TRIMETHYL PENTANYL DIISOBUTYRATE

(CAS #6846-50-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: December 20, 2023

Expiration Date: December 20, 2028

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GreenScreen® Executive Summary for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

Trimethyl pentanyl diisobutyrate is a clear, colorless liquid intended for use as a low-viscosity plasticizer and non-phthalate alternative. It is a non-flammable secondary plasticizer that has higher hardness than phthalates, higher volatility, and higher water extractability. Trimethyl pentanyl diisobutyrate is used in the manufacturing of apparel, building materials, furniture, toys/sporting goods, traffic cones, vinyl compounds, inks, paints, and coatings.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)

No data gaps (DG) exist.

The GreenScreen® Benchmark Score for trimethyl pentanyl diisobutyrate has not changed over time. The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2016 and with this 2023 version 1.4 update.

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

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

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

GreenScreen® Hazard Summary Table for Trimethyl pentanyl diisobutyrate

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

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

GreenScreen® Chemical Assessment for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

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

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 27, 2015

Quality Control (v.1.2) Performed By:
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Title: Toxicologist
Organization: ToxServices LLC
Date: November 10, 2015

GreenScreen® Assessment (v.1.3) Updated By:
Name: Mouna Zachary, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: April 21, 2016

Quality Control (v.1.3) Performed By:
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Title: Toxicologist
Organization: ToxServices LLC
Date: April 22, 2016

GreenScreen® Assessment (v.1.4) Updated By:
Name: Margaret H. Rabotnick, M.P.H.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: October 18, 2023

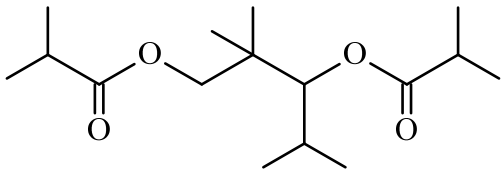
Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: December 20, 2023

Expiration Date: December 20, 2028[2]

Chemical Name: Trimethyl pentanyl diisobutyrate

CAS Number: 6846-50-0

Chemical Structure(s):



Also called: 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate; 2,2,4-trimethylpentane-1,3-diyl bis(2-methylpropanoate); TXIB; Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester; 2,2,4-Trimethylpentanediol-1,3-diisobutyrate; Isobutyric acid, 1-isopropyl-2,2-dimethyltrimethylene ester; 1-Isopropyl-2,2-dimethyltrimethylene diisobutyrate; 2,2,4-Trimethyl-1,3-pentanediol ester; [2,2,4-trimethyl-3-(2-methylpropanoyloxy)pentyl] 2-methylpropanoate; 1,3-Pentanediol, 2,2,4-trimethyl-, diisobutyrate; Kodaflex txib; 4KZA479DWQ (PubChem 2023)

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

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Trimethyl pentanyl diisobutyrate has a relatively complete toxicological dataset. The U.S. EPA's Analog Identification Methodology (AIM) and the PubChem related records search were used in an attempt to identify surrogates to fill the remaning data gaps, but no suitable surrogates with sufficient data were identified.

Identify Applications/Functional Uses:
1. Plasticizer
2. Viscosity Adjustor
3. Coalescing/Processing Aid
(PubChem 2023; U.S. CPSC 2018)

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

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E)

No data gaps (DG) exist.

Figure 1: GreenScreen® Hazard Summary Table for Trimethyl pentanyl diisobutyrate

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

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

Environmental Transformation Products
Trimethyl pentanyl diisobutyrate is readily biodegradable and thus is not expected to produce relevant environmental transformation products through this process. Trimethyl pentanyl diisobutyrate is most

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

often disposed of through incineration (OECD 1995). Based on its structure, potential combustion products are CO and CO_2. Because these are naturally occurring in the environment, they are not considered to be relevant transformation products. Trimethyl pentanyl diisobutyrate may undergo slow hydrolysis under basic conditions (OECD 1995, ECHA 2023). The EAWAG-BBD Pathway Prediction System (EAWAG 2014) identified 14 likely aerobic biodegradation products. Because none of these is an LT-1 chemical, the final Benchmark score is not modified.

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]
End of life, in use	Hydrolysis; Biodegradation	2-methylpropanoic acid	79-31-2	Y	Y	LT-UNK
End of life, in use	Hydrolysis; Biodegradation	(3-hydroxy-1-isopropyl-2,2-dimethyl-propyl) 2-methylpropanoate	18491-15-1	Y	Y	Not in Pharos database
End of life, in use	Hydrolysis; Biodegradation	(3-hydroxy-2,2,4-trimethyl-pentyl) 2-methylpropanoate	25265-77-4	Y	Y	LT-UNK
End of life, in use	Hydrolysis; Biodegradation	2,2,4-trimethylpentane-1,3-diol	144-19-4	Y	Y	LT-UNK
End of life, in use	Biodegradation	(1S)-1-isopropyl-2,2-dimethyl-3-oxo-propyl] 2-methylpropanoate	No CAS#	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	1-hydroxy-2,2,4-trimethyl-pentan-3-one	15094-30-0	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	3-hydroxy-2,2,4-trimethyl-pentanal	918-79-6	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	(3S)-2,2,4-trimethyl-3-(2-methylpropanoyloxy)pentanoate	No CAS#	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	2,2,4-trimethyl-3-oxo-pentanal	1482-01-5	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	3-hydroxy-2,2,4-trimethyl-pentanoate	35763-45-2	Y	Y	Not in Pharos database
End of life, in use	Biodegradation	2,2,4-trimethyl-3-oxo-pentanoate	No CAS#	Y	Y	Not in Pharos database

Introduction

Trimethyl pentanyl diisobutyrate is a clear, colorless liquid intended for use as a low-viscosity plasticizer and non-phthalate alternative (U.S. CPSC 2018). It is a non-flammable secondary plasticizer that has higher hardness than phthalates, higher volatility, and higher water extractability (U.S. CPSC 2018). Trimethyl pentanyl diisobutyrate is used in the manufacturing of apparel, building materials, furniture, toys/sporting goods, traffic cones, vinyl compounds, inks, paints, and coatings (U.S. CPSC 2018).

[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 2023) 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).

ToxServices assessed trimethyl pentanyl diisobutyrate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

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

Trimethyl pentanyl diisobutyrate is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[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 scores for each human health and environmental endpoint. The output for trimethyl pentanyl diisobutyrate can be found in Appendix C.

- Trimethyl pentanyl diisobutyrate is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Trimethyl pentanyl diisobutyrate is not listed on the U.S. DOT list.
- Trimethyl pentanyl diisobutyrate is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters
    - Environment Canada – CEPA Domestic Substances List (DSL) – Inherently Toxic in the Environment (iTE)

Hazard Statement and Occupational Control

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

Table 2: GHS H Statements for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0) (ECHA 2023)

H Statement	H Statement Details
H361	Suspected of damaging fertility or the unborn child
H412	Harmful to aquatic life with long lasting effects

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

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Safety glasses, protective clothing, respiratory with ABEK filter, and prevent contact with skin	Sigma-Aldrich 2023	None identified	N/A

Physicochemical Properties of Trimethyl pentanyl diisobutyrate

Trimethyl pentanyl diisobutyrate is a clear, colorless liquid at standard temperature and pressure. It has poor solubility in water and is semi volatile. Its log K_{ow} of 4.91 suggests it may bioaccumulate.

Table 4: Physical and Chemical Properties of Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)		
Property	**Value**	**Reference**
Molecular formula	$C_{16}H_{30}O_4$	PubChem 2023
SMILES Notation	CC(C)C(C(C)(C)COC(=O)C(C)C)OC(=O)C(C)C	PubChem 2023
Molecular weight	286.41 g/mol	PubChem 2023
Physical state	Liquid	ECHA 2023
Appearance	Clear, colorless liquid with slight odor	ECHA 2023
Melting point	-70°C -94°C	ECHA 2023 PubChem 2023
Boiling point	281°C 380°C	ECHA 2023 PubChem 2023
Vapor pressure	$1.13x10^{-2}$ mmHg at 25°C $8.5x10^{-3}$ mmHg	ECHA 2023 PubChem 2023
Water solubility	13 mg/L at 25°C	ECHA 2023
Dissociation constant	Not applicable	
Density/specific gravity	0.94 g/mL at 20°C	ECHA 2023
Partition coefficient	Log Kow = 4.91 at 25°C (estimated)	ECHA 2023

Toxicokinetics

The available toxicokinetic and metabolic profile of trimethyl pentanyl diisobutyrate indicates that following oral exposure, the substance is rapidly absorbed, metabolized, and eliminated in the urine and feces.

Absorption: Rats received approximately 186.7 mg/kg bw of [14]C-labeled 2,2,4-trimethylpentane-1,3-diol (TMPD), a potential metabolite of trimethyl pentanyl diisobutyrate, and were sacrificed on day 6. TMPD was rapidly absorbed where greater than 88% of the administered dose was recovered in the urine within 48 hours of dosing and 2% was recovered in feces.

Distribution: Adult male rats administered a single gavage dose of 256 mg/kg of undiluted [14]C-labeled trimethyl pentanyl diisobutyrate showed only 2.9% of the dose retained in organs and carcass at day 8. The amount found in the rat body decreased to 0.99% by day 15 and only 0.7% of the dose was present in the carcass at day 22 (ECHA 2023).

Metabolism: The metabolic fate of trimethyl pentanyl diisobutyrate involves some non-absorption and partial hydrolysis in the gut based on the occurrence of both [14]C-labeled trimethyl pentanyl diisobutyrate and a mono-isobutyrate ester of TMPD in the feces. The major metabolic pathway for TMPD following ingestion was by O-glucuronide formation (75%) followed by smaller proportions of the dose eliminated as the oxidation product 3-hydroxy-2,2,4-trimethylvaleric acid and its glucuronide (7%), unchanged TMPD (1.5%), and 2-methylmalonic acid (4%). Approximately half of the absorbed dose of orally administered [14]C-labeled trimethyl pentanyl diisobutyrate was accounted for as products of complete hydrolysis to the parent glycol TMPD (ECHA 2023).

Elimination: Adult male rats were administered a single gavage dose of 256 mg/kg of undiluted radiolabeled trimethyl pentanyl diisobutyrate and urine, feces, expired air were collected for up to 22 days post treatment. The test material was rapidly absorbed, metabolized, and excreted with at least 95% of the administered dose collected in the urine (47.3-72.5%), feces (14.45-31.20%), and cage washings (11.9-16.5%) within a few days of dosing. Urinary radioactivity was eliminated within 72 hours and fecal elimination was complete by day 7 post treatment. No radioactivity was detected in expired air (ECHA 2023).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Trimethyl pentanyl diisobutyrate was assigned a score of Low for carcinogenicity based on the weight of evidence from modeling results. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative for carcinogenicity (CPA 2018b). The confidence in the score is low as it is based on modeling and no measured data were identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- VEGA 2023
  - If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
    - CAESAR v2.1.10 model predicts trimethyl pentanyl diisobutyrate to be a non-carcinogen with low confidence. The global ADI is 0.324, indicating that the prediction is not reliable and is, therefore, disregarded (Appendix D).
    - ISS v1.0.3 model predicts trimethyl pentanyl diisobutyrate to be a carcinogen with moderate confidence. The ADI is 0.763, indicating that the prediction is reliable. However, ToxServices notes that the low concordance index (0.516) reduces reliability in the prediction, and most of the structurally similar chemicals with positive experimental values and predictions in the training set also contain structural alerts not present in the target compound; therefore, the reliability of this model is low (Appendix D).
    - IRFMN/ISSCAN-CGX v1.0.2 model predicts trimethyl pentanyl diisobutyrate to be a carcinogen with moderate confidence. The ADI is 0.794, indicating that the prediction is reliable (Appendix D).

        - IRFMN/Antares v1.0.2 model predicts trimethyl pentanyl diisobutyrate to be a possible non-carcinogen with low confidence. The ADI is 0.530, indicating that the prediction is not reliable and is, therefore, disregarded (Appendix D).
        - IRFMN oral classification v1.0.1 predicts trimethyl pentanyl diisobutyrate is a non-carcinogen with moderate confidence. The ADI is 0.625, indicating that the prediction not reliable and is, therefore, disregarded (Appendix D).
        - IRFMN inhalation classification v1.0.1 predicts trimethyl pentanyl diisobutyrate is a non-carcinogen with high confidence. The ADI is 0.899, indicating that the prediction is reliable (Appendix D).
- DTU 2023
    - Danish (Q)SAR Database for the CAS number 6846-50-0 reports that trimethyl pentanyl diisobutyrate is in the domains of the CASE Ultra FDA RCA cancer models for the female rat, rat, male mouse, female mouse, and mouse and it is predicted to be negative by all these models. It is out of the domains of CASE Ultra FDA RCA cancer models for the male rat and rodent. Trimethyl pentanyl diisobutyrate is in the domains of the Leadscope FDA RCA cancer models for the male rat, male mouse, female mouse, mouse, and rodent, which predict that it is positive, negative, negative, negative, and negative, respectively. It is out of the domains of Leadscope FDA RCA cancer models for female rat and rat. Regarding the liver specific cancer in rat or mouse model, the Battery, CASE Ultra, and Leadscope predictions are negative and the compound is in the applicability domain; trimethyl pentanyl diisobutyrate is predicted as positive and the compound is in the applicability domain of the SciQSAR model (Appendix E).
- U.S. EPA 2021
    - Attempts to model the carcinogenic potential of trimethyl pentanyl diisobutyrate using OncoLogic (v9.0) were made; however, this chemical does not fit into any of the chemical classes evaluated by OncoLogic. Therefore, trimethyl pentanyl diisobutyrate cannot be evaluated using OncoLogic.
- Toxtree 2018
    - Trimethyl pentanyl diisobutyrate contains a structural alert for nongenotoxic carcinogenicity; substituted n-alkylcarboxylic acids (Appendix F).
        - Chemicals with this structural alert are potential nongenotoxic carcinogens due to peroxisome proliferation (OECD 2023)
- Based on the weight of evidence, a score of Low was assigned. VEGA models produced mixed results. Of the two models with reliable results, one, the ISS model (also predicted by Toxtree), predicted trimethyl pentanyl diisobutyrate to be a carcinogen with moderate confidence. The remaining reliable model in VEGA predicted trimethyl pentanyl diisobutyrate to be a non-carcinogen with high confidence. The results from Danish (Q)SAR models were predominately negative. It was in the domain for five of seven of the E Ultra FDA RCA cancer models, which all predicted it to be negative, as well as in the domain for five of the seven Leadscope FDA RCA cancer models, four of which predicted it to be negative. Regarding the liver specific cancer in rat or mouse model, it was in the applicability domain for the model battery and the prediction was negative in three out of four models. OncoLogic could not be used to predict the carcinogenic potential of trimethyl pentanyl diisobutyrate as it is not included in any of the chemical classes supported by the program. According to the ISS model reported by Toxtree and VEGA, trimethyl pentanyl diisobutyrate does contain an alert for non-genotoxic carcinogenicity; however, the specific structural alert, substituted n-alkylcarboxylic acids, is related to its potential to cause peroxisome proliferation (OECD 2023). Peroxisomal proliferation mechanism in the liver has not been found in humans for chemicals known to cause these effects in the liver of rodents (IARC 1994, Youssef and

Badr 2011). Therefore, the relevance of this structural alert to humans is low. In addition, the conclusions from the ECHA dossier indicate it is not likely to be carcinogenic as it is not mutagenic (see genotoxicity section below) and no (histo)pathological alterations indicative for a potential carcinogenic effect were observed in the available repeated dose toxicity studies (ECHA 2023). Collectively, the weight of evidence from predominantly negative modeling results supports a score of Low.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for mutagenicity/genotoxicity based on negative results in several *in vitro* bacterial and mammalian cell mutagenicity and mammalian cell clastogenicity 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 because it is based on consistently negative results in several high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *In vitro*: Trimethyl pentanyl diisobutyrate (purity not specified) was negative in a mammalian cell gene mutation assay that was conducted according to OECD Guideline 476. Chinese hamster Ovary (CHO) cells were exposed to concentrations of 10, 15, 20, 25, 30, and 40 µg/mL without metabolic activation, and 250, 500, 750, 1,000, 1,500, 2,000 µg/mL with metabolic activation. Excessive cytotoxicity was observed in a pretest at concentrations of 62.2 µg/mL and above without metabolic activation, and no cytotoxicity was observed with metabolic activation. There were no increases in revertant colonies at any dose. Positive, negative, and vehicle controls were considered valid (Klimisch score of 1, reliable without restriction).
  - *In vitro*: Trimethyl pentanyl diisobutyrate (purity not specified) was negative in a GLP-compliant bacterial mutagenicity assay that was conducted according to EU Method B.13/14 in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* WP2 uvr A pKM 101 tested at concentrations of 100, 250, 500, 1,000, 2,500, and 5,000 µg/plate with and without metabolic activation. Cytotoxicity was observed in TA100 at 1,000 µg/plate and above with but not without metabolic activation metabolic activation, but no cytotoxicity was observed in WP2 *uvr* A. There were no increases in revertant colonies. Positive and vehicle controls were considered valid (Klimisch score of 1, reliable without restriction).
  - *In vitro*: Trimethyl pentanyl diisobutyrate (purity not specified) was negative in a GLP-compliant *in vitro* mammalian cell chromosome aberration test that was similar to OECD Guideline 473/OPPTS 870.5375/EU Method B.10 in CHO cells. In the initial assay, cells were treated at concentrations of 12.5, 17.5, 25.0, 37.5, 50.0 and 100 µg/mL without metabolic activation and 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1,000, 2,000, and 4,000 µg/mL with metabolic activation. In the confirmatory assay, cells were treated with concentrations of 6.25, 12.5, 17.5, 25.0, 37.5, and 50.0 µg/mL without metabolic activation and 125, 175, 250, 350, 500, and 1,000 µg/mL with metabolic activation. In the range finding study, complete cytotoxicity was observed at concentrations of 133 µg/mL and above without metabolic activation and 400 µg/mL and above with metabolic activation. There was no evidence of induction of chromosomal aberrations. Positive and vehicle controls were considered valid (Klimisch score of 1, reliable without

restriction).

