16, 2026

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GreenScreen® Executive Summary for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is a phenolic antioxidant that is also known as Irganox 1076. It is used as a non-discoloring stabilizer in numerous polymers, including in polyurethane resins complying with 21 CFR § 177.1680 (except for use in contact with infant formula and breast milk) and in polycyclooctene (PCOE) and olefin polymers. It is also used as a stabilizer in plastics, synthetic fibers, elastomers, adhesives, waxes, oils, and fats.

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2a
  - Very High Persistence-P + Moderate Bioaccumulation-B + Moderate Group II* Human Toxicity (systemic toxicity (repeated dose)-STr*)
  - Very High P + Moderate B + Moderate Group I Human Toxicity (developmental toxicity-D)
  - Very High P + Moderate B + Moderate Group II Human Toxicity (neurotoxicity single dose-Ns)
- Benchmark 2c
  - Very High P + Moderate Group II* Human Toxicity (STr*)
  - Very High P + Moderate Group I Human Toxicity (D)
  - Very High P + Moderate Group II Human Toxicity (Ns)
- Benchmark 2e
  - Moderate Group I Human Toxicity (D)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity and endocrine activity and *in silico* modeling for endocrine activity and respiratory sensitization. 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 octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's NAMs dataset include a limited *in vivo* data available, and the absence of experimental data and established test methods for respiratory sensitization. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's Type II (extrapolation output) uncertainties include the uncertain predictability of *in vitro* estrogen binding assays of *in vivo* estrogenicity and anti-estrogenicity, the uncertain *in vivo* relevance of *in silico* predictions of endocrine activity, the limitation of *in vitro* assays in mimicking metabolic systems, and the OECD Toolbox only identifying structural alerts without defining applicability domains. Some of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's type II uncertainties can be alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

GreenScreen® Hazard Summary Table for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate

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*	*M*	DG	**L**	**L**	**M**	*M*	*L*	**L**	*L*	**L**	**L**	**L**	*L*	*vH*	*M*	*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 Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

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

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Chris Schlosser, M.F.S.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: January 19, 2012

Quality Control Performed By:
Name: Margaret H. Whitaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: January 23, 2012

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Zach Guerrette, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: July 31, 2014

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: August 5, 2014

GreenScreen® Assessment (v.1.4) Updated By:
Name: Brandon Reid, M.P.H.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: February 4, 2019

Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: February 20, 2019

GreenScreen® Assessment (v.1.4) Updated By:
Name: Thea Clipson, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: July 30, 2021, November 15, 2021

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 11, 2021, November 16, 2021

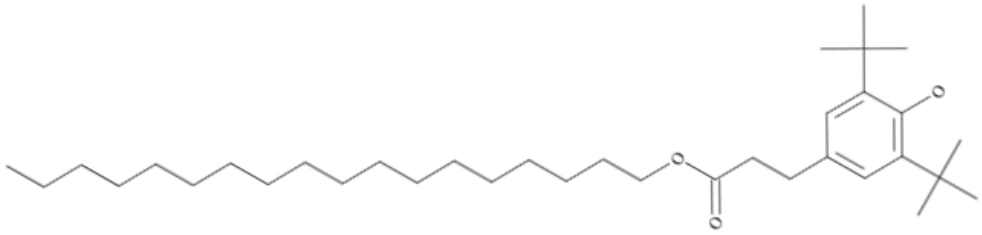
Expiration Date: November 16, 2026[2]

Chemical Name: Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate

CAS Number: 2082-79-3

[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).

Chemical Structure(s):



(ChemIDplus 2021)

Also called:
Hydrocinnamic acid, 3,5-di-t-butyl-4-hydroxy-, octadecyl ester; Irganox 1076; ADK Stab AO 50; Anox PP 18; Antioxidant 1076; AO 4; Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester; E 376; EC 218-216-0; EINECS 218-216-0; HSDB 5865; Hydrocinnamic acid, 3,5-di-t-butyl-4-hydroxy-, octadecyl ester; Hydrocinnamic acid, 3,5-di-tert-butyl-4-hydroxy-, octadecyl ester; I 1076; IR 1076; Irganox 1906; Irganox 1976; Irganox I 1076; Irganox L 107; Mark AO 50; Naugard 76; Octadecyl 3,5-bis(tert-butyl)-4-hydroxyhydrocinnamate; Octadecyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate; Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; Ralox 530; Stearyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate; Stearyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; Stearyl 3-(4-hydroxy-3,5-di-tert-butyl-4-hydroxyphenyl)propionate; Stearyl beta-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; Sumilizer BP 76; Tominokusu SS; U 276; Ultranox 276; UNII-V88J661G2P; 3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid octadecyl ester; Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester; Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; Hydrocinnamic acid, 3,5-di-tert-butyl-4-hydroxy-, octadecyl ester; Octadecyl 3-(3',5'-di-tert-butyl-4'-hydroxyphenyl)propionate (ChemIDplus 2021).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
No surrogates were incorporated into the assessment as sufficient data were available to assign a benchmark score for this chemical, and no surrogates with data were available to fill the data gap for endocrine activity.

Identify Applications/Functional Uses:
1. Antioxidant (OECD 2006)

Known Impurities[3]:
The following impurities were identified: metiloxcarboxylic acid (benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy- (<0.2%), metilox (benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester (<0.2%) and 1-octadecanol (< 0.2%) (OECD 2006). The screen is performed on the theoretical pure substance.

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.

GreenScreen® Summary Rating for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate[4,5,6,7]:

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2a
  - Very High Persistence-P + Moderate Bioaccumulation-B + Moderate Group II* Human Toxicity (systemic toxicity (repeated dose)-STr*)
  - Very High P + Moderate B + Moderate Group I Human Toxicity (developmental toxicity-D)
  - Very High P + Moderate B + Moderate Group II Human Toxicity (neurotoxicity single dose-Ns)
- Benchmark 2c
  - Very High P + Moderate Group II* Human Toxicity (STr*)
  - Very High P + Moderate Group I Human Toxicity (D)
  - Very High P + Moderate Group II Human Toxicity (Ns)
- Benchmark 2e
  - Moderate Group I Human Toxicity (D)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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 Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate

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*	**M**	DG	**L**	**L**	*M*	**L**	*L*	**L**	*L*	**L**	**L**	**L**	*L*	*H*	*M*	*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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate undergoes rapid primary degradation. The main degradation products of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate are metilox

[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.

acid (CAS #20170-32-5) and 1-octadecanol (CAS #112-92-5) (ECB Undated). In addition, 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionoic acid methyl ester (CAS #6386-38-5) was identified as a degradation product in a non-guideline, non-GLP aerobic degradation study (ECHA 2021a). As none of these chemicals are LT-1, they do not impact the overall Benchmark Score of the parent compound.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[8,9]
Unknown	Primary biodegradation	Metilox acid	20170-32-5	Yes	Yes	LT-U
Unknown	Primary biodegradation	1-Octadecanol	112-92-5	Yes	Yes	LT-U
End of life	Aerobic biodegradation	3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propionoic acid methyl ester	6386-38-5	Yes	Yes	LT-P1

Introduction

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is a phenolic antioxidant and is used as a non-discoloring stabilizer for organic substrates like plastics, synthetic fibers, elastomers, adhesives, waxes, oils and fats. It protects against thermo-oxidative degradation (OECD 2006).

ToxServices assessed octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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).

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 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),[10] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).
[10] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

scores for each human health and environmental endpoint. The output for octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate can be found in Appendix C.

- Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is not listed on the U.S. DOT list.
- Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is on the following lists for multiple endpoints.
    - EC – CEPA DSL – Inherently Toxic to Humans (iT human)
    - German FEA - Substances Hazardous to Waters - Class 0 – Non-Hazardous to Waters
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

No European Union (EU) harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate. A majority of EU notifiers, as well as the REACH registration dossier authors, did not self-classify octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate for any hazard endpoints (ECHA 2021a,b). General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respiratory particle filter, chemical resistant gloves, safety glasses	ECHA 2021a	N/A	

Physicochemical Properties of Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is a white powder at standard temperature and pressure. It has low vapor pressure (2.53 x10^{-7} Pa at 20°C) and water solubility (0.00285 mg/L at 20°C). It is predicted to be significantly more soluble in octanol than in water as indicated by the predicted log K_{ow} of 14.5, which suggests that it is not bioavailable.

Table 3: Physical and Chemical Properties of Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

Property	Value	Reference
Molecular formula	C35-H62-O3	ChemIDplus 2021
SMILES Notation	CCCCCCCCCCCCCCCCCCCCOC(=O)C Cc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C	ChemIDplus 2021
Molecular weight	530.872 g/mol	ChemIDplus 2021
Physical state	Solid at 20°C and 1013 hPa	ECHA 2021a
Appearance	White to off-white powder	ECHA 2021a
Melting point	51-52°C	ECHA 2021a
Boiling point	323°C at 1013 hPa	ECHA 2021a
Vapor pressure	2.53 x10^{-7} Pa at 20°C	ECHA 2021a
Water solubility	0.00285 mg/L at 20°C (OECD 105)	ECHA 2021a
Dissociation constant	pKa = 12.06 at 25°C (estimated)	ECHA 2021a

Table 3: Physical and Chemical Properties of Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)		
Property	**Value**	**Reference**
Density/specific gravity	1,012 kg/m³ at 20°C (OECD 109)	ECHA 2021a
Partition coefficient	Log K_{ow} > 14.5 at 25°C (estimated)	ECHA 2021a

Toxicokinetics

In an absorption study in rats (strain and sex not specified), animals were injected with C14 labeled test compound into gut lumen at a single dose of 978, 995, or 1,010 µg/animal. After 3 hours, the rats were euthanized, and the intestines were removed to determine the amount of the compound left to deduce absorption. Study authors determined that the test substance was well absorbed from the gut, at 31.6%-55.9% (Klimisch 2, reliable with restrictions) (ECHA 2021a).