- OECD 1995; U.S. CPSC 2011, 2018
    - Trimethyl pentanyl diisobutyrate (99.7% purity) was negative in a GLP-compliant bacterial mutagenicity assay that was conducted according to Japanese Guidelines for Screening Mutagenicity testing of chemicals in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *E. coli* uvrA when tested at concentrations of 0, 312.5, 625, 1,250, 2,500 and 5,000 µg/plate. Cytotoxicity was observed at 5,000 µg/plate with and without metabolic activation, and precipitation was observed at 1,250 µg/plate. There were no increases in revertant colonies in either of two replicates. No additional details were provided.
    - Trimethyl pentanyl diisobutyrate (99.7% purity) was negative in a GLP-compliant *in vitro* mammalian cell chromosome aberration assay that was conducted according to Japanese Guidelines for Screening Mutagenicity testing of chemicals in Chinese Hamster lung (CHL) cells when tested at concentrations up to 0.04 mg/L with and without metabolic activation. Cytotoxicity was observed at 0.018 mg/L with metabolic activation and 0.04 mg/L without metabolic activation. There were no increases in structural chromosomal aberrations or polyploidy with either continuous or short-term treatment. No additional details were provided.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Moderate for reproductive toxicity based on effects on sperm count and total number of implants in an oral reproductive and developmental toxicity screening study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animals (CPA 2018b). The confidence in the score is low as the toxicological significance of effects on sperm counts is uncertain and effects on number of implants occurred at a high dose in the presence of mild to moderate clinical toxicity and cannot conclusively be attributed to a reproductive effect.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; OECD 1995; U.S. CPSC 2011, 2018
    - In a GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test conducted according to OECD Guideline 422, Crj:CD(SD) rats (12/sex/dose) were administered trimethyl pentanyl diisobutyrate (purity 99.7%) via gavage at doses of 0, 30, 150, or 750 mg/kg/day for 44 days beginning 14 days prior to mating (males) or from 14 days prior to mating through lactation day 3 (females). Slight decrease in body weight was measured in high dose group males. The mean estrous cycle length of females in the high dose group was statistically significantly shorter than that of the control group, but all cycle lengths were within the range of historical controls for the testing facility. No differences in copulation indices were observed. Gestation period, numbers of corpora lutea, implantation sites, pups born, live pups born, sex ratio, number of live pups on day 4 after birth, and number of stillborns were similar across all groups. No significant differences in gestation index, implantation index, delivery index, live birth index, or viability at day 4 after birth were reported. No effects were reported on the weights or histopathology of reproductive organs. OECD and ECHA identified a reproductive toxicity NOAEL of 750 mg/kg/day; which was the highest dose tested (Klimisch score of 2, reliable with restriction).
- ECHA 2023; U.S. CPSC 2011, 2018
    - In a GLP-compliant reproductive and developmental toxicity screening study conducted

according to OECD Guideline 421/ EPA OPPTS 870.3550, Sprague-Dawley rats (12/sex/dose) were administered trimethyl pentanyl diisobutyrate (99.0% purity) in the diet at concentrations of 0, 1.5, 4.5, or 15.0 mg/g food (reported to be equivalent to 0, 91, 276 and 905 mg/kg/day for males and 0, 120, 359, and 1,135 mg/kg/day for females). Males were treated continuously for a total of 51 days beginning on the first day of a 14 day premating period, and females were treated continuously for a total of 40-51 days beginning on the first day of the premating period. Females were sacrificed on lactation day 4 or 5, or on gestation day 23 if they did not deliver a litter. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, testes and epididymis weights, ovarian and uterine content, gross pathology, and histopathology. Reproductive indices (fertility index, gestation duration and post-implantation loss) were also measured. Offspring were evaluated for survival, mean litter size, sex ratio, body weight, and external and internal abnormalities. Minimal to moderate clinical signs of toxicity were observed in the mid and high dose groups. Mean body weights were significantly reduced in females of the high dose group on gestation day 20. Mean body weight gain was reduced in both sexes on day 7 of the premating period in the high dose group (reductions of 27% in males and 48% in females); mean feed consumption and feed utilization in males and feed consumption in females were also reduced in these groups. Mean absolute and/or relative sperm counts were reduced in the low and high dose groups, and the mean epididymal sperm counts were reduced in all groups. Authors noted that the reduction in epididymal sperm counts did not exhibit a dose response and may be due to high control values. Authors also noted that the reduction in the number of sperm per tissue and weight-adjusted testicular spermatid heads occurred in the absence of effects on epididymal sperm counts and therefore the significance is unclear. There were no effects on sperm motility. There was a statistically significant decrease in the total number of implants in the high dose group. There were no effects on pre and post-implantation loss, reproductive performance, fertility index, fecundity index, precoital index, or gestation duration. There were also no treatment-related effects on histopathology of the weights or histopathology of the ovaries, right testes, or epididymis. Authors reported a reproductive toxicity NOAEL of 276 mg/kg/day for males and 359 mg/kg/day for females and LOAEL of 905 mg/kg/day for males and 1,135 mg/kg/day for females, based on the decrease in total number of implants (Klimisch score of 1, reliable without restriction).

- Based on the weight of evidence, a score of Moderate was assigned. In one reproductive toxicity screening study in rats, reductions in sperm counts were observed in all dose groups, and a reduction in total number of implants was observed in the high dose group. Although authors reported that the toxicological significance of effects on sperm counts is uncertain and effects on number of implants occurred at a high dose in the presence of mild to moderate clinical toxicity, ToxServices considered these effects to be limited or marginal evidence of reproductive toxicity and assigned a Moderate.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Trimethyl pentanyl diisobutyrate was assigned a score of Moderate for developmental toxicity based on effects on pup body weight, skeletal variations, and pups alive in oral prenatal developmental toxicity and reproductive and developmental toxicity screening studies in rats and rabbits. 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 low as it is not possible to conclusively determine if effects represent selective developmental toxicity.

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

  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, female New Zealand White rabbits (22/dose) were administered trimethyl pentanyl diisobutyrate (99.2% purity) via oral gavage at concentrations of 0, 100, 300, or 1,000 mg/kg/day on gestation days 1 to 28. No mortality or clinical signs of toxicity were described as treatment-related. No treatment-related effects on body weight or weight gain were reported. A significant reduction in food consumption in high dose animals was reported through gestation day 24, but resolved thereafter. No treatment-related effects on organ weights or gross pathological findings were reported. No treatment-related effects on number of abortions, litter loss, pregnancy duration, number of pregnant animals, and number of deceased offspring were reported. The mean numbers of resorptions and post-implantation losses were significantly higher in the high dose group animals. No effects on fetal body weight, sex ratio, litter size, postnatal survival, external or visceral malformations were reported. An increase in the incidence of short supernumerary cervical ribs was reported in all dose groups but these were within the range of historical controls. Slight delayed ossification of the 1st to 4th or 6th sternebrae was observed in mid and high dose group animals but these findings were also within the range of historical controls. The REACH dossier authors assigned a developmental NOAEL of 300 mg/kg/day (LOAEL of 1,000 mg/kg/day) based on the increased post-implantation loss and number of resorptions in high dose group animals (Klimisch score of 1, reliable without restriction).
- U.S. CPSC 2011, 2018
  - In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, female Sprague-Dawley rats (25/dose) were administered trimethyl pentanyl diisobutyrate (98.95% purity) in the diet at concentrations of 0, 0.15, 0.45, or 1.5% (reported to be equivalent to 0, 118, 343, and 1,077 mg/kg/day) on gestation days 1-20 and were sacrificed on gestation day 20. Maternal body weight gain was significantly reduced in the high dose group. One female from each of the exposed groups was not gravid. There were no effects on corpora lutea, implantation sites, viable fetuses, or early/late resorptions. There was a dose dependent decrease in male, female, and combined fetal weight in the high dose group that was significant compared to the control group but fell within the range of historical control data. No external or visceral malformations were observed. Bent scapula was observed in one fetus in the mid dose group and 4 fetuses in the high dose group. There was a statistically significant increase in the mean proportion of unossified sternebrae in the high dose group, and a non-statistically significant increase in the mean litter proportion of bent ribs. Authors considered the effects to be representative of skeletal variations rather than malformations. Authors reported a developmental toxicity NOAEL of 343 mg/kg/day and LOAEL of 1,077 mg/kg/day based on reductions in fetal body weight at the high dose.
- ECHA 2023; U.S. CPSC 2011, 2018
  - In the previously described GLP-compliant reproductive and developmental toxicity screening study that was conducted according to OECD Guideline 421/ EPA OPPTS 870.3550, Sprague-Dawley rats (12/sex/dose) were administered trimethyl pentanyl diisobutyrate (99.0% purity) in the diet at concentrations of 0, 1.5, 4.5, or 15.0 mg/g food (reported to be equivalent to 0, 91, 276, and 905 mg/kg/day for males and 0, 120, 359, and 1,135 mg/kg/day for females). Males were treated continuously for a total of 51 days beginning on the first day of a 14 day premating period, and females were treated continuously for a total of 40-51 days beginning on the first day of the premating period. Females were sacrificed on lactation day 4 or 5, or on gestation day 23 if they did not deliver

a litter. Minimal to moderate clinical signs of toxicity were observed in the mid and high dose groups. Mean body weights were significantly reduced females of the high dose group on gestation day 20. Mean body weight gain was reduced in both sexes on day 7 of the premating period in the high dose group (reductions of 27% in males and 48% in females); mean feed consumption and feed utilization in males and feed consumption in females were also reduced in these groups. Mean litter weights were decreased by 19-20% on postnatal days 0 and 4. The number of live pups on postnatal day 4 was reduced in the high dose group, and the mean number of pups dying on postnatal days 0-4 was increased in the mid dose group. There were no effects on pre and post-implantation loss, live and dead pups on postnatal day 0, percentage of male and female pups, mean pup body weight, or pup body weight change. Authors reported a developmental toxicity NOAEL of 276 mg/kg/day for males and 359 mg/kg/day for females (LOAEL of 905 mg/kg/day for males and 1,135 mg/kg/day for females) (Klimisch score of 1, reliable without restriction).

- ECHA 2023; OECD 1995; U.S. CPSC 2011, 2018
    - In the previously described GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422 in Crj:CD(SD) rats, animals (12/sex/dose) were administered trimethyl pentanyl diisobutyrate (99.7%) via gavage at doses of 0, 30, 150, or 750 mg/kg/day for 44 days beginning 14 days prior to mating (males) or from 14 days prior to mating through lactation day 3 (females). There were no treatment-related effects on pup weight or necropsy findings on postnatal day 4, and OECD and ECHA identified a NOAEL of 750 mg/kg/day (Klimisch score of 2, reliable with restriction).
- Based on the weight of evidence, a score of Moderate was assigned. An oral (gavage) reproductive and developmental toxicity screening study in rats showed no effects on developmental parameters at up to 750 mg/kg/day. However, in dietary studies in rats, one prenatal developmental toxicity study reported effects on pup body weight and skeletal variations with a NOAEL of 343 mg/kg/day and LOAEL of 1,077 mg/kg/day, another prenatal developmental toxicity study reported increased post-implantation loss and resorptions in rabbits exposed to 1,000 mg/kg/day, and a reproductive and developmental toxicity screening study reported effects on litter weight on postnatal days 0 and 4 and pups alive on postnatal day 4 with a LOAEL and NOAEL of 905 mg/kg/day and 276 mg/kg/day and 1,135 mg/kg/day and 359 mg/kg/day for males and females, respectively. Although these effects were only seen at doses approximately equivalent to the limit dose of 1,000 mg/kg/day and in the presence of mild maternal toxicity, due to the wide spacing of the doses it is not possible to determine if effects would have been seen at lower doses or in the absence of maternal toxicity. Furthermore, effects on pup litter weight and pups alive on postnatal day 4 indicate a potential effect on the pups themselves rather than a gestational effect. Therefore, a conservative score of Moderate was assigned, but confidence is reduced because it is not possible to conclusively determine if effects represent developmental toxicity that occurs independent of maternal toxicity.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Moderate for endocrine activity based on listing as a TEDX Potential Endocrine Disruptor and positive experimental results for inhibition of hormone binding to androgen and estrogen receptors. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when listed as a TEDX Potential Endocrine Disruptor (CPA 2018b). The confidence in the score is low as there is limited experimental evidence and modeling with conflicting results.

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

  - *Screening:* TEDX – Potential Endocrine Disruptors: Potential Endocrine Disruptor.
- Satoh et al. 2008. (TEDX Evidence for Supporting This Chemical as an Endocrine Disruptor)
  - Trimethyl pentanyl diisobutyrate (1,000 μM) showed partial inhibition of testosterone binding to androgen receptor in an AR binding assay.
  - Trimethyl pentanyl diisobutyrate (1,000 μM) showed partial inhibition of 17β-Estradiol (E_2) binding to estrogen receptor α.
  - Trimethyl pentanyl diisobutyrate (up to 100 μM) did not significantly affect the luciferase activity of the AR-EcoScreen cells, indicating it is not an androgen receptor agonist or antagonist.
  - Trimethyl pentanyl diisobutyrate (up to 100 μM) did not significantly affect the E_2 luciferase activity of the MVLN cells, indicating it is not an estrogen receptor agonist or antagonist.
- U.S. EPA 2023b
  - Trimethyl pentanyl diisobutyrate was active in 4/21 estrogen receptor (ER) assays, 0/14 androgen receptor (AR) assays, 1/3 steroidogenesis assays, and 1/12 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the ^{2}1st Century.
- DTU 2023
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models (Appendix H):
    - Trimethyl pentanyl diisobutyrate is predicted to be negative for estrogen receptor α binding (full training set and balanced training set, human *in vitro*) in Battery, CASE Ultra, Leadscope, and SciQSAR. Negative for estrogen receptor α activation (human *in vitro*) in Battery, CASE Ultra, Leadscope, and SciQSAR. Negative for estrogen receptor activation, CERAPP data (*in vitro*), in Leadscope.
    - Trimethyl pentanyl diisobutyrate is predicted to be negative for androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by the Battery, CASE Ultra, Leadscope, and SciQSAR models. Also predicted to be negative for androgen receptor binding, inhibition, and activation by Leadscope.
    - Trimethyl pentanyl diisobutyrate is predicted to be negative for thyroperoxidase (TPO) inhibition (QSAR1 and QSAR2, rat *in vitro*) by Leadscope.
    - All other predictions (PPAR inhibition, RAR inhibition, AhR activation, PXR activation, CYP3A4 induction, CAR activation/inhibition) were within domain and predicted to be negative by Leadscope.
- VEGA 2023
  - If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016) (Appendix I).
    - The VEGA estrogen receptor-mediated effect IRFMN-CERAPP v1.0.1 model predicts trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
      - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
    - The VEGA estrogen receptor relative binding affinity IRFMN model predicts trimethyl pentanyl diisobutyrate to be inactive with moderate confidence. The global ADI is 0.759, indicating that the prediction is reliable.

  - The VEGA androgen receptor-mediated effect (IRFMN/COMPARA) model predicts trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
    - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
  - The VEGA thyroid receptor alpha effect (NRMEA v1.0.1) model predicts trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
    - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
  - The VEGA thyroid receptor beta effect (NRMEA v1.0.1) model trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
    - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
  - The VEGA glucocorticoid receptor (Oberon v1.0.0) model predicts trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
    - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
  - The VEGA thyroperoxidase inhibitory activity (Oberon v1.0.1) model predicts trimethyl pentanyl diisobutyrate to be inactive with high confidence. The reliability of this prediction is high based on a global ADI of 1.
    - The ADI of 1 is stated to be the result of experimental data, but ToxServices was not able to identify the data supporting this result.
  - The VEGA endocrine disruptor activity screening (IRFMN v1.0.0) model predicts trimethyl pentanyl diisobutyrate to be inactive with no confidence rating. The reliability of this prediction is low based on the model's inability to perform an applicability domain check; therefore, this prediction is disregarded.
- Based on the weight of evidence, a score of Moderate was assigned. Trimethyl pentanyl diisobutyrate is listed as a TEDX Potential Endocrine Disruptor. Available modeling in Danish QSAR and VEGA predict that trimethyl pentanyl diisobutyrate is inactive in estrogen binding/activity, androgen effects, thyroid alpha/beta effects, glucocorticoid receptor activity, and thyroperoxidase inhibition. However, U.S. EPA's EDSP showed some positive activity in a small number of ER, steroidogenesis, and thyroid receptor assays. Trimethyl pentanyl diisobutyrate's screening listing as a potential endocrine disruptor is supported by very limited evidence of an inhibitory effect on AR and ERα binding in the presence of endogenous hormones. Overall, the available evidence suggests that the potential for endocrine activity cannot be ruled out, and ToxServices assigned a Moderate score 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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for acute toxicity based on its oral and dermal LD_{50} values being greater than 2,000 mg/kg/day. GreenScreen® criteria classify chemicals as a

Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg, and inhalation LC_{50} is greater than 20 mg/L/4h (vapor) or they are classified to GHS Category 5 (CPA 2018b). The confidence in the score is high because it is based on experimental data from several reliable studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; ECB 2000; OECD 1995; U.S. CPSC 2011, 2018
  - *Oral*: LD_{50} (rat, sex and strain not reported) = 3,200 mg/kg
  - *Dermal*: LD_{50} (Hartley guinea pig, sex not specified) > 18,530 mg/kg
  - *Inhalation*: LC_{50} (rat, sex and strain not specified) > 5.3 mg/L/6h (vapor)
- ECHA 2023; ECB 2000; U.S. CPSC 2011, 2018
  - *Oral*: LD_{50} (mouse, sex and strain not reported) > 6,400 mg/kg
- ECHA 2023; U.S. CPSC 2011, 2018
  - *Dermal*: LD_{50} (male and female New Zealand White rabbit) > 2,000 mg/kg (GLP, OECD 402)
  - *Inhalation*: LC_{50} (rat, sex and strain not specified) > 0.12 mg/L/6h (vapor)
- ECHA 2023
  - *Oral*: LD_{50} (rat, female Wistar) > 2,000 mg/kg (GLP, OECD 425)

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for systemic toxicity (single dose) based on a lack of effects on clinical signs, body weight, and gross pathology in acute oral and dermal toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when there is no evidence of systemic toxicity below the guidance value of 2,000 mg/kg in acute oral and dermal studies (CPA 2018b). The confidence in the score is high as it is based on experimental data from several reliable studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; ECB 2000; OECD 1995; U.S. CPSC 2011, 2018
  - *Oral*: In the acute oral study that identified an LD_{50} of > 3,200 mg/kg in rats, animals (2/dose) received 400, 800, 1,600, 3,200, or 6,400 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) via gavage and were observed for 14 days. There were no clinical signs, deaths, or effects on body weight. Moderate weakness and some vasodilatation were observed following treatment (Klimisch score of 2, reliable with restriction).
  - *Dermal*: In the acute dermal study in guinea pigs that identified an LD_{50} > 18,530 mg/kg, animals (1/dose) were administered 4,630, 9,260, or 18.53 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) to depilated skin for 24 hours under occlusion and were observed for 14 days. There were no deaths. Animals at the low dose lost weight, but the animals at the high dose gained weight (Klimisch score of 2, reliable with restriction).
  - *Inhalation*: In the acute inhalation study that identified an LC_{50} of > 5.3 mg/L in rats (sex and strain not specified), three animals were exposed to atmosphere containing 5.3 mg/L trimethyl pentanyl diisobutyrate (purity not reported) via whole body inhalation for 6 hours and were observed for 14 days. There were no clinical signs other than pink extremities and no effects on body weight (Klimisch score of 2, reliable with restriction).

- ECHA 2023; ECB 2000; U.S. CPSC 2011, 2018
    - *Oral*: In the acute oral study that identified an LD_{50} of 6,400 mg/kg in mice, animals (2/dose) received 800, 1,600, or 3,200 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) via gavage and were observed for 14 days. One animal in the high dose group died. There were no clinical signs or effects on body weight (Klimisch score of 2, reliable with restriction).
- ECHA 2023; U.S. CPSC 2011, 2018
    - *Dermal*: In the acute dermal study (GLP, OECD 402) in male and female New Zealand White rabbits that identified an LD_{50} > 2,000 mg/kg, animals (5/sex) were administered 2,000 mg/kg trimethyl pentanyl diisobutyrate (> 98% purity) to intact skin under semiocclusion for 24 hours and were observed for 14 days. There were no deaths, effects on body weight, or consistent gross pathological changes (Klimisch score of 1, reliable without restriction).
    - *Inhalation*: In the acute inhalation study that identified an LC_{50} of > 0.12 mg/L in rats (sex and strain not specified), three animals were exposed to atmosphere containing 0.12 mg/L trimethyl pentanyl diisobutyrate (purity not reported) via whole body inhalation for 6 hours and were observed for 14 days. There were no clinical signs or effects on body weight. There were no deaths, clinical signs other than a few instances of diarrhea, effects on body weight, or consistent gross pathological changes (Klimisch score of 2, reliable with restriction).
- ECHA 2023
    - *Oral*: In the acute oral study (GLP, OECD 425) in female Wistar rats that identified an LD_{50} > 2,000 mg/kg, animals (n=5) received 2,000 mg/kg trimethyl pentanyl diisobutyrate (> 98% purity) via gavage and were observed for 14 days. There were no deaths, clinical signs, effects on body weight, or changes in gross pathology (Klimisch score of 1, reliable without restriction).

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for systemic toxicity (repeated dose) based on NOAEL values of 100 mg/kg/day and greater in subchronic oral studies in rats and dogs. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when no adverse effects are seen below the guidance value of 100 mg/kg/day in a 90-day oral study (CPA 2018b). The confidence in the score is high as it is based on experimental data from several reliable studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 1995; ECHA 2023; U.S. CPSC 2011, 2018
    - *Oral*: In the previously described GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422 in Crj:CD(SD) rats, animals (12/sex/dose) were administered trimethyl pentanyl diisobutyrate (purity not reported) via gavage at doses of 0, 30, 150, or 750 mg/kg/day for 44 days beginning 14 days prior to mating (males) or from 14 days prior to mating through lactation day 3 (females). There were no deaths or clinical signs of toxicity. At the high dose, male body weight was significantly reduced and female food consumption was significantly increased. There were no effects on hematology. Increased creatinine and total bilirubin were measured in animals in the mid and high dose groups, and

total protein was increased in males in the high dose group. Liver weights were increased in males in the mid and high dose groups and kidney weights were increased in males in the high dose group. The incidence of brown colored livers was increased in males in the high dose group. An increase in basophilic change of the renal tubular epithelium and degeneration of hyaline droplets was observed in males in the 150 and 750 mg/kg/day dose groups. Necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, decreased fatty change, and swelling of the liver cells were seen in males at the high dose. OECD identified a NOAEL of 30 mg/kg/day and LOAEL of 150 mg/kg/day (Klimisch score of 2, reliable with restriction).

- *The LOAEL of 150 mg/kg/day and the NOAEL of 30 mg/kg/day are within the doubled GHS guideline values for Category 2 of 20-200 mg/kg/day for 45-day studies. Therefore, trimethyl pentanyl diisobutyrate is classified to GHS Category 2.*

- ECHA 2023
  - *Oral*: In a GLP-compliant subchronic oral toxicity study that was conducted according to U.S. FDA Toxicological Principles for the Safety of Food Ingredients in male and female CD[Crl:CD(SD)] rats, animals (20/sex/dose) were administered trimethyl pentanyl diisobutyrate (purity not reported) continuously in the diet for 13 weeks to yield doses of 0, 30, 150, or 750 mg/kg/day. There were no treatment-related deaths. At the high dose, body weights were reduced in both sexes by 5-7% beginning in weeks 8-10; the only statistically significant decrease was in males in week 9. Food consumption was slightly reduced at this dose. Cholesterol was significantly increased in high dose males on days 15, 45, and at termination, and in females on day 45 and at termination. Bilirubin, creatinine, and gamma glutamyltransferase were significantly increased in males at this dose. There was an increase in relative kidney weight in males at the high dose, but authors noted that this effect is not considered toxicologically significant as it was associated with an increase in hyaline droplets which is indicative of an effect specific to male rats. Both male and female liver weights (absolute and relative) were significantly increased in both sexes at the high dose. There were no toxicologically significant effects on the opthalmoscopic examination, hematology, urinalysis, or gross pathology. Hyaline droplets and minimal chronic progressive nephropathy were observed in males in all treatment groups. Authors identified a NOAEL and LOAEL of 150 mg/kg/day and 750 mg/kg/day in males and a NOAEL of 750 mg/kg/day in females. Authors noted that effects on cholesterol in females at the high dose indicate a potential effect on the liver, but that the minor nature of the effects allows for assignment of a NOAEL of 750 mg/kg/day. ToxServices assigned a more conservative NOAEL of 150 mg/kg/day for both sexes based on potential effects on the liver in both sexes (Klimisch score of 1, reliable without restriction).
    - *The LOAEL of 750 mg/kg/day and the NOAEL of 150 mg/kg/day are above the GHS guideline value for Category 2 of 100 mg/kg/day for 90-days studies. Therefore, trimethyl pentanyl diisobutyrate is not classified per GHS.*
- ECHA 2023; ECB 2000; U.S. CPSC 2011, 2018
  - *Oral*: In a subchronic oral toxicity study that was not conducted according to guidelines, male and female Albino rats (10/sex/dose, strain not specified) were administered trimethyl pentanyl diisobutyrate (≥ 99% purity) in the diet at concentrations of 0.1% or 1% for 51 days or 91 days, at 0.1% or 1% for 52 days followed by 0% for 47 days, or 0% for 52 days followed by 0.1 or 1% for 47 days. Animals were evaluated for clinical signs, feed consumption and efficiency, weight gain, hematology, clinical chemistry, gross pathology, and histopathology. Minimal reductions in growth (< 10%) at the high dose were reported in "some cases". Relative kidney weights were increased only in animals treated for 52 days

and authors therefore did not consider this effect to be toxicologically significant. Relative liver weights were "slightly" increased in animals of the high dose group just prior to euthanasia. There were no treatment-related toxicologically significant effects on hematology (hematocrit, hemoglobin, leukocyte, and differential counts according to the IUCLID dataset), clinical chemistry (alkaline phosphatase and serum glutamic-oxaloacetic transaminase), weights of organs other than the liver (kidney, gonads, brain, pituitary, adrenals, and thyroids), or histopathology. The authors concluded that the high dose caused reversible adaptive changes in liver and identified a NOAEL of 1% in the diet for 52 or 99 days. Based on average food consumption for a rat, this is equivalent to 960 mg/kg/day[11]. In a report compiled for the Danish EPA, Stuer-Lauridsen et al. (2001) reviewed this study, and reported a more conservative NOAEL of 0.1% (96 mg/kg/day) based on effects on liver weight at the high dose (960 mg/kg/day) (Klimisch score of 2, reliable with restriction).

- *Oral*: In a subchronic oral toxicity study that was conducted in male and female Holtzman rats, animals (10/sex/dose) were fed a diet containing 0, 0.1, or 1% trimethyl pentanyl diisobutyrate (purity not reported) for 102 days. Evaluations of hematology (hemoglobin, cell volume, leukocyte, and differential counts), organ weights, gross pathology, and histopathology were conducted. Male rats at the highest dose showed slight increase in liver weights, but this was considered by the study authors to be adaptive and not representative of a significant toxic effect as no abnormalities were reported in the liver or any other organ at autopsy. Kidney weights were reduced in females at both dose groups, but the effect was attributed to unusually high kidney weights in the control group. Authors reported a NOAEL of 1% (960 mg/kg/day), which was the highest dose tested (Klimisch score of 2, reliable with restriction).
- *Oral*: In a subchronic oral study in male and female Beagle dogs, animals (4/sex/dose) were fed a diet containing 0, 0.1, 0.35, or 1% trimethyl pentanyl diisobutyrate (purity not reported) 6 days/week for 103 days. Evaluations of hematology (hemoglobin, total and differential leukocyte counts), clinical chemistry (blood glucose, urea nitrogen, lactic dehydrogenase, serum glutamic-oxaloacetic transaminase, and prothrombin time), urinalysis (albumin, glucose, pH, specific gravity, ketones, occult blood, bile, and microscopic appearance of sediments), body weight, food intake, gross pathology (liver, kidneys, spleen, brain, pituitary, adrenals, thyroid, and gonads), and histopathology (liver, spleen, stomach, small and large intestines, pancreas, kidneys, bladder, adrenals, gonads, thyroid, pituitary, thymus, salivary glands, mesenteric lymph nodes, heart and aorta, lungs, bone marrow, skeletal muscle and peripheral nerve, spinal cord, brain, and gall bladder; control and high dose only). No treatment-related toxicologically significant effects were reported, and authors identified a NOAEL of 1% in the diet (296 mg/kg/day for males and 322 mg/kg/day for females after adjusting for intermittent exposure[12]) (Klimisch score of 2, reliable with restriction).

- Based on the weight of evidence, a score of Low was assigned. The subchronic oral study in rats conducted according to U.S. FDA guidelines identified a NOAEL and LOAEL of 150 and 750 mg/kg/day based on an increase in hyaline droplets and increased incidence of nephropathy. These effects may indicate male rat specific alpha 2u-globulin nephropathy (NTP 2023), which is not relevant to humans. Similar effects were observed in the OECD Guideline 422 study in rats, with a NOAEL and LOAEL of 30 and 150 mg/kg/day based on effects on the kidney in male rats. This

[11] 1% x 0.096 kg food/kg BW x 1,000 g/kg x 1,000 mg/g = 960 mg/kg BW (rat average food factor value for subchronic study from TERA Undated).