In a distribution and excretion study in rats, single oral doses of 10 mg/kg octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (^{14}C-labeled at the 3-position of the propionate group) were administered to 4 animals (OECD 2006, ECHA 2021a). After 48 hours, 23% of the test chemical radioactivity was found in the urine and 50% in the feces. After the full observation period of 168 hours, 96% of the radioactivity was eliminated with 35% in the urine and 61% in the feces. The highest concentration of radioactivity was detected in the heart (0.54 µg/g). Additionally, 0.21 µg/g was detected in the thyroid gland, 0.26 µg/g in fat, 0.14 µg/g in the liver, 0.13 µg/g in the kidneys, 0.09 µg/g in the aorta, and 0.07 µg/g in the blood (Klimisch 2, reliable with restrictions).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for carcinogenicity based on negative results obtained in two-year studies in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high 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 2-year combined chronic toxicity/carcinogenicity study conducted in a manner similar to OECD 453 was performed using CFY rats (50/sex/dose). Rats were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 500, 1,500, or 5,000 ppm (equivalent to 22, 64, and 218 mg/kg/day for males and 27, 81, and 275 mg/kg/day for females, respectively according to ECHA record) over a 2-year period. No statistically significant increases in tumors were reported under the tested conditions (Klimisch 2, reliable with restrictions).
  - A non-GLP-compliant 2-year combined chronic toxicity/carcinogenicity study conducted in a manner similar to OECD 453 was performed with Tif:MAGf mice (50/sex/dose). Mice were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 5, 50, or 500 ppm (equivalent to 0.6, 5.4, and 58 mg/kg/day for males and 0, 0.6, 5.4, and 54 mg/kg/day for females, respectively according to ECHA

record) over a 2-year period. No statistically significant increases in tumors were reported under the tested conditions (Klimisch 2, reliable with restrictions).

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity obtained in *in vitro* and *in vivo* assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- 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*: A non-GLP-compliant bacterial reverse mutation assay conducted in a manner similar to OECD 471 was performed with *Salmonella typhimurium* tester stains TA98, TA100, TA1535, and TA1537 exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified, DMSO solvent) at 5-100 µg/mL with metabolic activation and 100-250 µg/mL without activation. Negative results for mutagenicity were obtained with treatment in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vivo*: A non-GLP-compliant chromosomal aberration assay conducted in a manner similar to OECD 475 was performed with Chinese hamsters (4/sex/group). Hamsters were administered oral doses of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified; CMC solvent) at 0, 500, 1,000, or 2,000 mg/kg/day via gavage for 2 days. Animals were sacrificed 30 hours after dosing and no increases in the incidence of micronucleated cells were found in any dose groups (Klimisch 2, reliable with restrictions).
  - *In vivo*: A non-GLP-compliant micronucleus assay was performed with Chinese hamsters (3/sex/group). Hamsters were administered doses of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified; CMC solvent) at 0, 500, 1,000, or 2,000 mg/kg/day for 2 days. Animals were sacrificed 24 hours after dosing and no increases in the incidence of micronucleated cells were found in any dose groups (Klimisch 2, reliable with restrictions).
  - *In vivo*: A non-GLP-compliant dominant lethal assay was performed with male NMRI mice (20/dose). Mice were administered single oral doses of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified; CMC solvent) at 0, 1,000, or 3,000 mg/kg via gavage. Males were mated with females for up to 6 weekly mating periods. No evidence of dominant lethal effects or differences in mating ratio, number of implantation, or embryonic deaths was reported (Klimisch 2, reliable with restrictions).

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for reproductive toxicity based on the lack of reproductive toxicity observed in an oral two-generation rat study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available, and they are not GHS classified (CPA 2018b). The confidence in the score is low as the key study lacked a detailed evaluation of reproductive endpoints.

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

  - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2021a, OECD 2006
  - A GLP-compliant two-generation reproductive toxicity study conducted in a manner equivalent or similar to OECD 416 was performed with male and female CD rats (24-28/generation). Rats were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 500, 1,500, or 5,000 ppm (equivalent to 0, 32, 96, and 315 mg/kg/day in males and 0, 39, 111, and 373 mg/kg/day in females, respectively according to ECHA record) for 10-12 weeks pre-mating, during mating, during gestation and until weaning of offspring. Male reproductive parameters, estrus cycle, developmental milestones of pups and fertility index/gestation index were not examined. In the F0 generation, relative liver weights were significantly increased in males and females of the top dose group. In addition, males in the top dose had enlarged livers. Relative spleen weights were decreased in all treated male groups. In the F0 and F1 generations, mating performance, pregnancy rate, and duration of gestation were not affected by treatment. Total litter loss was increased at the top dose (0/26, 1/24, 2/24, 4/27) in the F1 generation. Additionally, litter size was significantly reduced in all dose groups of the F1 generation. In the F2 generation reductions in litter size did not reach statistical significance and were not dose-related. OECD concluded these effects were not clearly treatment-related considering historical controls and that there was no consistent pattern. The percentage of live pups per litter was significantly lower in the top dose group of the F1 generation. At the top dose post-natal survival was lower in both generations. Based on available data, the reproductive NOAEL is set at 315 mg/kg, the highest dose tested, according to the authors. Limited data were provided on the reproductive toxicity endpoints analyzed, and fertility index/gestation index were not examined (Klimisch 2, reliable with restrictions).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Moderate for developmental toxicity based on significantly decreased litter sizes and offspring survival in an OECD Guideline 416 two-generation rat study, and decreased body weights with reduced ossification of phalangeal nuclei in a rat developmental toxicity study, both in the presence of slight maternal toxicities. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animals (CPA 2018b). The confidence in the score is reduced as it is possible that the observed developmental effects are secondary to maternal systemic toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* MAK – Pregnancy Risk Group C
  - *Screening:* Japan – GHS – H361 – Suspected of damaging fertility or the unborn child (Toxic to reproduction – Category 2).
- ECHA 2021a, OECD 2006
  - A GLP-compliant two-generation reproductive toxicity study (OECD 416) was conducted using male and female CD rats (number not reported). Rats were administered doses of 0, 500, 1,500, and 5,000 ppm (0, 32, 96, and 315 mg/kg in males and 0, 39, 111, and 373 mg/kg in females according to ECHA record) in the food for 10-12 weeks pre-mating, during mating, during gestation and until weaning of offspring. In the F0 generation, relative liver weights were significantly increased in males and females of the top dose group. In addition, males in the top dose had enlarged livers. Relative spleen weights were decreased in all treated male groups. In the F0 and F1 generations, mating performance, pregnancy rate, and duration of gestation were not affected by treatment. Total litter loss

was increased at the top dose (0/26, 1/24, 2/24, 4/27) in the F1 generation. Additionally, litter size was significantly reduced in all dose groups of the F1 generation. In the F2 generation, reductions in litter size did not reach statistical significance and were not dose-related. OECD concluded these effects were not clearly treatment-related considering historical controls and that there was no consistent pattern. The percentage of live pups per litter was significantly lower in the top dose group of the F1 generation. At the top dose, post-natal survival was lower in both generations. (Klimisch 2, reliable with restrictions). *Based on reduced postnatal survival in both generations, and total litter loss and percent of live pups per litter in F1 generation, ToxServices established a developmental NOAEL and LOAEL of 96 and 32 mg/kg, respectively. Limited data were provided on the developmental toxicity endpoints analyzed. Developmental milestones of pups were not evaluated.*

  - A non-GLP-compliant prenatal developmental toxicity study (similar to OECD 414) was conducted using pregnant female Sprague-Dawley rats. (25/group). Rats were administered doses of 0, 150, 500, and 1,000 mg/kg in CMC from day 6 to day 15 of gestation via gavage. A dose-related decrease in food consumption, especially at the mid and high doses, was noted in parental animals, along with slightly reduced body weight gains in these dose groups. No effects on pregnancy rate, number of implantations, early and late resorptions and number of live fetuses were reported. Fetal body weight was significantly reduced in the top two dose groups. In the top dose group, an increased incidence of delayed ossification of the phalangeal nuclei of the hind limbs was observed (Klimisch 2, reliable with restrictions). *Based on available data, ToxServices assigned a NOAEL and LOAEL of 150 and 500 mg/kg based on reduced pup body weights in the mid-dose group.*
  - A non-GLP-compliant prenatal developmental toxicity study (similar to OECD 414) was conducted using pregnant female NMRI mice (30/group). Mice were administered doses of 0, 150, 500, and 1,000 mg/kg in CMC from day 6 to day 15 of gestation via gavage. No mortality or maternal toxicity was noted. No effects on pregnancy rate, number of implantations, early and late resorptions and number of live fetuses were reported. A NOAEL of 1,000 mg/kg was established for maternal and developmental toxicity by the study authors (Klimisch 2, reliable with restrictions).
- NITE 2016
  - Based on the studies described above, Japan concluded that developmental effects were observed in the presence of parental systemic toxicity and hence the compound was classified to GHS Category 2.

Endocrine Activity (E) Score (H, M, or L): DG
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Data Gap for endocrine activity based on a lack of sufficient 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.
- U.S. EPA 2021b
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was inactive in an estrogen receptor (ER) binding assay (using rat uterine cytosol (RUC) ER).
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be inactive for androgen receptor agonism, antagonism, and binding by the ToxCast COMPARA (Consensus) model, and it was predicted to be active (very weak) for estrogen receptor agonism and binding, but inactive for estrogen receptor antagonism by the ToxCast CERAPP Potency Level (Consensus) model.