[12] 6 days/7 days x (1% in food x 0.083 kg food/day x 1,000 g/kg x 1,000 mg/g) ÷ 2.4 kg BW = 296 mg/kg/day (subchronic body weights for male Beagle dog from U.S. EPA 1988); 6 days/7 days x (1% in food x 0.074 kg food/day x 1,000 g/kg x 1,000 mg/g) ÷ 1.97 kg BW = 322 mg/kg/day (subchronic body weights for female Beagle dog from U.S. EPA 1988)

may also potentially be a male rat specific effect, though the presence of hyaline droplets does not always indicate alpha 2u-globulin nephropathy (NTP 2023). Effects on the liver were also reported at the high doses in this study. In its review of this compound, EFSA identified the liver as a relevant target organ, with a NOAEL of 150 mg/kg/day based on the U.S. FDA study, while acknowledging that kidney effects were observed in male rats (EFSA 2006). Although extrapolating from the shorter study using adjusted guidance values indicates that liver and kidney effects occur within the range for a Moderate, such effects were not seen at a dose of 150 mg/kg/day in the 90 day study. In addition, two non-guideline studies in albino rats indicate a lack of effects on the liver at a dose of 96 mg/kg/day in the diet, which is approximately equal to the guidance value of 100 mg/kg/day, with effects observed at a LOAEL of 960 mg/kg/day in each study. A subchronic oral study in dogs also reported a lack of systemic effects at doses up to 296 mg/kg/day in males and 320 mg/kg/day in females. Therefore, rather than relying on the 44-day study in rats, ToxServices assigned a score of Low based on the weight of evidence from multiple subchronic studies indicating that systemic effects are not expected to occur below a dose of 100 mg/kg/day.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Trimethyl pentanyl diisobutyrate was assigned a score of Low for neurotoxicity (single dose) based on lack of clinical signs of toxicity related to neurotoxicity or effects on gross pathology of the brain in acute oral, dermal, and inhalation studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when there is no evidence of neurotoxicity below the guidance value of 2,000 mg/kg in acute oral and dermal studies (CPA 2018b). The confidence in the score is low as standard acute studies do not include specific evaluations of neurotoxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; ECB 2000; OECD 1995; U.S. CPSC 2011, 2018
  - *Oral*: In the acute oral study that identified an LD_{50} of > 3,200 mg/kg in rats, animals (2/dose) received 400, 800, 1,600, 3,200, or 6,400 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) via gavage and were observed for 14 days. There were no clinical signs, deaths, or effects on body weight. Moderate weakness and some vasodilatation were observed following treatment (Klimisch score of 2, reliable with restriction).
  - *Dermal*: In the acute dermal study in guinea pigs that identified an LD_{50} > 18,530 mg/kg, animals (1/dose) were administered 4,630, 9,260, or 18.53 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) to depilated skin for 24 hours under occlusion and were observed for 14 days. There were no deaths. Animals at the low dose lost weight, but the animals at the high dose gained weight (Klimisch score of 2, reliable with restriction).
  - *Inhalation*: In the acute inhalation study that identified an LC_{50} of > 5.3 mg/L in rats (sex and strain not specified), three animals were exposed to atmosphere containing 5.3 mg/L trimethyl pentanyl diisobutyrate (purity not reported) via whole body inhalation for 6 hours and were observed for 14 days. There were no clinical signs other than pink extremities and no effects on body weight (Klimisch score of 2, reliable with restriction).
- ECHA 2023; ECB 2000; U.S. CPSC 2011, 2018
  - *Oral*: In the acute oral study that identified an LD_{50} of 6,400 mg/kg in mice, animals (2/dose) received 800, 1,600, or 3,200 mg/kg trimethyl pentanyl diisobutyrate (purity not reported) via gavage and were observed for 14 days. One animal in the high dose group died. There were no clinical signs or effects on body weight (Klimisch score of 2, reliable with restriction).
- ECHA 2023; U.S. CPSC 2011, 2018

  - *Dermal*: In the acute dermal study (GLP, OECD 402) in male and female New Zealand White rabbits that identified an LD_{50} > 2,000 mg/kg, animals (5/sex) were administered 2,000 mg/kg trimethyl pentanyl diisobutyrate (> 98% purity) to intact skin under semiocclusion for 24 hours and were observed for 14 days. There were no deaths, effects on body weight, or consistent gross pathological changes (Klimisch score of 1, reliable without restriction).
  - *Inhalation*: In the acute inhalation study that identified an LC_{50} of > 0.12 mg/L in rats (sex and strain not specified), three animals were exposed to atmosphere containing 0.12 mg/L trimethyl pentanyl diisobutyrate (purity not reported) via whole body inhalation for 6 hours and were observed for 14 days. There were no deaths, clinical signs other than a few instances of diarrhea, effects on body weight, or consistent gross pathological changes (Klimisch score of 2, reliable with restriction).
- ECHA 2023
  - *Oral*: In the acute oral study (GLP, OECD 425) in female Wistar rats that identified an LD_{50} > 2,000 mg/kg, animals (n=5) received 2,000 mg/kg trimethyl pentanyl diisobutyrate (> 98% purity) via gavage and were observed for 14 days (Klimisch score of 1, reliable without restriction).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Trimethyl pentanyl diisobutyrate was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of effects on neurological endpoints at up to 750 mg/kg/day in a subchronic oral study in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when no evidence of neurotoxicity is seen below the guidance value of 100 mg/kg/day for a 90-day oral toxicity study (CPA 2018b). The confidence in the score is high because it is based on experimental data from a well conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral*: In the previously described GLP-compliant subchronic oral toxicity study that was conducted according to U.S. FDA Toxicological Principles for the Safety of Food Ingredients, CD[Crl:CD(SD)] rats (20/sex/dose) were administered trimethyl pentanyl diisobutyrate (purity not reported) continuously in the diet for 13 weeks to yield doses of 0, 30, 150, or 750 mg/kg/day. Neurobehavioral observations (changes in skin, fur, eyes, mucous membranes, autonomic activity, unusual respiratory patterns, changes in gait, posture, reactivity to handling, stereotypies, and bizarre behavior) were conducted once weekly during weeks 1-12 and a functional observational battery (FOB) consisting of observations in the home cage, open field, and during handling, and evaluations of activity, posture, behavior, movement, gait, reflex, response to stimuli, grip response, hindlimb splay, and pain perception were evaluated prior to treatment and during week 13. No treatment related effects were observed. ToxServices identified a NOAEL of 750 mg/kg/day for neurological effects (Klimisch score of 1, reliable without restriction).
- ECHA 2023; ECB 2000; U.S. CPSC 2011, 2018
  - *Oral*: In a previously described subchronic oral study in male and female Beagle dogs, animals (4/sex/dose) were fed a diet containing 0, 0.1, 0.35 or 1% trimethyl pentanyl diisobutyrate (purity not reported) 6 days/week for 103 days. Neurological reflexes were tested weekly. There was no evidence of excitation or depression in any of the animals, and there were no effects on reflexes. ToxServices identified a NOAEL of 1% in the diet (296

mg/kg/day for males and 322 mg/kg/day for females after adjusting for intermittent exposure[13]) (Klimisch score of 2, reliable with restriction).

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for skin sensitization based on negative results in skin sensitization assay in guinea pigs and a human RIPT. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on experimental data in humans and guinea pigs.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; U.S. CPSC 2011, 2018
  - In a human repeat insult patch test conducted in accordance with Good Clinical Practices, 203 subjects (40 males, 163 females) were induced and challenged with a 1% solution of trimethyl pentanyl diisobutyrate (purity not reported) in acetone under occlusive patches on the skin of the back. Two individuals displayed "slight, confluent or patchy erythema", one of which resolved by 96 hours and one of which did not. The study authors concluded that the substance is not sensitizing (Klimisch score of 1, reliable without restriction).
  - In a skin sensitization study conducted using an Eastman Kodak Company study design, guinea pigs (4-5/group, sex not specified) were induced and challenged, by epicutaneous exposure with 1% concentration of trimethyl pentanyl diisobutyrate. None of the animals showed a positive response, while all positive control animals responded appropriately. The study authors concluded that trimethyl pentanyl diisobutyrate is not a skin sensitizer (Klimisch score of 2, reliable with restriction).
- Based on the weight of evidence, a score of Low was assigned. The only animal study available is a non-guideline sensitization assay in guinea pigs, and although it involved only a limited number of animals and was not conducted according to established guidelines, no positive responses were observed and appropriate responses in the positive control group indicate that the assay was sufficient to detect sensitizing responses. A well conducted human RIPT was also negative.

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

Trimethyl pentanyl diisobutyrate was assigned a score Low for respiratory sensitization based on lack of dermal sensitization potential following ECHA (2017)'s guidance. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - Trimethyl pentanyl diisobutyrate does not contain any structural alerts for respiratory sensitization (Appendix J).

[13] 6 days/7 days x (1% in food x 0.083 kg food/day x 1,000 g/kg x 1,000 mg/g) ÷ 2.4 kg BW = 296 mg/kg/day (subchronic body weights for male Beagle dog from U.S. EPA 1988); 6 days/7 days x (1% in food x 0.074 kg food/day x 1,000 g/kg x 1,000 mg/g) ÷ 1.97 kg BW = 322 mg/kg/day (subchronic body weights for female Beagle dog from U.S. EPA 1988)

- 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 trimethyl pentanyl diisobutyrate 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 trimethyl pentanyl diisobutyrate, and as trimethyl pentanyl diisobutyrate does not contain any structural alerts for respiratory sensitization (OECD 2023), trimethyl pentanyl diisobutyrate is not expected to be a respiratory sensitizer.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for skin irritation/corrosivity based on negative results in a dermal irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; U.S. CPSC 2011, 2018
  - In a GLP-compliant skin irritation study performed according to OECD Guideline 404, three New Zealand White rabbits (2 males and 1 female) were exposed to 0.5 mL of undiluted trimethyl pentanyl diisobutyrate (purity > 98%) on the shaved skin under semi-occlusive conditions for 4 hours and observed at 24, 48 and 72 hours later. Mild irritation was observed, which was completely reversible at 72 hours. The average score (24 to 72 hours, average of all animals) for edema and erythema were 0 and 0.3, respectively. Based on this, the study authors concluded that trimethyl pentanyl diisobutyrate is not irritating to the rabbit skin and is not classified per GHS (Klimisch score of 1, reliable without restriction).
- OECD 1995; ECB 2000; U.S. CPSC 2011, 2018
  - Trimethyl pentanyl diisobutyrate was reported to be slightly irritating to the skin of guinea pigs when administered at a dose of 5 mg/kg. Small skin flaking, desquamation, and hair loss were visible after one week and the desquamation and sparse hair persisted after two weeks. No other details were provided.
- Based on the weight of evidence, a score of Low was assigned. Slight irritation was reported in guinea pigs, but the study was not well described and no irritation was observed in the high quality guideline study in rabbits, which ToxServices weighed more heavily in the score.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for eye irritation/corrosivity based on negative results in an ocular irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on experimental data from a well-conducted study.

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

  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023; OECD 1995; ECB 2000; U.S. CPSC 2011, 2018
  - Trimethyl pentanyl diisobutyrate (purity not reported) was not irritating in a GLP-compliant ocular irritation test that was conducted according to OECD Guideline 405 in three New Zealand White rabbits that were administered 0.1 mL of the test substance (undiluted) without rinsing and three rabbits that were administered the test substance immediately followed by washing with running distilled water. Slight redness was observed at 1 hour and resolved within 24 hours. The mean scores at 24, 48, and 72 hours for corneal opacity, iris, redness, and chemosis were 0 in all animals (Klimisch score of 2, reliable with restriction).
- Based on the weight of evidence a score of Low was assigned. Only one study was identified, but it is a high quality guideline study and reported no evidence of irritation.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *H*
Trimethyl pentanyl diisobutyrate was assigned a score of High for acute aquatic toxicity based on an EC_{50} value of 8 mg/L in algae. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when the most conservative L/EC_{50} values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score is low as it is unclear if the EC_{50} of 8 mg/L in algae is nominal or experimental and a second algae study did not show the same toxicity at 7.49 mg/L.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan - GHS – H401: Toxic to aquatic life (Hazardous to the aquatic environment (acute) – Category 2)
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment
- OECD 1995
  - 96-hour LC_{50} (*Oryzias latipes*, rice fish) = 18 mg/L (OECD 203)
  - 24-hour EC_{50} (*Daphnia magna*, water flea) = 300 mg/L (OECD 202)
  - 72-hour EC_{50} (*Selenastrum capricornutum*, green algae) = 8.0 mg/L (OECD 201)
- ECHA 2023; ECB 2000
  - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) > 1.55 mg/L
  - 96-hour EC_{50} (*Gammarus fasciatus*, freshwater shrimp) > 1.55 mg/L
  - 96-hour EC_{50} (*Asellus intermedius*, isopod crustacean) > 1.55 mg/L
  - 96-hour EC_{50} (*Helisoma trivolvis*, freshwater snail) > 1.55 mg/L
  - 96-hour EC_{50} (*Dugesia tigrina*, aquatic flatworm) > 1.55 mg/L
  - 96-hour EC_{50} (*Lumbriculus variegatus*, aquatic blackworm) > 1.55 mg/L
  - 48-hour EC_{50} (*Daphnia magna*, water flea) > 1.46 mg/L
- ECHA 2023
  - 72-hour EC_{50} (*Pseudokirchnerella subcapitata*, green algae) > 7.49 mg/L (GLP, OECD 201)
- Based on the weight of evidence, a score of High was assigned. OECD (1995) did not specify if the reported values were nominal or measured, but did report a NOEC of 5.3 mg/L for the algae study, indicating some toxicity was seen in the study. On the other hand, the algae study described in the ECHA dossier noted that the test substance absorbs to algae cell and glass surface, making it challenging to measure the tested concentrations in the study. Nominal concentrations of 5.92, 8.89, 13.3, 20 and 30 mg/L lead to measured mean concentrations of 1.57, 1.76, 2.25, 3.56 and 7.49, respectively. A growth inhibition of 14.9% was observed at the highest tested concentration, and therefore the EC_{50} is greater than 7.49 mg/L. Based on the highest tested nominal concentration of

30 mg/L exceeding the theoretical water solubility of the test substance, The REACH dossier authors argued that there are no adverse effects at or near the water solubility of the substance. While the nominal concentrations exceeded the water solubility, the measured concentrations did not reach the experimental maximum water solubility of 12 – 15 mg/L due to the loss from adsorption to glass and algae. Therefore, it is more appropriate to use the measured concentration rather than nominal concentration to evaluate this endpoint. As some toxicity was observed in both algae studies, ToxServices did not agree with the conclusion of "no adverse effects at saturation". Based on the most conservative EC_{50} of 8 mg/L in algae, ToxServices assigned a High score for this endpoint. However, as it is not clear if this value was nominal or experimental, and that a second algae study reported by ECHA found only a 14.9% growth inhibition at a similar measured concentration of 7.49 mg/L in a different algae species, the confidence with the score was reduced.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *H*
Trimethyl pentanyl diisobutyrate was assigned a score of High for chronic aquatic toxicity based on a NOEC of 0.7 mg/L in algae. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when the most conservative chronic NOEC values are between 0.1 and 1 mg/L (CPA 2018b). The confidence in the score is low because while the lowest NOEC is below 1 mg/L, the LOEC in the same study is above 1 mg/L, which makes it unclear if the true NOEC would be greater than the cutoff of 1 mg/L.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan - GHS – H412: Harmful to aquatic life with long lasting effects (Hazardous to the aquatic environment (chronic) – Category 3)
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment
- OECD 1995
  - 21-day NOEC (*Daphnia magna*, water flea) = 3.2. mg/L (reproduction) (OECD 202)
  - 72-hour NOEC (*Selenastrum capricornutum*, green algae) = 5.3 mg/L (OECD 201)
- ECHA 2023
  - 21-day NOEC (*Daphnia magna*, water flea) = 0.7 mg/L (reproduction) (GLP, OECD 202 with modified 21-day exposure), LOEC = 1.3 mg/L
  - 72-hour NOEC (*Pseudokirchnerella subcapitata*, green algae) = 3.56 mg/L (growth), 2.25 mg/L (biomass) (GLP, OECD 201)
  - 96-hour NOEC (*Lepomis macrochirus*, bluegill sunfish) > 6 mg/L (GLP, OECD 203)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): L
Trimethyl pentanyl diisobutyrate was assigned a score of Low for persistence based on meeting the GHS rapid degradation criteria and on being predicted to predominantly partition to soil. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they meet the rapid degradation criteria under GHS, and they primarily partition to soil, water, or sediment (CPA 2018b). The confidence in the score is high as it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 1995
  - A hydrolysis half-life of 178 days at pH 9 at 25°C was measured in a GLP-compliant test conducted according to OECD Guideline 111. The substance was stable at pH 4 and 7.

  - Trimethyl pentanyl diisobutyrate (100 mg/L, purity not reported) achieved 4-82% (BOD), 2-84% (TOC), and 3-100% (GC) biodegradation in 28 days in a GLP-compliant test conducted according to OECD Guideline 301C using standard activated sludge inoculum. OECD concluded that the substance is inherently biodegradable.
- ECHA 2023
  - Trimethyl pentanyl diisobutyrate (99.189% purity, 10 mg/L starting concentration) reached 70.73% degradation in a GLP-compliant test conducted according to OECD Guideline 301B (CO_2 Evolution Test) using non-adapted domestic activated sludge inoculum. It did not meet the 10-day window, as 10% was reached between days 3 and 6 and the 60% pass level was not reached until days 20-24. Trimethyl pentanyl diisobutyrate was considered readily biodegradable, but failing 10-day window (Klimisch score of 1, reliable without restriction).
  - Another GLP-compliant ready biodegradability test conducted according to OECD Guideline 301B (CO_2 Evolution Test) was performed with domestic, non-adapted activated sludge exposed to trimethyl pentanyl diisobutyrate (purity 99%) at 20 mg/L for 28 days. At the end of the exposure period the level of degradation was 60%. The biodegradation of the test substance reached 50% at the end of the 10-d window. Based on this, the substance was considered readily biodegradable but failing the 10-day window criteria (Klimisch score of 1, reliable with restriction).
  - Trimethyl pentanyl diisobutyrate (99% purity, 20 mg/L starting concentration) achieved 54% and 55% biodegradation in 28 days in two separate replicates in a GLP-compliant test that was conducted according to OECD Guideline 301B (CO_2 Evolution Test) using non-adapted activated sludge inoculum (Klimisch score of 1, reliable without restriction).
  - Trimethyl pentanyl diisobutyrate (99% purity, 20 mg/L starting concentration) achieved 32% and 59% biodegradation in 28 days in two separate replicates in a GLP-compliant test that was conducted according to OECD Guideline 301B (CO_2 Evolution Test) using non-adapted activated sludge inoculum (Klimisch score of 1, reliable without restriction).
- ECB 2000
  - Trimethyl pentanyl diisobutyrate (purity not specified, 650 ppm starting concentration) achieved > 99.9% biodegradation in 12 days using activated sludge inoculum. No further details were provided.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that trimethyl pentanyl diisobutyrate is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 80.3% will partition to soil with a half-life of 75 days, 18.3% will partition to water with a half-life of 37.5 days, 0.887% will partition to sediment with a half-life of 22.4 hours, and 0.494% will partition to sediment with a half-life of 337.5 days (Appendix K).
- Based on the weight of evidence, a score of Low was assigned. OECD concluded that trimethyl pentanyl diisobutyrate is inherently biodegradable, based on an OECD Guideline 301C study demonstrating 4-82 and 3-100% biodegradation in 28 days. Mixed results were obtained from biodegradation studies conducted according to OECD Guideline 301B with trimethyl pentanyl diisobutyrate. These studies demonstrated 32-70.73% biodegradation in 18 days. The tested compound was considered readily biodegradable in two of the four 301B studies at the starting concentration of 10 or 20 mg/L; meeting the GHS rapid degradability criteria. However, trimethyl pentanyl diisobutyrate did not meet the criteria in two other 301B tests at the starting concentration of 20 mg/L. According to the OECD guidance, positive results in ready biodegradability tests are considered valid regardless of negative results, when the scientific quality of the positive study is appropriate (OECD 2001). Therefore, ToxServices relied on the OECD 301B study that reported

70.73% degradation in 28 days to assign a score of Low for this endpoint. Modeling predicts that this chemical will partition primarily to soil.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Trimethyl pentanyl diisobutyrate was assigned a score of Very Low for bioaccumulation based on an experimental BCF of 1.95. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when the BCF is less than 100 (CPA 2018b). The confidence in the score is high as it is based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC - CEPA DSL – Bioaccumulative (based on predicted data for BCF/BAF).
- OECD 1995
  - Trimethyl pentanyl diisobutyrate has a measured log K_{ow} of > 4.11 from an OECD Guideline test 107.
- ECHA 2023
  - In a GLP-compliant test conducted according to OECD Guideline 305 (Bioconcentration: Flow-through Fish Test) in *Lepomis macrochirus* (bluegill sunfish) exposed to trimethyl pentanyl diisobutyrate (purity 99%) at concentrations of 0.00519 mg/L and 0.0517 mg/L for 23 days with a 14 day depuration period, the whole body BCF values were 194 and 183, respectively. A whole body extract was also evaluated to determine residue representing the parent compound, and indicated that approximately 1% of the radioactivity represented the parent compound as a result of extensive metabolism. Authors, therefore, calculated a BCF of 1.95 for the parent compound (Klimisch score of 1, reliable without restriction).
- U.S. EPA 2017
  - BCFBAF predicts a BCF 806.5 L/kg wet-wt using the regression based model based on a measured log K_{ow} of 4.91, and a BCF of 19.11 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix K).
- Based on the weight of evidence, a score of Very Low was assigned. The experimental log K_{ow} of > 4.91 indicates some potential for bioaccumulation, but a bioaccumulation study of good quality demonstrated extensive metabolism and the whole body BCF value of 1.95 was determined for trimethyl pentanyl diisobutyrate; which corresponds to a score of Very Low. The DSL screening list classifies this chemical as bioaccumulative and U.S. EPA EPISuite modeling predicts a BCF of 806.5 in a regression-based method, corresponding to a score of Very High and Moderate, respectively. However, the basis for this classification is prediction from QSAR models. As experimental data of good quality (GLP and OECD compliant) are weighed more heavily than screening lists and predicted data, ToxServices assigned score of Very Low for this endpoint.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Trimethyl pentanyl diisobutyrate was assigned a score of Low for reactivity based on an HMIS rating of 0 and a structure indicating that it is not an organic peroxide, does not contain reactive groups associated with self-reactive substances, is not an organometallic substance that may produce flammable gases on contact with water, and does not contain alerts for explosivity. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score is low due to the 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.
- Eastman Chemical Company 2022
  - A material safety data sheet for trimethyl pentanyl diisobutyrate states that it has a reactivity rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives") (NFPA 2016 and ILPI 2022).
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of trimethyl pentanyl diisobutyrate. These procedures are listed in the GHS (UN 2023).
  - Based on the structure of its components or moieties, trimethyl pentanyl diisobutyrate is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix L).
  - Based on the structure of its components or moieties, trimethyl pentanyl diisobutyrate is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of trimethyl pentanyl diisobutyrate has 4 oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.

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

Trimethyl pentanyl diisobutyrate was assigned a score of Low for flammability based on not being classified as a flammable liquid per GHS. GreenScreen® criteria classify chemicals as a Low hazard for flammability when available data indicate that the chemical does not warrant GHS classification for flammability and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score is high as it is based on measured flash point.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - Trimethyl pentanyl diisobutyrate has a measured flash point of 136°C from a closed cup test conducted according to ASTM 3278 (Flash-Point) (Klimisch score of 2, reliable with restriction).
    - *This value is greater than the cut-off value for GHS category 4 (93^0C) for flammable liquids and, therefore, trimethyl pentanyl diisobutyrate is not classified as a flammable liquid under GHS (UN 2023)*.

Use of New Approach Methodologies (NAMs)[14] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 5, Type I (input data) uncertainties in trimethyl pentanyl diisobutyrate's NAMs dataset include limited, or lack of, experimental data for carcinogenicity, endocrine activity, respiratory sensitization, and persistence, and lack of established test methods for respiratory sensitization. Trimethyl pentanyl diisobutyrate's Type II (extrapolation output) uncertainties include lack of defined applicability domains of some modeling software examining structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and *in vitro* receptor binding activity assays, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of trimethyl pentanyl diisobutyrate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** Limited *in vivo* data for estrogen, androgen, and steroid signaling pathways are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Persistence:** No experimental data are available on environmental partitioning and half-lives of ultimate degradation in each compartment.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). Of the three models in VEGA that produced reliable (i.e., Global AD index > 0.7) predictions, the concordance index of the ISS model is 0.516 and IRFMN/ISSCAN-CGX model is 0.662, which is below the

[14] 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).

	desirable score of 0.7, and the read-across chemicals used in this model has additional functional groups than the target compound, limiting the confidence of the prediction from this model. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[15]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[16] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[17]. **Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors. EDSP Tox 21 assays do not cover all critical endocrine pathways. Of the seven models in VEGA that produced reliable (i.e., Global AD index > 0.7) predictions, the accuracy of prediction for similar molecules index of the IRFMN estrogen relative binding affinity model is 0.529, which is below the desirable score of 0.7, and the read-across chemicals used in this model has additional functional groups than the target compound, limiting the confidence of the prediction from this model. In addition, ToxServices was unable to identify the experimental data indicated as the basis for several predictions in VEGA models. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/ /Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	

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

Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays *In silico* modeling: Danish QSAR/VEGA
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301 Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

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	Trimethyl pentanyl diisobutyrate	6846-50-0	*L*	L	*M*	*M*	*M*	L	L	L	*L*	L	L	*L*	L	L	*H*	*H*	L	vL	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Trimethyl pentanyl diisobutyrate	2

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

Table 6

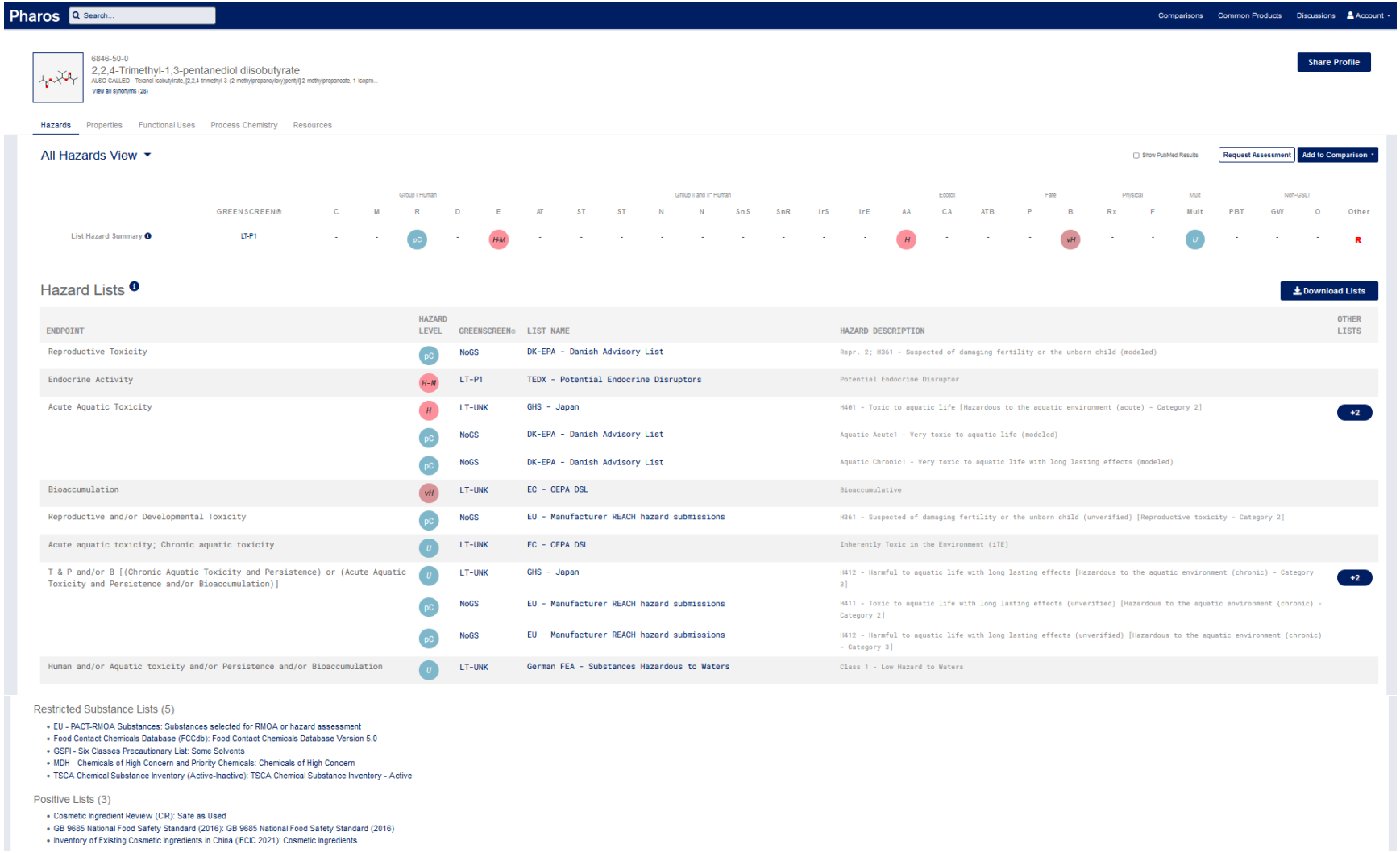
Chemical Name	Final GreenScreen® Benchmark Score
Trimethyl pentanyl diisobutyrate	2

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 Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)



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6846-50-0

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate

ALSO CALLED Texanol isobutyrate, [2,2,4-trimethyl-3-[(2-methylpropanoyl)oxy]pentyl] 2-methylpropanoate, 1-isopro...

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		Group I Human								Group II and II* Human							Ecotox			Fate		Physical		Mult	Non-GSLT			
	GREENSCREEN®	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
List Hazard Summary	LT-P1	-	-	vH	-	H-M	-	-	-	-	-	-	-	-	-	H	-	-	-	vH	-	-	U	-	-	-	R

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Reproductive Toxicity	vH	NoGS	DK-EPA - Danish Advisory List	Repr. 2; H361 - Suspected of damaging fertility or the unborn child (modeled)	
Endocrine Activity	H-M	LT-P1	TEDX - Potential Endocrine Disruptors	Potential Endocrine Disruptor	
Acute Aquatic Toxicity	H	LT-UNK	GHS - Japan	H401 - Toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 2]	+2
	vH	NoGS	DK-EPA - Danish Advisory List	Aquatic Acute1 - Very toxic to aquatic life (modeled)	
	vH	NoGS	DK-EPA - Danish Advisory List	Aquatic Chronic1 - Very toxic to aquatic life with long lasting effects (modeled)	
Bioaccumulation	vH	LT-UNK	EC - CEPA DSL	Bioaccumulative	
Reproductive and/or Developmental Toxicity	vH	NoGS	EU - Manufacturer REACH hazard submissions	H361 - Suspected of damaging fertility or the unborn child (unverified) [Reproductive toxicity - Category 2]	
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - Japan	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]	+2
	vH	NoGS	EU - Manufacturer REACH hazard submissions	H411 - Toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 2]	
	vH	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

Restricted Substance Lists (5)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- GSPI - Six Classes Precautionary List: Some Solvents
- MDH - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

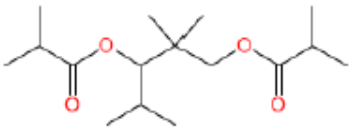
Positive Lists (3)

- Cosmetic Ingredient Review (CIR): Safe as Used
- GB 9685 National Food Safety Standard (2016): GB 9685 National Food Safety Standard (2016)
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2021): Cosmetic Ingredients

APPENDIX D: VEGA Carcinogenicity Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

1. Prediction Summary

Prediction for compound Molecule 0 -

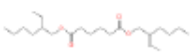


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not optimal
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- predicted substance falls into a neuron that is populated by no compounds of the training set

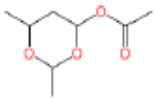
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.054
P(NON-Carcinogen): 0.946
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



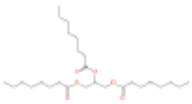
Compound #1

CAS: 103-23-1
Dataset id:315 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



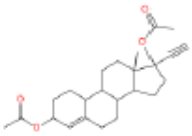
Compound #2

CAS: 828-00-2
Dataset id:254 (Test Set)
SMILES: O=C(OC1OC(OC(C)C1)C)C
Similarity: 0.766
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



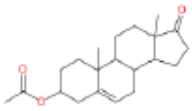
Compound #3

CAS: 538-23-8
Dataset id:759 (Test Set)
SMILES: O=C(OCC(OC(=O)CCCCCCC)COC(=O)CCCCCCC)CCCCCCC
Similarity: 0.739
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



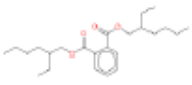
Compound #4

CAS: 297-76-7
Dataset id:321 (Training Set)
SMILES: O=C(OC4C=C3CCC2C(CCC1(C)(C2(CCC1(C#C)(OC(=O)C))))C3CC4)C
Similarity: 0.734
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 853-23-6
Dataset id:199 (Test Set)
SMILES: O=C(OC3CC2=CCC1C4CCC(=O)C4(C)(CCC1C2(C)CC3))C
Similarity: 0.726
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 117-81-7
Dataset id:316 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.324 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.796 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.527 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
⚠	Concordance for similar molecules Concordance index = 0.527 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✔	Model class assignment reliability Pos/Non-Pos difference = 0.891 Explanation: model class assignment is well defined..
✖	Neural map neurons concordance Neurons concordance = 0.5 Explanation: predicted substance falls into a neuron that is populated by no compounds of the training set..

Symbols explanation:

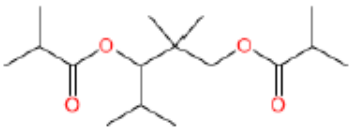
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- some similar molecules found in the training set have experimental values that disagree with the predicted value
The following alerts have been found: SA41 Substituted n-alkylcarboxylic acids

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

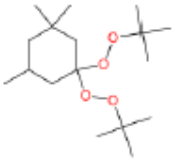
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 103-23-1
Dataset id:52 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Carcinogen
Predicted value : Carcinogen

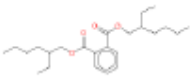
Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids

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



Compound #2

CAS: 6731-36-8
Dataset id:802 (Training Set)
SMILES: O(OC1(OOC(C)(C)C)(CC(C)CC(C)(C)C1))C(C)(C)C
Similarity: 0.791
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

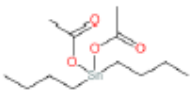


Compound #3

CAS: 117-81-7
Dataset id:53 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

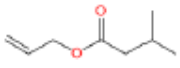
Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids

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



Compound #4

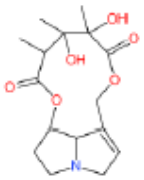
CAS: 1067-33-0
Dataset id:738 (Training Set)
SMILES: O=C(O[Sn](OC(=O)C)(CCCC)CCCC)C
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 2835-39-4
Dataset id:35 (Training Set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.717
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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



Compound #6

CAS: 315-22-0
Dataset id:759 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA37 Pyrrolizidine Alkaloids

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.763 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.81 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
⚠	Concordance for similar molecules Concordance index = 0.516 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: SA41 Substituted n-alkylcarboxylic acids

Substituted n-alkylcarboxylic acids

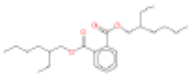
Following, the most similar compounds from the model's dataset having the same fragment.