- VEGA 2021
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be inactive by the Estrogen Receptor Relative Binding Affinity model (IRFMN) with low reliability [Global applicability domain (AD) Index = 0] (Appendix D).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be non-active by the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with strong reliability (Global AD Index = 0.904, similarity index = 0.818, accuracy index = 1, concordance index = 1) (Appendix D).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be non-active by the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with strong reliability (Global AD Index = 0.904, similarity index = 0.817, accuracy index = 1, concordance index = 1) (Appendix D).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be inactive by the Thyroid Receptor Alpha effect (NRMEA) 1.0.0 model with strong reliability (Global AD Index = 0.904, similarity index = 0.823, accuracy index = 1, concordance index = 1) (Appendix D).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be inactive by the Thyroid Receptor Beta effect (NRMEA) 1.0.0 model with strong reliability (Global AD Index = 0.907, similarity index = 0.823, accuracy index = 1, concordance index = 1) (Appendix D).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be inactive by the Aromatase activity (IRFMN) 1.0.0 model with strong reliability (Global AD Index = 0.909, similarity index = 0.826, accuracy index = 1, concordance index = 1) (Appendix D).
- DTU 2021(only results that are in the applicability domains are reported below)
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate contains no structural alerts for estrogen receptor binding (Appendix E).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be negative for estrogen receptor α binding (full training set and balanced training set, human *in vitro*), and activation (human *in vitro*) by the Case Ultra and SciQSAR models. However, it was predicted to be positive for estrogen receptor α binding (full and balanced training set, human *in vitro*) by the Leadscope model, and negative for estrogen receptor α activation (human *in vitro*) by the Leadscope model.
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be negative based on experimental data and by the model battery for androgen receptor inhibition (human *in vitro*) consisting Case Ultra, Leadscope and SciQSAR models.
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to be positive by the Leadscope model for androgen receptor binding, CoMPARA data (*in vitro*) and androgen receptor inhibition, CoMPARA data (*in vitro*), and to be negative for androgen receptor activation, CoMPARA data (*in vitro*) (Appendix E).
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was predicted to positive by thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*) models (Appendix E).
- ECHA 2021a
    - A non-GLP-compliant 2 year chronic toxicity/carcinogenicity assay conducted according to OECD 452 was performed with CFY rats (50/sex/dose). Rats were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate (purity not specified) at 0, 500, 1,500, or 5,000 ppm (equivalent to 0, 22, 64, and 218 mg/kg for males and 0, 27, 81, and 275 mg/kg for females, respectively according to ECHA record) over a 2-year period. Thyroid weights were significantly increased in the high dose groups, while the

weight of the adrenals and spleen was significantly decreased in the mid and high dose groups. In animals necropsied at study termination an enlarged thyroid was reported. Histopathology (10 rats/sex of the control and high dose groups) showed prostatitis in males and endometritis in females (Klimisch 2, reliable with restrictions).
    - A non-GLP-compliant 2 year chronic toxicity/carcinogenicity assay conducted according to OECD 451was performed with Tif:MAGf mice (50/sex/dose). Mice were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 5, 50, or 500 ppm (equivalent to 0.6, 5.4, and 58 mg/kg/day for males and 0, 0.6, 5.4, and 54 mg/kg/day for females, respectively according to ECHA record) over a 2-year period. Microscopic evaluation showed subscapular proliferation in the adrenal gland, dilatation and chronic inflammation in the seminal vesicles, cysts in the ovaries, and hyperplasia of the uterus in all dose groups, and controls (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Data Gap was assigned. Repeated oral exposure to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate caused prostatis, endometritis, and significant changes in thyroid weights. However, there were no data on whether these changes were related to endocrine activity. The available *in vitro* high through-put and modeling results and weight of evidence indicate that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not likely to interact with ER, AR, or thyroid receptors or affect steroidogenesis. However, no *in vivo* data are available to determine octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate's effects on circulating estrogen, androgen, and thyroid hormone levels. Therefore, ToxServices assigned a score of Data Gap 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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for acute toxicity based on oral LD_{50} values greater than 4,640 mg/kg, inhalation LC_{50} values greater than 0.667 mg/L (highest achievable concentration), and dermal LD_{50} values greater than 2,000 mg/kg in acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral LD_{50} values are greater than 2,000 mg/kg, dermal LD_{50} values are greater than 2,000 mg/kg, and inhalation LC_{50} values are greater than 5 mg/L (dust) (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
    - *Oral*: LD_{50} (Tif:RAIf (SPF) rat) > 5,000 mg/kg (non-GLP-compliant, similar to OECD 401) (Klimisch 2, reliable with restrictions).
    - *Oral*: LD_{50} (rat) > 10,000 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions).
    - *Oral*: LD_{50} (rat) > 15,000 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions).
    - *Oral*: LD_{50} (rat) > 4,640 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions).

- *Inhalation*: 4-hour aerosol, nose-only LC_{50} (Tif. RAI rat) > 1.81 mg/L (highest achievable concentration) (non-GLP-compliant, similar to OECD 403) (Klimisch 2, reliable with restrictions)
- *Inhalation*: 4-hour aerosol, nose-only LC_{50} (Tif. RAI rat) > 0.667 mg/L (highest achievable concentration) (non-GLP-compliant) (Klimisch 2, reliable with restrictions)
- *Dermal*: LD_{50} (Tif. RAI rat) > 2,000 mg/kg (GLP-compliant, OECD 402) (Klimisch 1, reliable without restriction)
- *Dermal*: LD_{50} (rabbit) > 2,000 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions)

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxicity observed in the acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when negative data, and no GHS classification are available (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
  - *Oral:* In an acute toxicity study that reported an LD_{50} > 5,000 mg/kg in rats, Tif:RAIf(SPF) rats (5/sex) received a single gavage dose of 5,000 mg/kg test substance and then were observed for 14 days. No animals died prior to scheduled necropsy. Clinical signs observed include slight sedation, exophthalmos, slight dyspnea, ruffled fur, slight diarrhea, and curved body position, where were all reversible by 14 days. All animals gained body weight and gross necropsy findings were unremarkable (Klimisch 2, reliable with restrictions).
  - *Oral:* In an acute toxicity study that reported an LD_{50} > 10,000 mg/kg in rats, animals (species unspecified, 5/sex) received two gavage dose of 5,000 mg/kg each at an interval of 5 hours and were observed for 8 days. None of the animals died during the study period. Clinical observations were limited to drowsiness and dullness. No data were reported on body weight or gross pathology (Klimisch 2, reliable with restrictions).
  - *Oral:* In an acute toxicity study that reported an LD_{50} > 15,000 mg/kg in rats, animals (species unspecified, 5/sex) received three gavage dose of 5,000 mg/kg each at an interval of 5 hours and were observed for 8 days. None of the animals died during the study period. Clinical observations were limited to drowsiness and dullness. No data were reported on body weight or gross pathology (Klimisch 2, reliable with restrictions).
  - *Oral:* In an acute toxicity study that reported an LD_{50} > 4,640 mg/kg in rats, animals (species unspecified) received a single gavage dose of 1,000 (2 animals), 2,150 (2 animals), and 4,640 (10 animals) mg/kg and were observed for 14 days. Two/10 animals at the highest dose died. Clinical observations included unsteadiness, decreased activity and sleepy appearance that were reversible within 24 hours. No data were reported on body weight. Gross pathology findings were unremarkable (Klimisch 2, reliable with restrictions).
  - *Inhalation:* In an acute toxicity study in rats that reported a 4-hour LC_{50} > 1.81 mg/L, Tif. RAI rats (10/sex/dose) were exposed to the test substance aerosol by nose-only inhalation at concentrations of 0.5, 1.025 and 1.811 (highest achievable concentration) mg/L for 4 hours and were then observed for 14 days. None of the animals died during the study period.

Clinical signs were limited to exophthalmos, ruffled fur and ventral body position (reversibility not specified). All animals gained weight during the study. Gross pathology findings were unremarkable (Klimisch 2, reliable with restrictions).

- *Inhalation:* In an acute toxicity study in rats that reported a 4-hour LC_{50} > 0.667 mg/L, Tif. RAI rats (9/sex/dose) were exposed to the test substance aerosol by nose-only inhalation at 0.667 mg/L (highest achievable concentration) for 4 hours and were then observed for 7 days. None of the animals died during the study period. Clinical signs were limited to dyspnea, trismus, lateral position and slight apathy, which were reversible within 24 hours. Body weight data were not reported. Gross pathology findings were unremarkable (Klimisch 2, reliable with restrictions).
- *Dermal:* In an acute toxicity study in rats that reported an LD_{50} > 2,000 mg/kg, Tif:TAI F (SPF) rats (5/sex) were exposed to the test substance on the skin under semiocclusion at 2,000 mg/kg for 24 hours, and then observed for 14 days. None of the animals died. Clinical signs observed include piloerection and hunched posture which were reversible within 2 days. All animals gained weight normally. Gross necropsy revealed a scurfy ear in one male and no abnormalities in other animals (Klimisch 1, reliable without restriction).
- *Dermal:* In an acute toxicity study in rabbits that reported an LD_{50} > 2,000 mg/kg, animals (2/sex, strain unspecified) were exposed to the test substance on the skin under occlusion at 200, 632, or 2,000 mg/kg for 24 hours, and then observed for 14 days. None of the animals died. There were no clinical signs observed in this study. All animals gained weight normally. Gross necropsy findings were unremarkable (Klimisch 2, reliable with restrictions).

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Moderate for systemic toxicity (repeated dose) based on consistent liver effects throughout multiple repeated dose studies. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is classified as a GHS Category 2 Repeat Dose toxicant due to significant treatment-related effects between the 10 and 100 mg/kg GHS guidance values. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when a GHS Category 2 Repeat Dose toxicant classification is available (CPA 2018b). The confidence in the score is high as it is based on experimental data and supported by presence on a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* New Zealand – GHS – Category 6.9B (oral) (equivalent to GHS Category 2 specific target organ/systemic toxicity (repeated exposure)).
- ECHA 2021a
  - *Oral:* A GLP compliant 28-day oral gavage study conducted according to OECD 407 was performed with Sprague-Dawley rats (5/sex/dose). Rats were administered oral doses of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate (99.9% purity in hydroxypropylcellulose) at 0, 5, 30, 100, or 300 mg/kg/day via gavage. Increases in liver weights were measured in the mid and high dose groups, with hypertrophy in the high dose group. Microsomal enzymes (cytochrome P450, ethoxyresorufin Ode-ethylase, pentoxyresorufin O-depentylase, epoxide hydrolase, morphine-UDP-glucuronosyltransferase and bilirubin-UDP-glucuronosyltransferase) were investigated. Significant increases were seen in males at 100 and 300 mg/kg and in females at 300 mg/kg. Cytosolic protein content was decreased significantly in males at 300 mg/kg. Based on the liver effects a NOAEL of

30 mg/kg (LOAEL = 100 mg/kg) was established by the study authors (Klimisch 1, reliable without restriction).