CAS: 103-23-1
Dataset id:52 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832

Experimental value : Carcinogen
Predicted value : Carcinogen

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

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

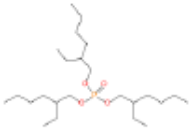


CAS: 117-81-7
Dataset id:53 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722

Experimental value : Carcinogen
Predicted value : Carcinogen

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

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



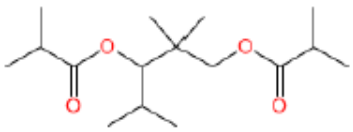
CAS: 78-42-2
Dataset id:69 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.705

Experimental value : Carcinogen
Predicted value : Carcinogen

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

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

The following relevant fragments have been found: Carcinogenity alert no. 29

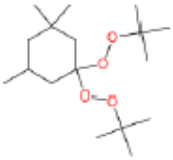
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 29
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

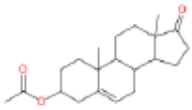
CAS: 103-23-1
Dataset id:43 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #2

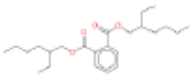
CAS: 6731-36-8
Dataset id:734 (Training Set)
SMILES: O(OC1(OOC(C)(C)C)(CC(C)CC(C)(C)C1))C(C)(C)C
Similarity: 0.791
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

CAS: 853-23-6
Dataset id:816 (Training Set)
SMILES: O=C(OC3CC2=CCC1C4CCC(=O)C4(C)(CCC1C2(C)CC3))C
Similarity: 0.726
Experimental value : Carcinogen
Predicted value : Carcinogen

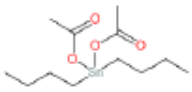
Alerts (not found also in the target): Carcinogenity alert no. 5; Carcinogenity alert no. 39



Compound #4

CAS: 117-81-7
Dataset id:44 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

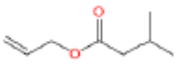
Alerts (found also in the target): Carcinogenity alert no. 29



Compound #5

CAS: 1067-33-0
Dataset id:710 (Training Set)
SMILES: O=C(O[Sn](OC(=O)C)(CCCC)CCCC)C
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

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



Compound #6

CAS: 2835-39-4
Dataset id:28 (Training Set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.717
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.794 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.774 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✔	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
⚠	Concordance for similar molecules Concordance index = 0.661 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 29

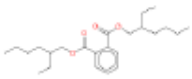
Structural alert for carcinogenity defined by the SMARTS:C(OC)C(C)C

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

CAS: 103-23-1
Dataset id:43 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832

Experimental value : Carcinogen
Predicted value : Carcinogen

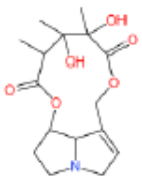
Alerts (found also in the target): Carcinogenity alert no. 29



CAS: 117-81-7
Dataset id:44 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722

Experimental value : Carcinogen
Predicted value : Carcinogen

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



CAS: 315-22-0
Dataset id:592 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
Similarity: 0.708

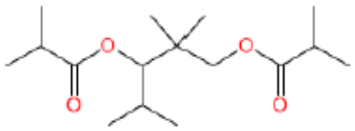
Experimental value : Carcinogen
Predicted value : Carcinogen

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

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 20

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

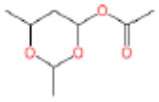
Prediction is Possible NON-Carcinogen, but the result may be not reliable.
A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found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

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

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

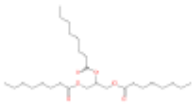
Compound #1

CAS: 103-23-1
Dataset id:315 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



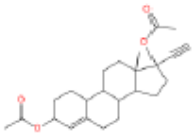
Compound #2

CAS: 828-00-2
Dataset id:254 (Test Set)
SMILES: O=C(OC1OC(OC(C)C1)C)C
Similarity: 0.766
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

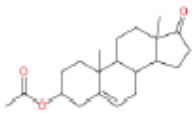
CAS: 538-23-8
Dataset id:759 (Test Set)
SMILES: O=C(OCC(OC(=O)CCCCCCC)COC(=O)CCCCCCC)CCCCCCC
Similarity: 0.739
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

CAS: 297-76-7
Dataset id:321 (Training Set)
SMILES: O=C(OC4C=C3CCC2C(CCC1(C)(C2(CCC1(C#C)(OC(=O)C))))C3CC4)C
Similarity: 0.734
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

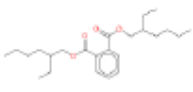
Alerts (not found also in the target): Carcinogenity alert no. 100; Carcinogenity alert no. 124



Compound #5

CAS: 853-23-6
Dataset id:199 (Test Set)
SMILES: O=C(OC3CC2=CCC1C4CCC(=O)C4(C)(CCC1C2(C)CC3))C
Similarity: 0.726
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 85; Carcinogenity alert no. 119



Compound #6

CAS: 117-81-7
Dataset id:316 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 88

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.53 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.772 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.363 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.363 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

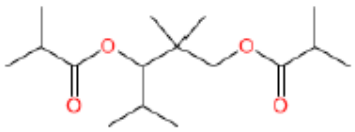
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

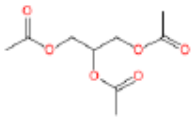
Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

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

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

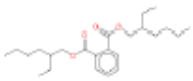
Compound #1

CAS: 103-23-1
Dataset id:94 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



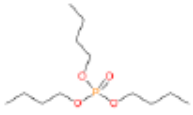
Compound #2

CAS: 102-76-1
Dataset id:706 (Test Set)
SMILES: O=C(OCC(OC(=O)C)COC(=O)C)C
Similarity: 0.789
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



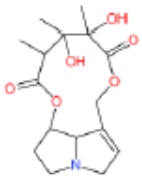
Compound #3

CAS: 117-81-7
Dataset id:44 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



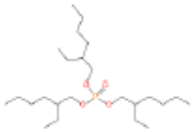
Compound #4

CAS: 126-73-8
Dataset id:299 (Training Set)
SMILES: O=P(OCCCC)(OCCCC)OCCCC
Similarity: 0.712
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 315-22-0
Dataset id:209 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 78-42-2
Dataset id:313 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.705
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.625 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.809 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✗	Accuracy of prediction for similar molecules Accuracy index = 0.483 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✗	Concordance for similar molecules Concordance index = 0.483 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

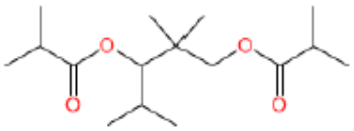
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

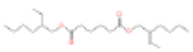


Prediction: Reliability:

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

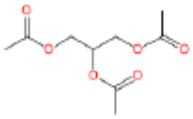
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



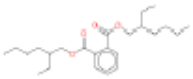
Compound #1

CAS: 103-23-1
Dataset id:391 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



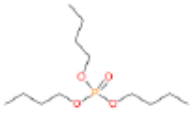
Compound #2

CAS: 102-76-1
Dataset id:701 (Training Set)
SMILES: O=C(OCC(OC(=O)C)COC(=O)C)C
Similarity: 0.789
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



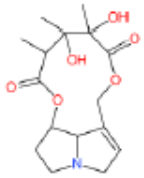
Compound #3

CAS: 117-81-7
Dataset id:38 (Training Set)
SMILES: O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



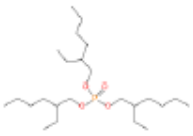
Compound #4

CAS: 126-73-8
Dataset id:708 (Training Set)
SMILES: O=P(OCCCC)(OCCCC)OCCCC
Similarity: 0.712
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 315-22-0
Dataset id:176 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 78-42-2
Dataset id:741 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.705
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.899 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.809 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

APPENDIX E: Danish QSAR Carcinogenicity Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

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

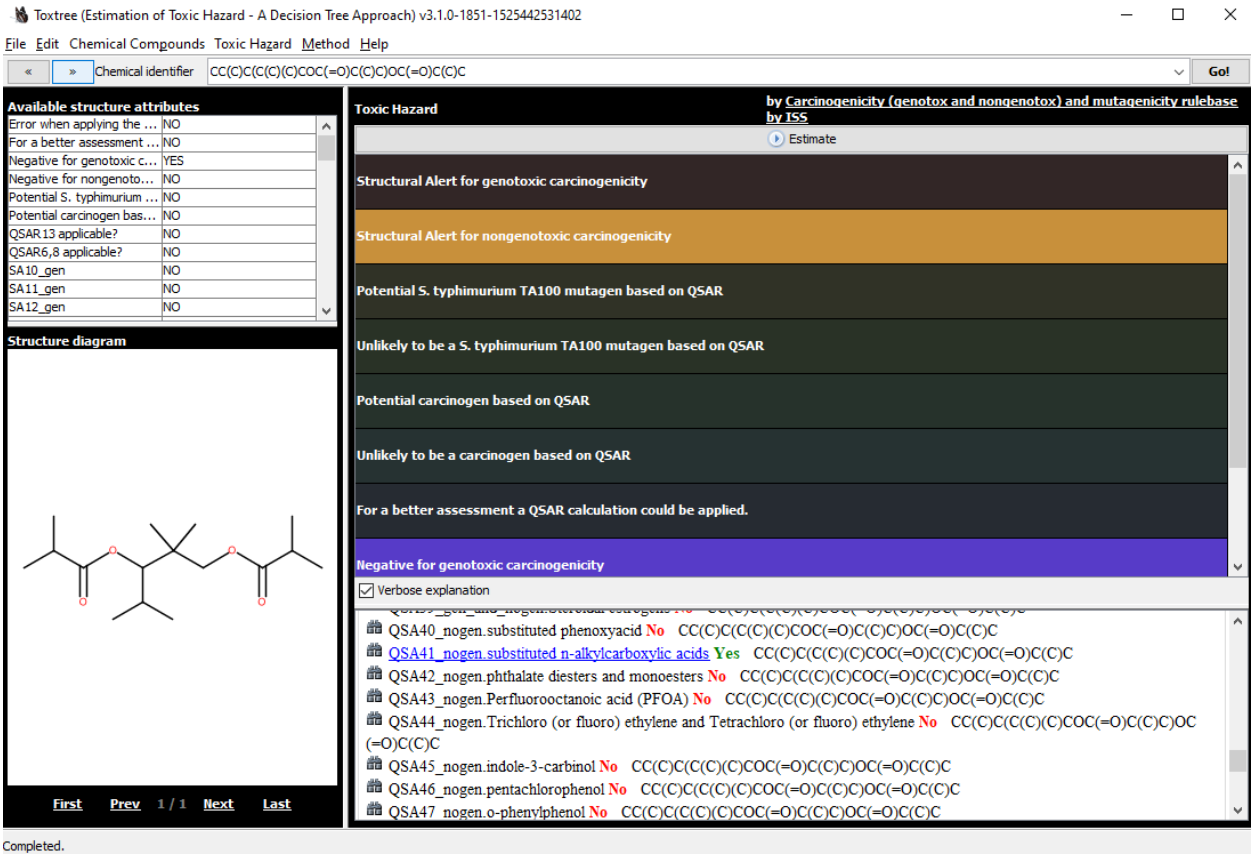
OECD QSAR Toolbox v.4.2 profilers

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

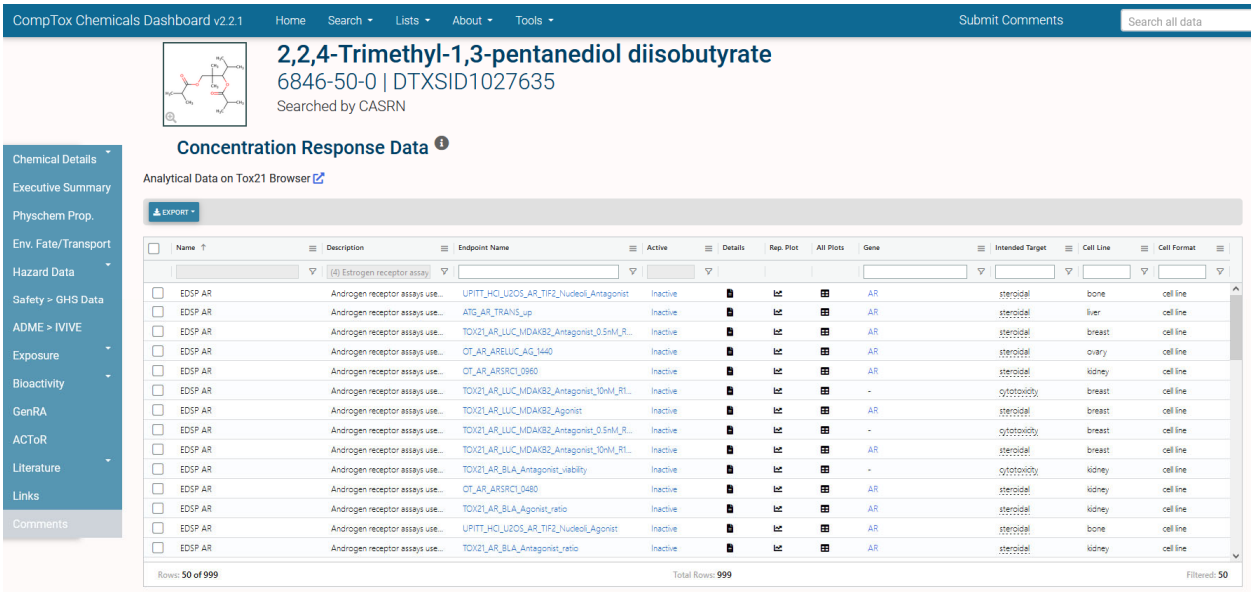
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	NEG_IN	NEG_IN	POS_IN

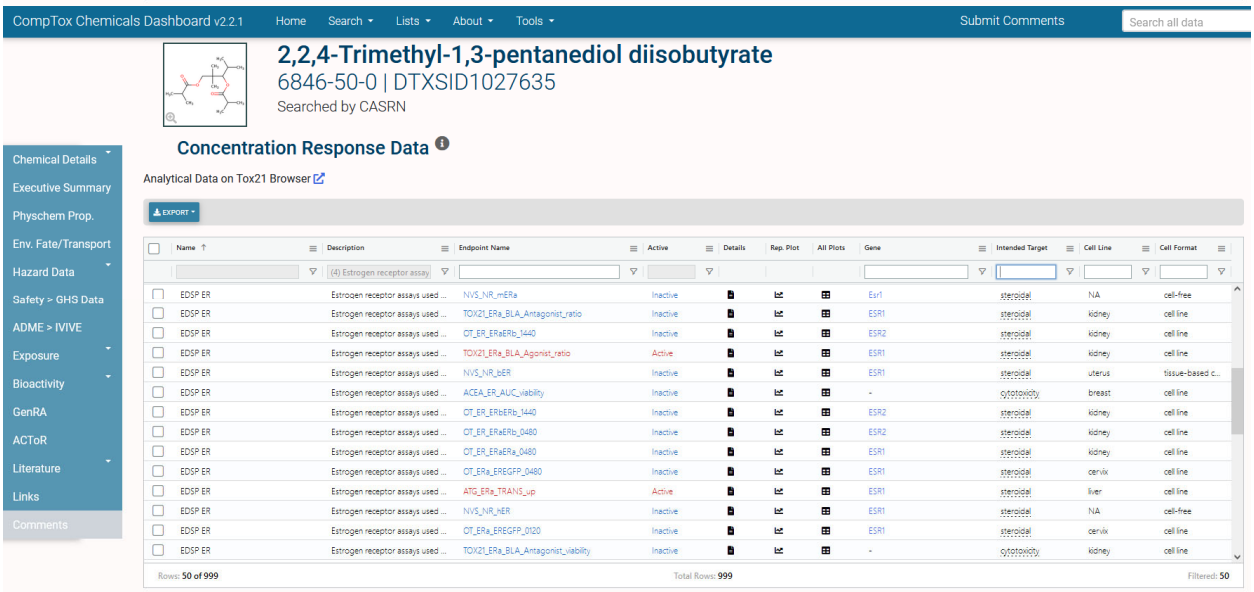
DTU-developed models

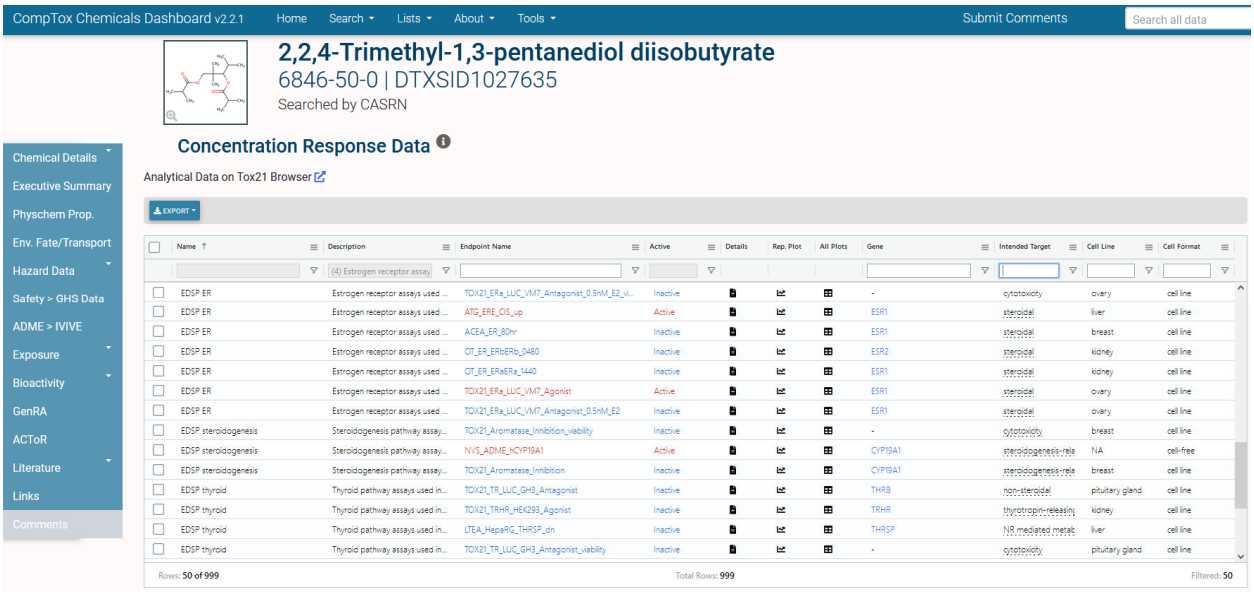
APPENDIX F: Toxtree Carcinogenicity Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

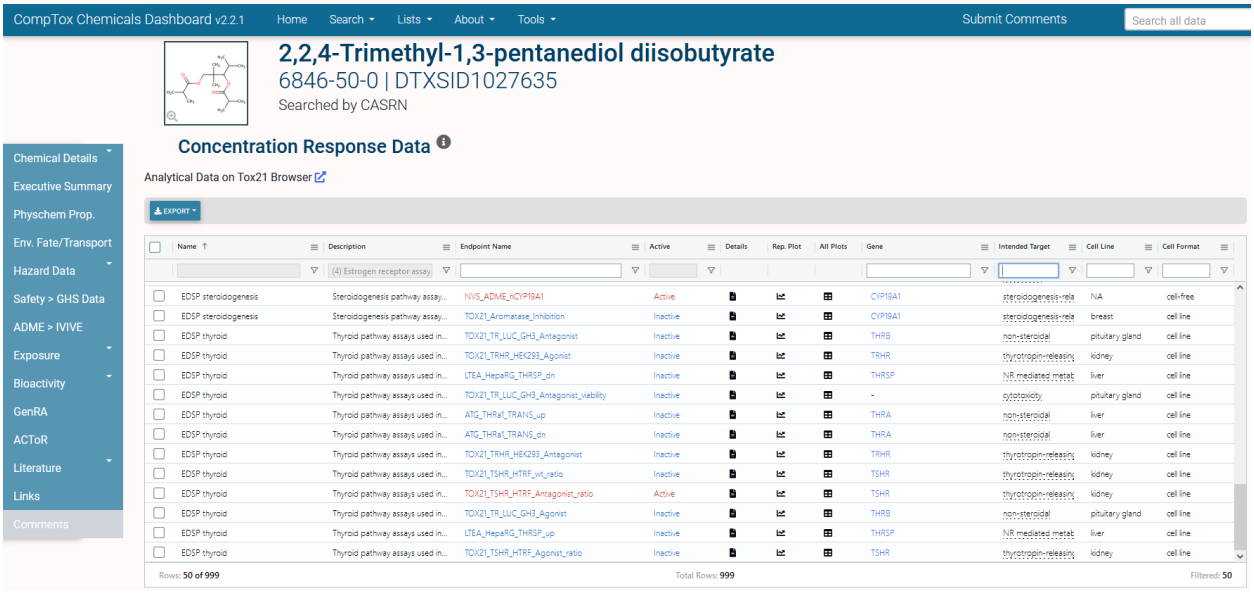


APPENDIX G: CompTox Endocrine Disruption Screening Program (EDSP) for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)









APPENDIX H: Danish QSAR Endocrine Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

Endocrine and Molecular Endpoints

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

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
specificity					
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			45814.54	3417.772	197.8807
- µM			159955.8	11932.73	690.8759
- 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			9268.375	62.3711	123.283
- µM			32359.38	217.761	430.4274
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at max. 10 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) Inhibition at any concentration (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Retinoic Acid Receptor (RAR) inhibition at max. 10 µM (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon Receptor (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	INC_OUT	NEG_OUT	INC_OUT	NEG_OUT
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_OUT	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_OUT	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (Human *in vitro*)	NEG	N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (Human	NEG	N/A	N/A	NEG_IN	N/A

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

DTU-developed models

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

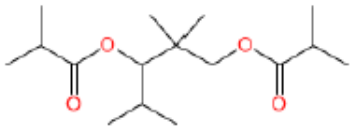
OECD QSAR Toolbox v.4.2 profilers

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

APPENDIX I: VEGA Endocrine Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

1. Prediction Summary

Prediction for compound Molecule 0 -

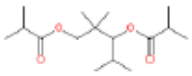


EXPERIMENTAL DATA

E xperimental value is NON-active. Model prediction is NON-active (GOOD reliability).
The following relevant fragments have been found: ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: NON-active
Predicted ER-mediated effect: NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 1
No. alerts for possible non-activity: 2
Structural Alerts: ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 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:1091 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Compound #2

CAS: N.A.
Dataset id:673 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881
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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

Compound #3

CAS: N.A.
Dataset id:401 (Training Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835
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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

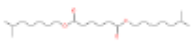
Compound #4

CAS: N.A.
Dataset id:372 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
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 also 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

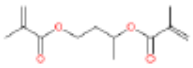


Compound #5

CAS: N.A.
Dataset id:900 (Training Set)
SMILES: O=C(OCCCCCC(C)C)CCCCC(=O)OCCCCCC(C)C
Similarity: 0.829
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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2



Compound #6

CAS: N.A.
Dataset id:888 (Training Set)
SMILES: O=C(OCCC(OC(=O)C(=C)C)C)C(=C)C
Similarity: 0.826
Experimental value : NON-active
Predicted value : NON-active

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Symbols explanation:

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

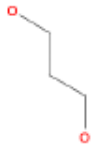
⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

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

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

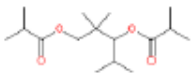
(Molecule 0) Reasoning on fragments/structural alerts - 1 of 3:.

Fragment found: ER non-activity alert no. 29



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

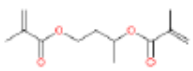
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id:1091 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9



CAS: N.A.
Dataset id:888 (Training Set)
SMILES: O=C(OCCC(OC(=O)C(=C)C)C)C(=C)C
Similarity: 0.826

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

CAS: N.A.
Dataset id:678 (Training Set)
SMILES: O=C(OCC(O)CO)CCCCCCCCCCC
Similarity: 0.797

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Alerts (not found also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2; ER possible non-activity alert no. 3

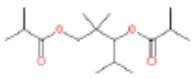
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

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

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

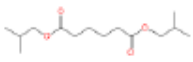
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id:1091 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

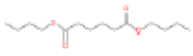


CAS: N.A.
Dataset id:673 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881

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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2



CAS: N.A.
Dataset id:401 (Training Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835

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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

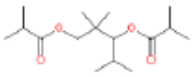
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: ER possible non-activity alert no. 9

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

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



CAS: N.A.
Dataset id:1091 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1

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

Alerts (found also in the target): ER non-activity alert no. 29; ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

CAS: N.A.
Dataset id:673 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881

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 also in the target): ER non-activity alert no. 1; ER possible non-activity alert no. 2

CAS: N.A.
Dataset id:401 (Training Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835

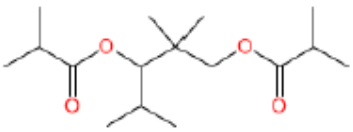
Experimental value : NON-active
Predicted value : NON-active

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

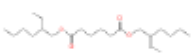


Prediction: Reliability:

Prediction is Inactive, but the result shows some critical aspects, which require to be checked:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not optimal

Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 12
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

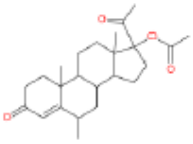


Compound #1

CAS: 103-23-1
Dataset id:9 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive

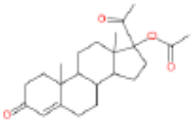
Compound #2

CAS: 40596-69-8
Dataset id:5 (Training Set)
SMILES: O=C(OC(C)C)C=C(C=CCC(C)CCCC(OC)(C)C)C
Similarity: 0.761
Experimental value : Inactive
Predicted value : Active



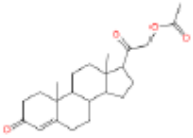
Compound #3

CAS: 71-58-9
Dataset id:88 (Training Set)
SMILES: O=C(OC3(C(=O)C)(CCC2C4CC(C1=CC(=O)CCC1(C)C4(CCC23(C)))C))C
Similarity: 0.746
Experimental value : Inactive
Predicted value : Inactive



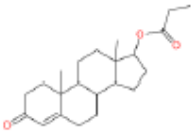
Compound #4

CAS: 302-23-8
Dataset id:111 (Training Set)
SMILES: O=C(OC3(C(=O)C)(CCC2C4CCC1=CC(=O)CCC1(C)C4(CCC23(C))))C
Similarity: 0.745
Experimental value : Inactive
Predicted value : Inactive



Compound #5

CAS: 56-47-3
Dataset id:122 (Training Set)
SMILES: O=C(OCC(=O)C2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))C
Similarity: 0.739
Experimental value : Inactive
Predicted value : Inactive



Compound #6

CAS: 57-85-2
Dataset id:108 (Training Set)
SMILES: O=C(OC2CCC3C4CCC1=CC(=O)CCC1(C)C4(CCC23(C)))CC
Similarity: 0.736
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.759 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.792 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.529 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

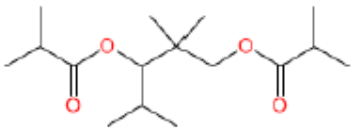
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

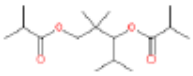


EXPERIMENTAL DATA

E xperimental value is NON-active. Model prediction is NON-active (GOOD reliability).
The following relevant fragments have been found: ER alert no. 59, inactive

Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: NON-active
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 1
Structural Alerts: ER alert no. 59, inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

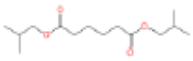
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 6846-50-0
Dataset id:984 (Training Set)
SMILES: CC(C)C(=O)OC(C(C)C)C(C)(C)COC(=O)C(C)C
Similarity: 1
Experimental value : NON-active
Predicted value : NON-active

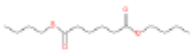
Alerts (found also in the target): ER alert no. 59, inactive



Compound #2

CAS: 141-04-8
Dataset id:1184 (Training Set)
SMILES: CC(C)COC(=O)CCCCC(=O)OCC(C)C
Similarity: 0.881
Experimental value : NON-active
Predicted value : NON-active

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



Compound #3

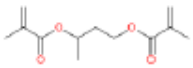
CAS: 105-99-7
Dataset id:539 (Training Set)
SMILES: CCCCOC(=O)CCCCC(=O)OCCCC
Similarity: 0.835
Experimental value : NON-active
Predicted value : NON-active

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

Compound #4

CAS: 103-23-1
Dataset id:349 (Training Set)
SMILES: CCCCC(COC(=O)CCCCC(=O)OCC(CCCC)CC)CC
Similarity: 0.832
Experimental value : NON-active
Predicted value : NON-active

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



Compound #5

CAS: 1189-08-8
Dataset id:1379 (Training Set)
SMILES: CC(=C)C(=O)OCCC(C)OC(=O)C(C)=C
Similarity: 0.826
Experimental value : NON-active
Predicted value : NON-active

Alerts (not found also in the target): ER alert no. 33, inactive

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

Compound #6

CAS: 110-33-8
Dataset id:908 (Training Set)
SMILES: CCCCCCOC(=O)CCCCC(=O)OCCCCCC
Similarity: 0.824
Experimental value : NON-active
Predicted value : NON-active

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

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

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

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

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

Symbols explanation:

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

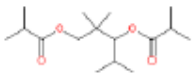
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: ER alert no. 59, inactive

Fragment related to ER inactivity (high reliability), defined by the SMARTS:OCC(C)(C)CO

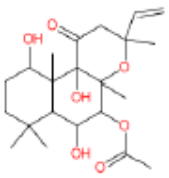
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 6846-50-0
Dataset id:984 (Training Set)
SMILES: CC(C)C(=O)OC(C(C)C)C(C)(C)COC(=O)C(C)C
Similarity: 1

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

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

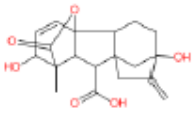


CAS: 66575-29-9
Dataset id:1221 (Training Set)
SMILES: CC1(C)CCC(O)C2(C)C1C(O)C(OC(C)=O)C1(C)OC(C)(CC(=O)C12O)C=C
Similarity: 0.716

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

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

Alerts (not found also in the target): ER alert no. 16, active; ER alert no. 18, inactive; ER alert no. 25, inactive; ER alert no. 75, inactive



CAS: 77-06-5
Dataset id:362 (Training Set)
SMILES: CC12C3C(C(O)=O)C45CC(O)(CCC4C3(C=CC1O)OC2=O)C(=C)C5
Similarity: 0.687

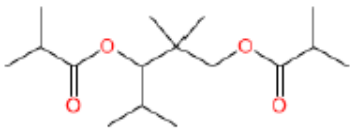
Experimental value : NON-active
Predicted value : NON-active

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

Alerts (not found also in the target): ER alert no. 11, active; ER alert no. 25, inactive; ER alert no. 43, inactive; ER alert no. 118, inactive; ER alert no. 121, inactive; ER alert no. 137, active

1. Prediction Summary

Prediction for compound Molecule 0 -

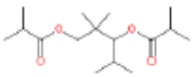


EXPERIMENTAL DATA

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

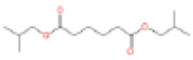
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: Inactive
Predicted TR alpha class: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



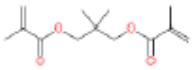
Compound #1

CAS: 6846-50-0
Dataset id:2523 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1
Experimental value : Inactive
Predicted value : Inactive



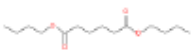
Compound #2

CAS: 141-04-8
Dataset id:2536 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881
Experimental value : Inactive
Predicted value : Inactive



Compound #3

CAS: 1985-51-9
Dataset id:2525 (Training Set)
SMILES: O=C(OCC(C)(C)COC(=O)C(=C)C)C(=C)C
Similarity: 0.837
Experimental value : Inactive
Predicted value : Inactive

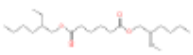


Compound #4

CAS: 105-99-7
Dataset id:2788 (Training Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835
Experimental value : Inactive
Predicted value : Inactive

Compound #5

CAS: 6938-94-9
Dataset id:2285 (Training Set)
SMILES: O=C(OC(C)C)CCCCC(=O)OC(C)C
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive



Compound #6

CAS: 103-23-1
Dataset id:2550 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Symbols explanation:

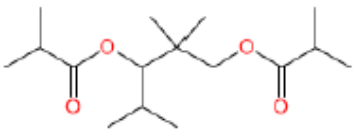
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

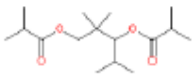


EXPERIMENTAL DATA

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

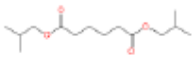
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: Inactive
Predicted TR beta class: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



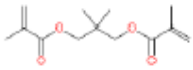
Compound #1

CAS: 6846-50-0
Dataset id:2535 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1
Experimental value : Inactive
Predicted value : Inactive