- *Based on the 28-day duration of this study, this value is compared to adjusted guidance values of 30-300 mg/kg/day for a Moderate.*

- *Oral:* A non-GLP-compliant 90-day toxicity study conducted in a manner similar to OECD 409 was performed with Beagle dogs (6/sex/dose group, 5 in main test, 1 in recovery group). Dogs were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 1,000, 3,000, or 10,000 ppm (equivalent to 0, 31.5, 92.2, and 295.4 mg/kg in males and 0, 34.5, 97.2, and 335.7 mg/kg in females, respectively according to ECHA record). Significantly decreased hemoglobin and hematocrit were reported in the high dose group. Increased bilirubin was measured in the mid and high dose groups. There was a significant increase in liver weight that was only partially reversible after a 28-day recovery period at the mid and high doses. Histopathological findings were unremarkable. A NOAEL of 31.5 mg/kg for males and 34.5 mg/kg for females was established by the study authors, based on irreversible increase in liver weight. The LOAELs were 92.2 mg/kg and 97.2 mg/kg for males and females, respectively (Klimisch 2, reliable with restrictions).
- *Oral:* A non-GLP-compliant 2-year chronic toxicity/carcinogenicity assay conducted according to OECD 452 was performed with CFY rats (50/sex/dose). Rats were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate (purity not specified) at 0, 500, 1,500, or 5,000 ppm (equivalent to 0, 22, 64, and 218 mg/kg for males and 0, 27, 81, and 275 mg/kg for females, respectively according to ECHA record) over a 2-year period. Liver and thyroid weights were significantly increased in the high dose groups, while the weights of the adrenals and spleen were significantly decreased in the mid and high dose groups. In animals necropsied at study termination, an enlarged thyroid and subpleural foci in the lung were reported. Histopathology (10 rats/sex of the control and high dose groups) showed prostatitis in males and endometritis in females and no treatment related effects in the liver. Based on findings on body weight in females and organ weights a NOAEL of 64 mg/kg (LOAEL = 218 mg/kg) was set by the study authors (Klimisch 2, reliable with restrictions).
- *Oral:* A non-GLP-compliant 2 year chronic toxicity/carcinogenicity assay conducted according to OECD 451was performed with Tif:MAGf mice (50/sex/dose). Mice were provided diets containing octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) at 0, 5, 50, or 500 ppm (equivalent to 0.6, 5.4, and 58 mg/kg/day for males and 0, 0.6, 5.4, and 54 mg/kg/day for females, respectively according to ECHA record) over a 2-year period. Liver weights were increased in all female dose groups and the low and mid dose groups in males. Microscopic evaluation showed fatty changes and lymphocytic infiltration in the liver, extramedullary hematopoiesis and hemosiderosis in the spleen, subscapular proliferation in the adrenal gland, lymphocytic infiltration in the kidney and urinary bladder, dilatation, and chronic inflammation in the seminal vesicles, cysts in the ovaries, and hyperplasia of the uterus in all dose groups, and controls. The ECHA record indicated that no treatment-related organ weight changes or microscopical changes were found and identified the NOAEL at 54 mg/kg/day (the highest dose tested) (Klimisch 2, reliable with restrictions).
- *Inhalation:* A non-GLP-compliant 21-day inhalation toxicity study conducted according to OECD 412 was performed with RAI f rats (10/sex/group). Rats were exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) aerosol at 0, 23, or 543 mg/m^3 (equivalent to 0, 0.023, and 0.543 mg/L, respectively) for 6 hours/day, 5 times/week, for 21 days. The equivalent concentrations for a 7 day/week exposure

frequency were 0, 0.016, and 0.388 mg/L, respectively. Liver weights were increased at all concentrations tested (no dose-response relationship). No histopathological findings were reported. Study authors reported a NOAEC of 543 mg/m^3 (0.388 mg/L) based on no histopathological finding corresponding with liver weights (Klimisch 2, reliable with restrictions).
    - *Due to the 21-day duration of this study, this value is compared to an adjusted guidance value of 0.0866-0.866 mg/L for a Moderate.*
- OECD 2006
    - All studies show effects on liver weight, possibly related to the induction of liver enzymes as indicated by the 28-day study. Furthermore, corresponding histopathology were observed in the 28-day rat study (liver hypertrophy and increased hepatocytic vacuolization) and 2-year mouse study (fatty changes and lymphocytic infiltration in the liver). SIDS authors reported a NOAEL of 30 mg/kg for oral toxicity based on liver effects.
- Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is classified as a GHS Category 2 toxicant due to significant effects observed in animal studies following repeat oral doses of 10 to 100 mg/kg (UN 2019).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects in acute oral toxicity studies classifying it to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when classified to GHS Category 3 (CPA 2018b). The confidence in the score is low as it is unclear whether effects were neurotoxic or non-specific in nature.
- 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
    - Effects observed in the previously described acute oral toxicity tests include slight sedation, drowsiness, dullness, decreased activity, unsteadiness, and sleepy appearance. The animals generally recovered within 24 hours. No dose levels were specified at which these effects were observed. It is not clear whether these effects are neurotoxic in nature or were manifested by discomfort the animals experienced following the dosing. ToxServices conservatively classified octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate to GHS category 3 based on transient narcotic effects observed.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): *L*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for neurotoxicity (repeated dose) based on negative results obtained in a dog subchronic toxicity test. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when negative data, and no GHS classification are available (CPA 2018b). The confidence in the score is low as available data are limited to sensory activity from a subchronic toxicity study.
- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
    - In the non-GLP-compliant 90-day toxicity study conducted in a manner similar to OECD 409 was performed with Beagle dogs (6/sex/dose group) summarized in the repeated dose section above, the dogs were evaluated for sensory activity via a simple noise test. No treatment-

related effects were observed (Klimisch 2, reliable with restrictions). *A neurotoxicity NOAEL of 295.4 mg/kg/day was identified by ToxServices based on the lack of neurotoxicity observed in this study*.

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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 non-GLP-compliant Maurer optimization study conducted according to OECD 406 was performed with Pirbright-Hartley guinea pigs (20/dose group, sex not specified). Guinea pigs were induced intradermally 3 times weekly for 2 weeks with a 0.1% solution of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate in polyethylene glycol + saline (70:30). Fourteen days after the last induction injection, a 0.1% challenge dose was injected and the reactions were scored 24 hours later. Positive reactions were observed in 1/20 animals in the negative control group and in 4/20 animals receiving octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate. All 20 of the animals in the positive control group exhibited positive reactions. The study authors concluded that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not sensitizing to skin (Klimisch 2, reliable with restrictions).

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate does not contain any structural alerts for respiratory sensitization (Appendix F)
- DTU 2021
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate was predicted to be negative and in domain by the Leadscope model for respiratory sensitization in humans (Appendix G).
- 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 octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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 octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate, and as octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate does not contain any structural alerts for respiratory sensitization (OECD 2020a), octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is not expected to be a respiratory sensitizer.

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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 conducted according to EP OPP 81-5 was performed with New Zealand White rabbits (3/sex) administered dermal application of 500 mg octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) to abraded and intact skin under occlusive dressing for 24 hours. An observation period of 7 days followed the exposure period. For intact skin, the mean erythema score was 0.56/4 and the edema score was 0.11/4. For abraded skin, the mean erythema score was 0.94/4 and the mean edema score was 0.22/4. All effects were fully reversible within 4 days for intact skin and within 7 days for abraded skin. The study authors concluded that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not irritating to the skin (Klimisch 2, reliable with restrictions).
    - *The effects observed in this study are not sufficient to classify octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate 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 rabbits that reported an LD_{50} > 2,000 mg/kg, animals (2/sex, strain unspecified) were exposed to the test substance on the skin under occlusion at 200, 632, or 2,000 mg/kg for 24 hours, and then observed for 14 days. Mild skin irritation was observed which was reversible by 24 hours after the patch removal (Klimisch 2, reliable with restrictions) (Klimisch 2, reliable with restrictions).

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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:* Not present on any screening lists for this endpoint.
- ECHA 2021a

- A GLP-compliant ocular irritation test conducted according to OECD 405 was performed with New Zealand rabbits (3 without rinsing, 3 with rinsing; sex not specified) administered eye instillations of 0.1 mL octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (purity not specified) for 30 seconds. Half of the animals had their eyes rinsed while the other half did not. The animals were observed for 7 days following installation with reactions scored at 24, 48, and 72 hours. The mean cornea score was 0/4 (six animals), the mean iris score was 0/2 (six animals), the mean conjunctiva score was 0.67/3 for non-rinsed animals and 0.33/3 for rinsed animals, and the chemosis score was 0.22/4 for non-rinsed animals and 0/4 for rinsed animals. The conjunctival effects were not fully reversible within seven days for the non-rinsed animals. All other effects were reversible within 7 days. The study authors concluded that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not irritating to the eyes (Klimisch 2, reliable with restrictions).
    - *The effects observed in this study are not sufficient to classify octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate 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).*

Ecotoxicity (Ecotox)

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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:* New Zealand – GHS – Category 9.1 (fish) (equivalent to GHS Category 2/3 acute aquatic toxicant/chronic aquatic toxicity category 4).
- ECHA 2021a
    - 96-hour LC_{50} (*Lepomis macrochirus*, bluegill) > 100 mg/L (non-GLP-compliant, OECD 203) (Klimisch 2, reliable with restrictions)
    - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) > 100 mg/L (GLP-compliant, OECD 203) (Klimisch 2, reliable with restrictions)
    - 24-hour mobility EC_{50} (*Daphnia magna*) > 100 mg/L (non-GLP-compliant, OECD 202) (Klimisch 2, reliable with restrictions)
    - 72-hour growth rate and biomass EC_{50} (*Desmodesmus subspicatus*, green algae) > 30 mg/L (GLP-compliant, EU Method C.3) (Klimisch 2, reliable with restrictions)
- Based on a water solubility of 0.00285 mg/L at 20°C as determined in an OECD 105 test (ECHA 2021a), no adverse effects are expected on aquatic biota at saturation.

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

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate 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 the value was modeled.

- 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
  - 21-day reproduction NOELR (loading rate) (*D. magna*) ≥ 2 mg/L (GLP-compliant, OECD 211) (Klimisch 1, reliable without restriction)
  - 72-hour growth rate and biomass NOEC (*D. subspicatus*, green algae) = 30 mg/L (GLP-compliant, EU Method C.3) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2017a
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is designated to the Esters and Phenols ECOSAR chemical classes. The most predicted conservative chronic toxicity values (ChVs) are 1.1 x 10^{-7} mg/L in fish, 2.4 x 10^{-7} mg/L in daphnid, and 4.5 x 10^{-6} mg/L in green algae. However, the measured log K_{ow} of > 14.5 far exceeds the maximum log K_{ow} cutoff of 8.0 for these chronic effects, meaning that no effects are expected at saturation in water (Appendix H).
- Based on a water solubility of 0.00285 mg/L at 20°C as determined in an OECD 105 test (ECHA 2021a), no adverse effects are expected on aquatic biota at saturation.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Very High for persistence based on a predicted half-life of 542 days in sediment, its major compartment. Experimental data indicate that primary biodegradable occurred at a rapid rate, but ultimate degradation is slow. It did not pass ready biodegradation tests and hence does not meet the GHS rapid degradability criteria. While primary degradation may be used to support GHS rapid degradability, the degradation products must not be classified as hazardous under GHS to the aquatic environment (UN 2021). The degradation product metilox acid (CAS #20170-32-5) is predicted to be a GHS Category 2 chronic aquatic hazard by Danish EPA, the primary degradation product 1-octadecanol (CAS #112-92-5) is self-classified as an acute aquatic toxicant by EU notifiers as well as by Canada, and the other degradation product 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionoic acid methyl ester (CAS #6386-38-5) is classified as a GHS Category 2 chronic aquatic hazard by Japan and EU notifiers and is determined to be inherently toxic in the environment (iTE) by Canada (Pharos 2021), therefore, primary degradation data could not be used to support rapid degradability. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when the half-life in sediment is > 180 days (CPA 2018b). The confidence in the score is low as it is based on modeled predictions.

- 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 GLP-compliant primary biodegradability study conducted according to OECD 301 (subpart not specified) was performed with non-adapted, domestic activated sludge exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate (purity not specified) at 0.093 mg/L for 10 days. At the end of the exposure period, the level of primary degradation was 86%. The study authors concluded that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate is degradable (Klimisch 1, reliable without restriction).
  - A GLP-compliant ready biodegradability test conducted according to OECD 301 C was performed with non-adapted, domestic activated sludge exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate (purity not specified) at 100 mg/L for 28 days. At the

end of the exposure period, the level of biodegradation was 21-39%. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate was not considered to be readily biodegradable in this test (Klimisch 1, reliable without restriction).
    - A non-GLP-compliant ready biodegradability test conducted according to OECD 301 B was performed with activated sludge (adaptation not specified) exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate (purity not specified) at 10-20 mg/L for 28 days. At the end of the exposure period, the level of biodegradation was 32-35%. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate was not considered to be readily biodegradable in this test (Klimisch 2, reliable with restrictions).
    - In a non-guideline, non-GLP aerobic degradation study, domestic activated sludge (adaptation not specified) was exposed to the radiolabeled test substance for 5 days. 0.1% of the recovered radioactivity was in CO_2, 69.8% as extractable products, and 7.0% as non-extractable products. Chemical analysis of the extractable products found 10.5% 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid methyl ester, 7.7% unchanged parent compound, and 53.6% unknown chemicals (Klimisch 2, reliable with restrictions).
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate is not expected to be readily biodegradable (see Appendix H). Fugacity modeling (default EQC model due to log K_{ow} >7) predicts 68.5% will partition to sediment with a half-life of 542 days, 30% will partition to soil with a half-life of 120 days, and 1.39% will partition to water with a half-life of 60 days (Appendix I).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *M*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Moderate for bioaccumulation based on a BCF of 532 for the degradation product metilox acid. GreenScreen® criteria classify chemicals as a Moderate hazard for bioaccumulation when BCF/BAF values are between 500 and 1,000 (CPA 2018b). The confidence in the score is low as it is based in part on expert judgment.

- 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, ECB Undated
    - A GLP-compliant bioaccumulation study conducted according to OECD 305 C was performed with carp (*Cyprinus carpio*) exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoate (purity not specified) at 0.05 - 0.5 mg/L for 6 weeks. The BCF values were < 210 for 0.05 mg/L and <210-1,470 for 0.50 mg/L (Klimisch 2, reliable with restrictions).
- ECB Undated:
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate has a moderate to high potential for bioaccumulation.
    - The primary degradation product metilox acid has experimental BCFs of 94-108 at high concentrations and 373-532 at low concentrations.
    - Due to its fast primary biodegradation, bioaccumulation of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is unlikely to occur in the environment.
    - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not considered to be bioaccumulative or very bioaccumulative based on data on its degradation product.
- U.S. EPA 2017b

  - BCFBAF estimates a BAF value of 2.975 based on an estimated log K_{ow} of 13.41 (see Appendix I).
- Based on the weight of evidence a score of Moderate was assigned. The experimental BCF values for octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate are as high as 1,470, but are also as low as < 210, indicating a low to high potential for bioaccumulation. As noted by the ECB in the PBT/vPvB assessment for this chemical, bioaccumulation is unlikely as it rapidly undergoes primary biodegradation. The BCF values for the degradation product range from 91-532, indicating a Very Low to Moderate potential. ToxServices assigned a Moderate based on the BCF of 532 for the degradation product, as this is the value cited by the ECB in its PBT/vPvB assessment of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for reactivity based on a statement that it is not explosive and on the lack of structural alerts for explosive or oxidizing properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification can be assigned for any of the GHS reactivity sub-endpoints (CPA 2018b). The confidence in the score was low based on a lack of 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.
- OECD 2006
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not explosive.
- ECHA 2021a
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate has no chemical groups associated with explosive or oxidizing properties.
- Based on this data, ToxServices did not classify octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate as a reactive chemical based on GHS criteria (UN 2019).

Flammability (F) Score (vH, H, M, or L): L
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate was assigned a score of Low for flammability based on it not being classified as a flammable solid under GHS criteria (UN 2019) due to negative results in a flammability test. 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
  - In a flammability test, octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate had a brief ignition followed by rapid extinction at 25°C. The test could not be performed at 100°C as this chemical melts at temperatures less than 100°C.
- OECD 2006
  - Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate has a flash point of 273°C. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate is not a flammable solid as it is not considered to be readily combustible.

- Based on this data, ToxServices did not classify octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate as a flammable chemical based on GHS criteria (UN 2019).

Use of New Approach Methodologies (NAMs)[11] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity and endocrine activity, and *in silico* modeling for endocrine activity and respiratory sensitization. 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 4, Type I (input data) uncertainties in octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's NAMs dataset include a limited *in vivo* data available, and the absence of experimental data and established test methods for respiratory sensitization. Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's Type II (extrapolation output) uncertainties include the uncertain predictability of *in vitro* estrogen binding assays of *in vivo* estrogenicity and anti-estrogenicity, the uncertain *in vivo* relevance of *in silico* predictions of endocrine activity, the limitation of *in vitro* assays in mimicking metabolic systems, and the OECD Toolbox only identifying structural alerts without defining applicability domains. Some of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate's type II uncertainties can be alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Endocrine activity**: *In vivo* experimental data are limited, and interpretability is limited. **Respiratory sensitization**: No experimental data are available, and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Endocrine activity** ToxCast models don't define applicability domain; the *in vivo* relevance of *in vitro* receptor binding activity screening assays and *in silico* modeling results of receptor binding activities is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in

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

	non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12]. **Respiratory sensitization**: The OECD Toolbox (OECD 2020a) 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	N	
Mutagenicity	Y	*In vitro* bacterial reverse mutation assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* data: DSSTox (KIERBL) EPA Estrogen Receptor Ki Binding Study *In silico* modeling: VEGA/Danish QSAR/ToxCast
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/Danish QSAR
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[12] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

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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 Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)pr	2082-79-3	L	L	*L*	*M*	DG	L	L	M	*M*	*L*	L	*L*	L	L	L	*L*	*vH*	*M*	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)pr	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)pr	2

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

Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

Pharos | Search... | Comparisons | Common Products | Discussions | Account

2082-79-3

Hydrocinnamic acid, 3,5-di-t-butyl-4-hydroxy-, octadecyl ester

ALSO CALLED 109265-64-7, 119764-08-8, 1352054-71-7, 156511-59-0, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-,octadecyl...

View all synonyms (26)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT				
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-P1	-	-	M	M-L	-	-	pC	-	-	-	pC	-	pC	pC	-	-	pC	-	-	-	-	H	pC	-	-	R

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Reproductive Toxicity	M	LT-UNK	GHS - Japan	H361 - Suspected of damaging fertility or the unborn child [Toxic to reproduction - Category 2]	
Developmental Toxicity incl. developmental neurotoxicity	M-L	LT-UNK	MAK	Pregnancy Risk Group C	

Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	
Skin Sensitization	pC	NoGS	DK-EPA - Danish Advisory List	Skin Sens. 1 - May cause an allergic skin reaction (modeled)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Terrestrial Ecotoxicity	pC	NoGS	GHS - New Zealand	9.2D - Slightly harmful in the soil environment	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	H	LT-UNK	GHS - New Zealand	6.9B (oral) - Harmful to human target organs or systems (Cat. 2)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - New Zealand	9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	+1
	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]	

T & P and/or B [(Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-P1	GHS - Japan	H411 - Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 2]
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (iTH)
PBT (Persistence, Bioaccumulation & Toxicity)	pC	NoGS	EU - ESIS PBT	Not fulfilling PBT & vPvB criteria

Restricted Substance Lists (1)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment

Positive Lists (2)

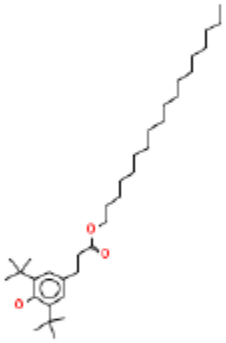
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients
- German FEA - Substances Hazardous to Waters: Non-Hazardous to Water (Water Hazard Class 0 NWG)

APPENDIX D: VEGA Endocrine Endpoint for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

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

1. Prediction Summary

Prediction for compound Molecule 0

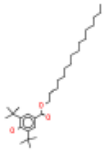


Prediction: Reliability:

Prediction is Inactive, 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:
- 1 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set.

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 15
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

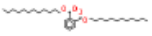
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 67845-93-6
Dataset id: 382 (Training set)
SMILES: O=C(OCCCCCCCCCCCCCCCC)c1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Similarity: 0.889

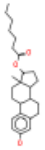
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 2432-90-8
Dataset id: 328 (Training set)
SMILES: O=C(OCCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCCC)
Similarity: 0.826

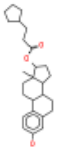
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 4956-37-0
Dataset id: 49 (Training set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCCCCC
Similarity: 0.821

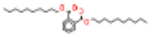
Experimental value: Active
Predicted value: Active



Compound #4

CAS: 313-06-4
Dataset id: 46 (Test set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCC5CCCC5
Similarity: 0.815

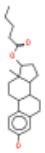
Experimental value: Active
Predicted value: Active



Compound #5

CAS: 84-77-5
Dataset id: 327 (Test set)
SMILES: O=C(OCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCC)
Similarity: 0.806

Experimental value: Inactive
Predicted value: Active



Compound #6

CAS: 979-32-8
Dataset id: 38 (Training set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCCC
Similarity: 0.805

Experimental value: Active
Predicted value: Active

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 = 0.854
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 = False
Explanation: 1 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set..

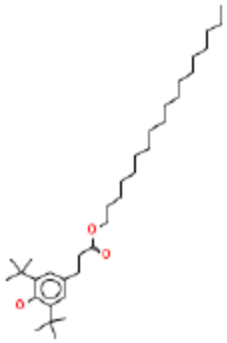
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

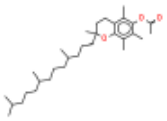


Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER non-activity alert no. 8; ER non-activity alert no. 24; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Experimental value: -
Predicted ER-mediated effect: NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 2
No. alerts for possible non-activity: 2
Structural alerts: ER non-activity alert no. 8; ER non-activity alert no. 24; ER possible non-activity alert no. 1; 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

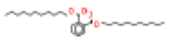


Compound #1

CAS: N.A.
Dataset id: 68 (Training set)
SMILES: O=C(Oc2c(c(c1OC(C)(CCc1c2C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C
Similarity: 0.831

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

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



Compound #2

CAS: N.A.
Dataset id: 1028 (Training set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.82

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

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

Alerts (not found in the target): ER non-activity alert no. 23

Compound #3

CAS: N.A.
Dataset id: 981 (Training set)
SMILES: O=C(OCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCC
Similarity: 0.805

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: 1204 (Training set)
SMILES: O=C(OCCCCCCCC(C)C)CCCCC(=O)OCCCCCCCC(C)C
Similarity: 0.804

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

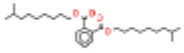
Compound #5

CAS: N.A.
Dataset id: 1160 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCCCCCCCCCC
Similarity: 0.798

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: 1305 (Training set)
SMILES: O=C(OCCCCCCCC(C)C)c1ccccc1(C(=O)OCCCCCCCC(C)C)
Similarity: 0.798

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

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

Alerts (not found in the target): ER non-activity alert no. 23

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.904
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.818
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.

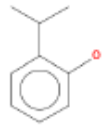
Symbols explanation:

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

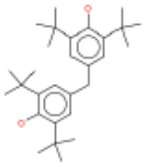
(Molecule 0) Reasoning on fragments/structural alerts - 1 of 4:

Fragment found: ER non-activity alert no. 8



Fragment related to non-activity for ER-mediated effect, defined by the SMARTS: c1(O)ccccc1C(C)C

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

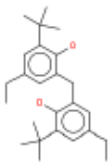


CAS: N.A.
Dataset id: 541 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)Cc2cc(c(O)c(c2)C(C)(C)C)C(C)(C)C)C(C)(C)C
Similarity: 0.759

Experimental value: NON-active
Predicted value: Possible active

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24

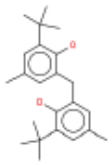
Alerts (not found in the target): ER possible activity alert no. 3



CAS: N.A.
Dataset id: 207 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CC)Cc2cc(cc(c2(O))C(C)(C)C)CC
Similarity: 0.743

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

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24



CAS: N.A.
Dataset id: 545 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)Cc2cc(cc(c2(O))C(C)(C)C)C
Similarity: 0.723

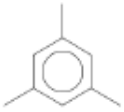
Experimental value: NON-active
Predicted value: NON-active

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

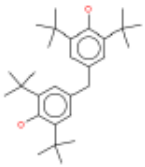
(Molecule 0) Reasoning on fragments/structural alerts - 2 of 4:

Fragment found: ER non-activity alert no. 24



Fragment related to non-activity for ER-mediated effect, defined by the SMARTS: c1c(C)cc(C)cc1C

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

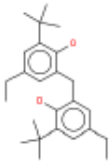


CAS: N.A.
Dataset id: 541 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)Cc2cc(c(O)c(c2)C(C)(C)C)C(C)(C)C)C(C)(C)C
Similarity: 0.759

Experimental value: NON-active
Predicted value: Possible active

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24

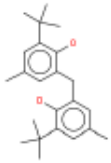
Alerts (not found in the target): ER possible activity alert no. 3



CAS: N.A.
Dataset id: 207 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CC)Cc2cc(cc(c2(O))C(C)(C)C)CC
Similarity: 0.743

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

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24



CAS: N.A.
Dataset id: 545 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)Cc2cc(cc(c2(O))C(C)(C)C)C
Similarity: 0.723

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

Alerts (found also in the target): ER non-activity alert no. 8; ER non-activity alert no. 24

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 3 of 4:

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(OCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCC
Similarity: 0.805

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: 0.804

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: 1160 (Training set)
SMILES: O=C(OCC(CC)CCCC)CCCCCCCCCCCCCCCCC
Similarity: 0.798

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

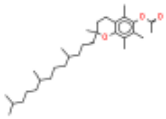
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 4 of 4:

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)

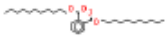
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 68 (Training set)
SMILES: O=C(Oc2c(c(c1OC(C)(CCc1c2C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C
Similarity: 0.831

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

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



CAS: N.A.
Dataset id: 1028 (Training set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.82

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

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

Alerts (not found in the target): ER non-activity alert no. 23

CAS: N.A.
Dataset id: 981 (Training set)
SMILES: O=C(OCCCCCCCCC)CCCCCCCCC(=O)OCCCCCCCCC
Similarity: 0.805

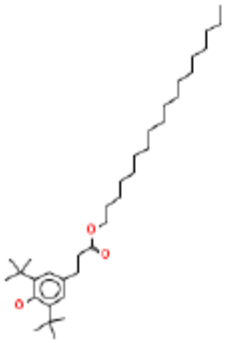
Experimental value: NON-active
Predicted value: NON-active

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

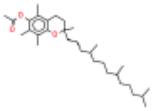


Prediction: Reliability:

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. 122, inactive

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
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. 122, 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: 52225-20-4
Dataset id: 1528 (Training set)
SMILES: CC(C)CCCC(C)CCCC(C)CCCC1(C)CCc2c(O1)c(C)c(C)c(OC(C)=O)c2C
Similarity: 0.831

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

Alerts (not found in the target): ER alert no. 32, inactive; ER alert no. 72, inactive

Compound #2

CAS: 122-62-3
Dataset id: 790 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.805

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

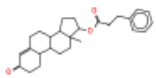
Alerts (not found in the target): ER alert no. 118, inactive

Compound #3

CAS: 2432-87-3
Dataset id: 1465 (Training set)
SMILES: CCCCCCCCOC(=O)CCCCCCCCC(=O)OCCCCCCCC
Similarity: 0.805

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

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



Compound #4

CAS: N.A.
Dataset id: 192 (Training set)
SMILES: CC12CCC3C4CCC(=O)C=C4CCC3C1CCC2OC(=O)CCc1ccccc1
Similarity: 0.801

Experimental value: Active
Predicted value: Active

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

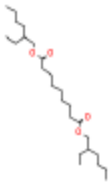
Compound #5

CAS: 22047-49-0
Dataset id: 1393 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCCCCCCCCCCC)CC
Similarity: 0.798

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

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

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



Compound #6

CAS: 103-24-2
Dataset id: 896 (Training set)
SMILES: CCCCC(COC(=O)CCCCCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.796

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

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.904
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.817
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.

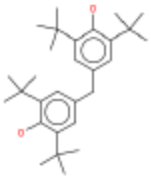
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: ER alert no. 122, inactive

Fragment related to ER inactivity (moderate reliability), defined by the SMARTS: CC(C)(C)c1cccc(c1)C(C)(C)C

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

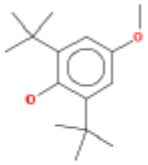


CAS: 118-82-1
Dataset id: 142 (Training set)
SMILES: CC(C)(C)c1cc(Cc2cc(c(O)c(c2)C(C)(C)C)C(C)(C)C)cc(c1O)C(C)(C)C
Similarity: 0.759

Experimental value: NON-active
Predicted value: Active

Alerts (found also in the target): ER alert no. 122, inactive

Alerts (not found in the target): ER alert no. 15, active; ER alert no. 134, active

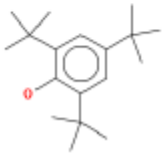


CAS: 489-01-0
Dataset id: 1253 (Training set)
SMILES: COc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Similarity: 0.709

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

Alerts (found also in the target): ER alert no. 122, inactive

Alerts (not found in the target): ER alert no. 55, inactive



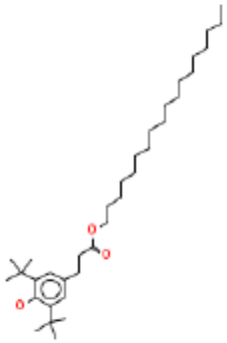
CAS: 732-26-3
Dataset id: 453 (Training set)
SMILES: CC(C)(C)c1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Similarity: 0.702

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

Alerts (found also in the target): ER alert no. 122, inactive

1. Prediction Summary

Prediction for compound Molecule 0

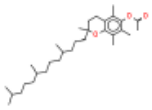


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Experimental value: -
Predicted TR alpha class: Inactive
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

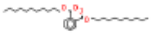
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 58-95-7
Dataset id: 3051 (Training set)
SMILES: O=C(Oc2c(c(c1OC(C)(CCc1c2C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C
Similarity: 0.831

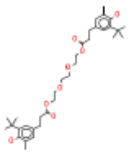
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 3648-20-2
Dataset id: 2837 (Training set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.82

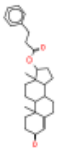
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 36443-68-2
Dataset id: 2907 (Training set)
SMILES:
O=C(OCCOCCOCCOC(=O)CCc1cc(c(O)c(c1)C(C)(C)C)C)CCc2cc(c(O)c(c2)C(C)(C)C)C
Similarity: 0.817

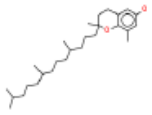
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: 1255-49-8
Dataset id: 2474 (Training set)
SMILES: O=C(OC2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CCc5ccccc5
Similarity: 0.814

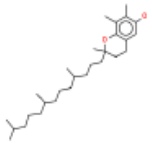
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 119-13-1
Dataset id: 4897 (Training set)
SMILES: Oc1cc(c2OC(C)(CCc2(c1))CCCC(C)CCCC(C)CCCC(C)C)C
Similarity: 0.814

Experimental value: Inactive
Predicted value: Inactive



Compound #6

CAS: 54-28-4
Dataset id: 5009 (Training set)
SMILES: Oc2cc1c(OC(C)(CC1)CCCC(C)CCCC(C)CCCC(C)C)c(c2C)C
Similarity: 0.812

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 = 0.823
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

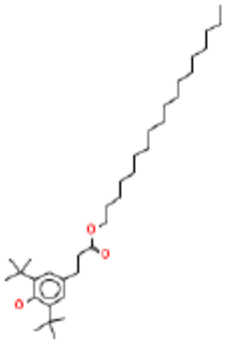
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

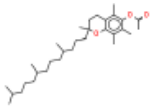


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Experimental value: -
Predicted TR beta class: Inactive
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

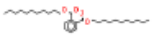
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 58-95-7
Dataset id: 3063 (Training set)
SMILES: O=C(Oc2c(c(c1OC(C)(CCc1c2C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C
Similarity: 0.831

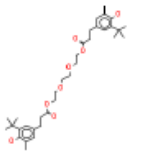
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 3648-20-2
Dataset id: 2849 (Training set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.82

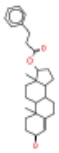
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 36443-68-2
Dataset id: 2919 (Training set)
SMILES:
O=C(OCCOCCOCCOC(=O)CCc1cc(c(O)c(c1)C(C)(C)C)C)CCc2cc(c(O)c(c2)C(C)(C)C)C
Similarity: 0.817

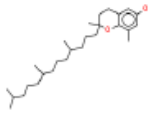
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: 1255-49-8
Dataset id: 2485 (Training set)
SMILES: O=C(OC2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CCc5ccccc5
Similarity: 0.814

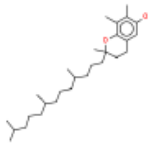
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 119-13-1
Dataset id: 4915 (Training set)
SMILES: Oc1cc(c2OC(C)(CCc2(c1))CCCC(C)CCCC(C)CCCC(C)C)C
Similarity: 0.814

Experimental value: Inactive
Predicted value: Inactive



Compound #6

CAS: 54-28-4
Dataset id: 5027 (Training set)
SMILES: Oc2cc1c(OC(C)(CC1)CCCC(C)CCCC(C)CCCC(C)C)c(c2C)C
Similarity: 0.812

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 = 0.823
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

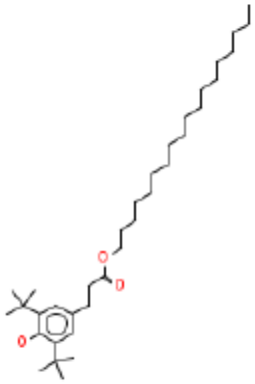
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

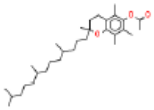


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCCCCCCCCCCCCCCCCCC)CCc1cc(c(O)c(c1)C(C)(C)C)C(C)(C)C
Experimental value: -
Aromatase activity: Inactive
Probability(Active Agonist): 0.164
Probability(Active Antagonist): 0.136
Probability(Inactive): 0.7
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

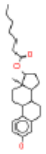
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 3188 (Training set)
SMILES: O=C(Oc2c(c(c1OC(C)(CCc1c2C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C
Similarity: 0.831

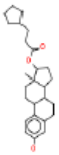
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: N.A.
Dataset id: 1629 (Test set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCCCCC
Similarity: 0.821

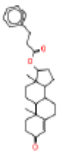
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: N.A.
Dataset id: 1628 (Training set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCC5CCCC5
Similarity: 0.815

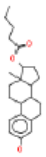
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: N.A.
Dataset id: 2940 (Training set)
SMILES: O=C(OC2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CCc5ccccc5
Similarity: 0.814

Experimental value: Active agonist
Predicted value: Inactive



Compound #5

CAS: N.A.
Dataset id: 1630 (Test set)
SMILES: O=C(OC2CCC3C4CCc1cc(O)ccc1C4(CCC23(C)))CCCC
Similarity: 0.805

Experimental value: Inactive
Predicted value: Inactive

Compound #6

CAS: N.A.
Dataset id: 1491 (Training set)
SMILES: O=C(OCCCCCCCC(C)C)CCCCC(=O)OCCCCCCCC(C)C
Similarity: 0.804

Experimental value: Inactive
Predicted value: Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.909
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.826
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

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

Symbols explanation:

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

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

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

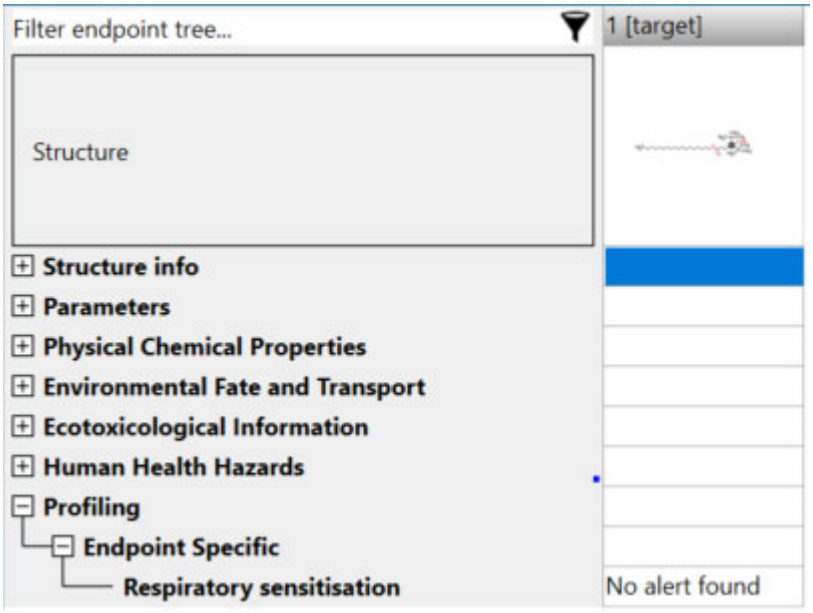
APPENDIX E: Danish QSAR Endocrine Activity Modeling for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		INC_OUT	NEG_IN	POS_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	NEG_IN	POS_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	POS_OUT	N/A
Androgen Receptor Inhibition (Human *in vitro*)	NEG	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	POS_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	POS_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	POS_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	POS_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			84917.34	308.5932	1197.833
- µM			159955.8	581.2861	2256.316
- 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			17178.95	442.4829	8.128236
- µM			32359.38	833.4894	15.31087

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	POS_IN	POS_OUT	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_IN	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	POS_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	POS_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	INC_OUT	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, impaired OH or NH2 group; Non binder, MW>500; Non binder, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	Non binder, impaired OH or NH2 group; 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 F: OECD Toolbox Respiratory Sensitization Results for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)



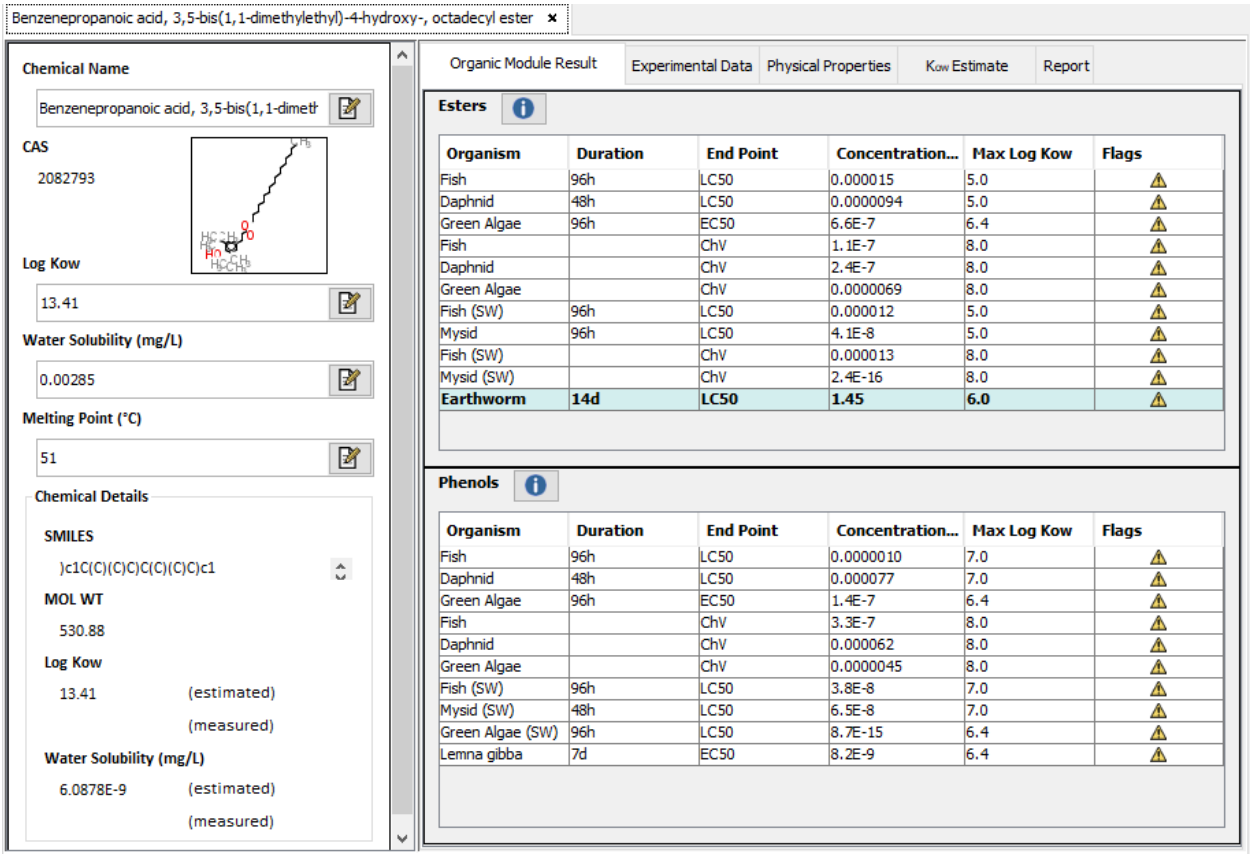
APPENDIX G: Danish QSAR Respiratory Sensitization Results for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

Irritation and Sensitization

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

DTU-developed models
**Based on commercial training set*

APPENDIX H: ECOSAR Modeling Results for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)



Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester

Chemical Name

Benzenepropanoic acid, 3,5-bis(1,1-dimeth

CAS

2082793

Log Kow

13.41

Water Solubility (mg/L)

0.00285

Melting Point (°C)

51

Chemical Details

SMILES

)c1C(C)(C)C)C(C)(C)C)c1

MOL WT

530.88

Log Kow

13.41 (estimated)

(measured)

Water Solubility (mg/L)

6.0878E-9 (estimated)

(measured)

Organic Module Result | Experimental Data | Physical Properties | Kow Estimate | Report

Esters

Organism	Duration	End Point	Concentration...	Max Log Kow	Flags
Fish	96h	LC50	0.000015	5.0	⚠
Daphnid	48h	LC50	0.0000094	5.0	⚠
Green Algae	96h	EC50	6.6E-7	6.4	⚠
Fish		ChV	1.1E-7	8.0	⚠
Daphnid		ChV	2.4E-7	8.0	⚠
Green Algae		ChV	0.0000069	8.0	⚠
Fish (SW)	96h	LC50	0.000012	5.0	⚠
Mysid	96h	LC50	4.1E-8	5.0	⚠
Fish (SW)		ChV	0.000013	8.0	⚠
Mysid (SW)		ChV	2.4E-16	8.0	⚠
Earthworm	**14d**	**LC50**	**1.45**	**6.0**	⚠

Phenols

Organism	Duration	End Point	Concentration...	Max Log Kow	Flags
Fish	96h	LC50	0.0000010	7.0	⚠
Daphnid	48h	LC50	0.000077	7.0	⚠
Green Algae	96h	EC50	1.4E-7	6.4	⚠
Fish		ChV	3.3E-7	8.0	⚠
Daphnid		ChV	0.000062	8.0	⚠
Green Algae		ChV	0.0000045	8.0	⚠
Fish (SW)	96h	LC50	3.8E-8	7.0	⚠
Mysid (SW)	48h	LC50	6.5E-8	7.0	⚠
Green Algae (SW)	96h	LC50	8.7E-15	6.4	⚠
Lemna gibba	7d	EC50	8.2E-9	6.4	⚠

APPENDIX I: EPI Suite™ Modeling Results for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate (CAS #2082-79-3)

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

CAS Number: 2082-79-3
SMILES : O=C(OCCCCCCCCCCCCCCCCCC)CCc(cc(c(O)c1C(C)(C)C)C(C)(C)C)c1
CHEM : Octadecyl 3-(3,5-di-tert-Butyl-4-hydroxyphenyl)propionate
MOL FOR: C35 H62 O3
MOL WT : 530.88
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : 323.00
Melting Point (deg C) : 52.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 0.00285
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 13.41

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 560.82 (Adapted Stein & Brown method)
Melting Pt (deg C): 241.01 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 9.72E-005 (Modified Grain method)
VP (Pa, 25 deg C) : 0.013 (Modified Grain method)
Subcooled liquid VP: 0.000172 mm Hg (25 deg C, Mod-Grain method)
: 0.023 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 3.895e-008
log Kow used: 13.41 (estimated)
melt pt used: 52.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 5.3088e-007 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.61E-006 atm-m3/mole (1.63E-001 Pa-m3/mole)
Group Method: 6.89E-007 atm-m3/mole (6.99E-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: 2.382E-002 atm-m3/mole (2.414E+003 Pa-m3/mole)
VP: 9.72E-005 mm Hg (source: MPBPVP)
WS: 0.00285 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 13.41 (KowWin est)
Log Kaw used: -4.182 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 17.592
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.5800
Biowin2 (Non-Linear Model) : 0.3619
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.0218 (months)
Biowin4 (Primary Survey Model) : 3.2441 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5138
Biowin6 (MITI Non-Linear Model): 0.0717
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.2994
Ready Biodegradability Prediction: NO

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.0229 Pa (0.000172 mm Hg)
Log Koa (Koawin est): 17.592
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.000131
Octanol/air (Koa) model: 9.59E+004
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.0047
Mackay model : 0.0104
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 43.1883 E-12 cm3/molecule-sec
Half-Life = 0.248 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 2.972 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.00753 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 3.721E+008 L/kg (MCI method)
Log Koc: 8.571 (MCI method)
Koc : 2.779E+008 L/kg (Kow method)
Log Koc: 8.444 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 3.040E-002 L/mol-sec
Kb Half-Life at pH 8: 263.865 days
Kb Half-Life at pH 7: 7.224 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.761 (BCF = 5.772 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 1.5246 days (HL = 33.46 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.048 (BCF = 0.8954)
Log BAF Arnot-Gobas method (upper trophic) = 0.473 (BAF = 2.975)
log Kow used: 13.41 (estimated)

Volatilization from Water:
Henry LC: 6.89E-007 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 1960 hours (81.68 days)
Half-Life from Model Lake : 2.158E+004 hours (899.1 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 0.153	5.94	1000
Water 13.7	1.44e+003	1000
Soil 85.9	2.88e+003	1000
Sediment 0.317	1.3e+004	0

Persistence Time: 1.66e+003 hr

Level III Fugacity Model: (MCI Method with Water percents)
Mass Amount (percent) Half-Life (hr) Emissions (kg/hr)

Air 0.153 5.94 1000
Water 13.7 1.44e+003 1000
water (1.06e-005)
biota (13.7)
suspended sediment (0.00593)
Soil 85.9 2.88e+003 1000
Sediment 0.317 1.3e+004 0
Persistence Time: 1.66e+003 hr

Level III Fugacity Model: (EQC Default)
Mass Amount Half-Life Emissions
(percent) (hr) (kg/hr)
Air 0.0537 5.94 1000
Water 1.39 1.44e+003 1000
water (8.1e-008)
biota (0.104)
suspended sediment (1.28)
Soil 30 2.88e+003 1000
Sediment 68.5 1.3e+004 0
Persistence Time: 4.74e+003 hr

APPENDIX J: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate. This GreenScreen® assessment has undergone several rounds of updates but the benchmark score remains 2.

Table 5: Change in GreenScreen® Benchmark™ for Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
January 23, 2012	BM-2	v. 1.2	New assessment
August 5, 2014	BM-2	v. 1.2	Updated with changes to the scores of the following endpoints: Endocrine activity: DG to *M* Single dose systemic toxicity: DG to **L** Single dose neurotoxicity: DG to **L** Repeated dose neurotoxicity: DG to **L** Eye irritation: *M* to **L** Chronic aquatic: *M* to **L**
February 20, 2019	BM-2	v. 1.4	Updated to version 1.4 criteria with changes to the scores of the following endpoints: Endocrine activity: *M* to DG Respiratory sensitization: DG to *L* Bioaccumulation: *vL* to *M*
August 11, 2021	BM-2	v. 1.4	Updated with changes to the scores of the following endpoints: Single dose neurotoxicity: **L** to *M* Persistence: *H* to *vH*
November 16, 2021	BM-2	v. 1.4	Minor updates without changing hazard scores

Licensed GreenScreen® Profilers

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v1.2) Evaluation Prepared by:

SIGNATURE BLOCK

Christopher E. Schlosser, M.F.S.
Associate Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v1.2) Evaluation QC'd by:

SIGNATURE BLOCK

Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v1.2) Evaluation Updated by:

SIGNATURE BLOCK

Zach Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v1.2) Evaluation QC'd by:

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Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v1.4) Evaluation Updated by:

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Brandon Reid, M.P.H.

Associate Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v 1.4) Evaluation QC'd by:

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Jennifer Rutkiewicz, Ph.D.
Senior Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v 1.4) Evaluation Updated by:

SIGNATURE BLOCK

Thea Clipson, Ph.D., M.S.
Toxicologist
ToxServices LLC

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)proprionate GreenScreen® (v 1.4) Evaluation QC'd by:

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