Compound #2

CAS: 141-04-8
Dataset id:2548 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881
Experimental value : Inactive
Predicted value : Inactive



Compound #3

CAS: 1985-51-9
Dataset id:2537 (Training Set)
SMILES: O=C(OCC(C)(C)COC(=O)C(=C)C)C(=C)C
Similarity: 0.837
Experimental value : Inactive
Predicted value : Inactive

Compound #4

CAS: 105-99-7
Dataset id:2800 (Training Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835
Experimental value : Inactive
Predicted value : Inactive

Compound #5

CAS: 6938-94-9
Dataset id:2295 (Training Set)
SMILES: O=C(OC(C)C)CCCCC(=O)OC(C)C
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive

Compound #6

CAS: 103-23-1
Dataset id:2562 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Symbols explanation:

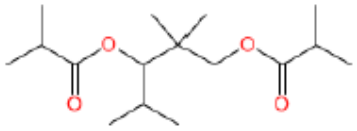
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

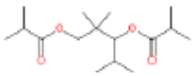


EXPERIMENTAL DATA

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

Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: Inactive
Predicted Receptor Activity: Inactive
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



Compound #1

CAS: N.A.
Dataset id:1697 (Training Set)
SMILES: CC(C)C(OC(=O)C(C)C)C(C)(C)COC(=O)C(C)C
Similarity: 1
Experimental value : Inactive
Predicted value : Inactive

Compound #2

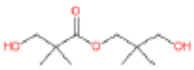
CAS: N.A.
Dataset id:1427 (Training Set)
SMILES: CC(C)COC(=O)CCCCC(=O)OCC(C)C
Similarity: 0.881
Experimental value : Inactive
Predicted value : Inactive

Compound #3

CAS: N.A.
Dataset id:1214 (Training Set)
SMILES: CCCCOC(=O)CCCCC(=O)OCCCC
Similarity: 0.835
Experimental value : Inactive
Predicted value : Inactive

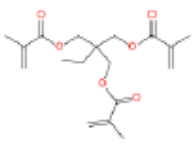
Compound #4

CAS: N.A.
Dataset id:1196 (Training Set)
SMILES: CCCCC(CC)COC(=O)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : Inactive
Predicted value : Inactive



Compound #5

CAS: N.A.
Dataset id:1306 (Training Set)
SMILES: CC(C)(CO)COC(=O)C(C)(C)CO
Similarity: 0.831
Experimental value : Inactive
Predicted value : Inactive



Compound #6

CAS: N.A.
Dataset id:1540 (Training Set)
SMILES: CCC(COC(=O)C(C)=C)(COC(=O)C(C)=C)COC(=O)C(C)=C
Similarity: 0.83
Experimental value : Inactive
Predicted value : Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Symbols explanation:

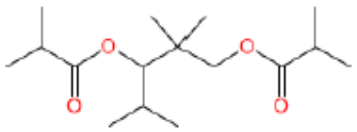
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

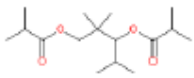


EXPERIMENTAL DATA

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

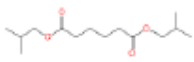
Compound: Molecule 0
Compound SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Experimental value: INA
Predicted TPO: INA
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



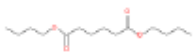
Compound #1

CAS: N.A.
Dataset id:896 (Training Set)
SMILES: O=C(OCC(C)(C)C(OC(=O)C(C)C)C(C)C)C(C)C
Similarity: 1
Experimental value : INA
Predicted value : INA



Compound #2

CAS: N.A.
Dataset id:919 (Training Set)
SMILES: O=C(OCC(C)C)CCCCC(=O)OCC(C)C
Similarity: 0.881
Experimental value : INA
Predicted value : INA



Compound #3

CAS: N.A.
Dataset id:879 (Test Set)
SMILES: O=C(OCCCC)CCCCC(=O)OCCCC
Similarity: 0.835
Experimental value : INA
Predicted value : INA

Compound #4

CAS: N.A.
Dataset id:934 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.832
Experimental value : INA
Predicted value : INA

Compound #5

CAS: N.A.
Dataset id:921 (Test Set)
SMILES: O=C(OCCCC)CCCCCCCCC(=O)OCCCC
Similarity: 0.815
Experimental value : INA
Predicted value : INA

Compound #6

CAS: N.A.
Dataset id:932 (Training Set)
SMILES: O(OC(C)(C)CCC(OOC(C)(C)C)(C)C)C(C)(C)C
Similarity: 0.813
Experimental value : INA
Predicted value : INA

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

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

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

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

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

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

Symbols explanation:

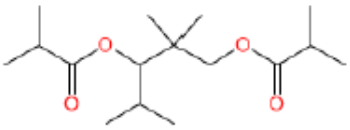
The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

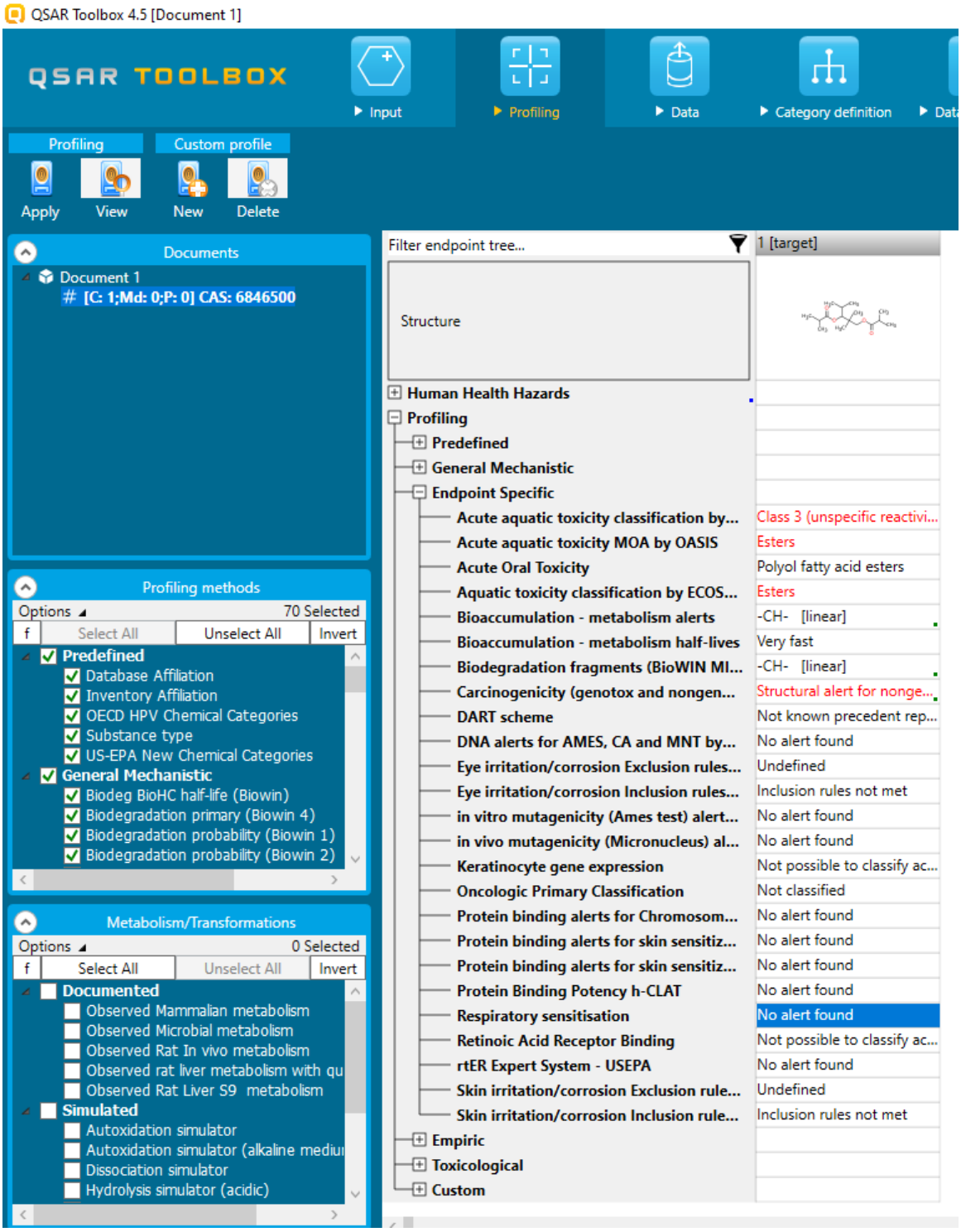


Prediction: Reliability:

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

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

APPENDIX J: OECD Toolbox Respiratory Sensitization Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)



APPENDIX K: EPI Suite™ Modeling Results for Trimethyl pentanyl diisobutyrate (CAS #6846-50-0)

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

CAS Number: 6846-50-0
SMILES : CC(C)C(C(C)(C)COC(=O)C(C)C)OC(=O)C(C)C
CHEM : Trimethyl pentanyl diisobutyrate
MOL FOR: C16 H30 O4
MOL WT : 286.42
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 4.91
Boiling Point (deg C) : 281.00
Melting Point (deg C) : -70.00
Vapor Pressure (mm Hg) : 0.0113
Water Solubility (mg/L): 13
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 4.91

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 271.50 (Adapted Stein & Brown method)
Melting Pt (deg C): -30.57 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00532 (Modified Grain method)
VP (Pa, 25 deg C) : 0.709 (Modified Grain method)
MP (exp database): -70 deg C
BP (exp database): 280 deg C
VP (exp database): 6.60E-04 mm Hg (8.80E-002 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 3.444
log Kow used: 4.91 (user entered)
melt pt used: -70.00 deg C
Water Sol (Exper. database match) = 15 mg/L (25 deg C)
Exper. Ref: OECD SIDS

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 11.457 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 9.42E-006 atm-m3/mole (9.55E-001 Pa-m3/mole)
Group Method: 1.07E-005 atm-m3/mole (1.08E+000 Pa-m3/mole)
Exper Database: 1.66E-05 atm-m3/mole (1.68E+000 Pa-m3/mole)

For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 3.276E-004 atm-m3/mole (3.319E+001 Pa-m3/mole)
VP: 0.0113 mm Hg (source: User-Entered)
WS: 13 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 4.91 (user entered)
Log Kaw used: -3.168 (exp database)
Log Koa (KOAWIN v1.10 estimate): 8.078
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7756
Biowin2 (Non-Linear Model) : 0.9954
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.6345 (weeks-months)
Biowin4 (Primary Survey Model) : 3.7390 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5319
Biowin6 (MITI Non-Linear Model): 0.3547
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.4284
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): 1.51 Pa (0.0113 mm Hg)
Log Koa (Koawin est): 8.078
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.99E-006
Octanol/air (Koa) model: 2.94E-005
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 7.19E-005
Mackay model : 0.000159
Octanol/air (Koa) model: 0.00234

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 11.4614 E-12 cm3/molecule-sec
Half-Life = 0.933 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 11.199 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000116 (Junge-Pankow, Mackay avg)

0.00234 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 490 L/kg (MCI method)
Log Koc: 2.690 (MCI method)
Koc : 3234 L/kg (Kow method)
Log Koc: 3.510 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 1.490E-002 L/mol-sec
Kb Half-Life at pH 8: 1.474 years
Kb Half-Life at pH 7: 14.745 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 2.907 (BCF = 806.5 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.3619 days (HL = 0.04346 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.281 (BCF = 19.11)
Log BAF Arnot-Gobas method (upper trophic) = 1.281 (BAF = 19.11)
log Kow used: 4.91 (user entered)

Volatilization from Water:
Henry LC: 1.66E-005 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 61.42 hours (2.559 days)
Half-Life from Model Lake : 811.9 hours (33.83 days)

Removal In Wastewater Treatment:
Total removal: 74.73 percent
Total biodegradation: 0.65 percent
Total sludge adsorption: 73.89 percent
Total to Air: 0.19 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.887**	**22.4**	**1000**
Water	**18.3**	**900**	**1000**
Soil	**80.3**	**1.8e+003**	**1000**
Sediment	**0.494**	**8.1e+003**	**0**

Persistence Time: 1e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.887	22.4	1000
Water	18.3	900	1000
water	(18.2)		

biota (0.074)
suspended sediment (0.0134)
Soil 80.3 1.8e+003 1000
Sediment 0.494 8.1e+003 0
Persistence Time: 1e+003 hr

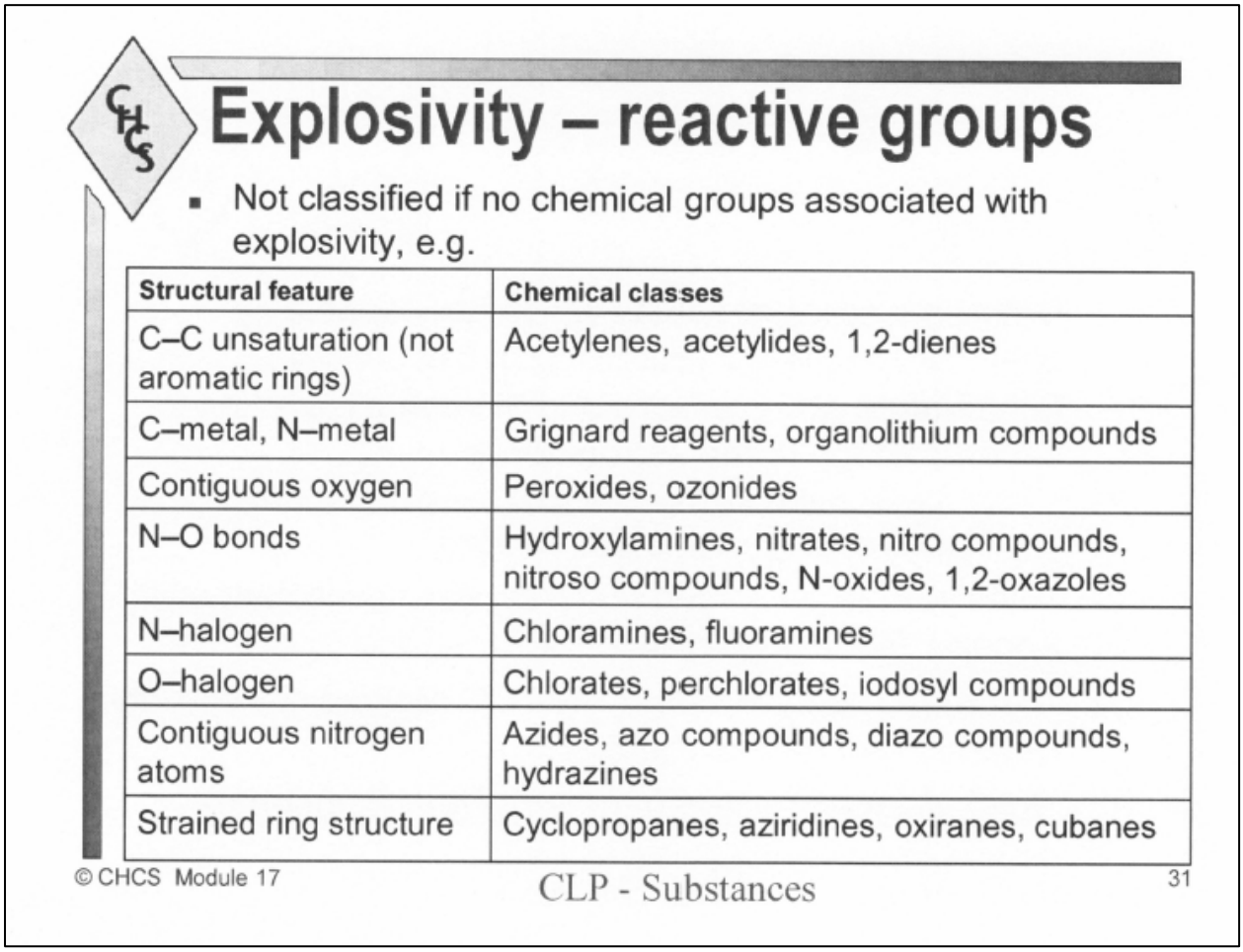
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.643	22.4	1000
Water	11.9	900	1000
water	(11.3)		
biota	(0.046)		
suspended sediment	(0.566)		
Soil	65	1.8e+003	1000
Sediment	22.4	8.1e+003	0

Persistence Time: 1.34e+003 hr

APPENDIX L: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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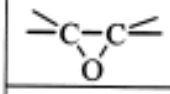
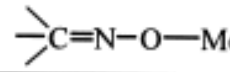
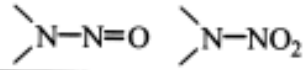
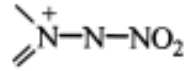
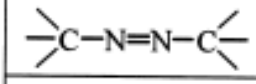
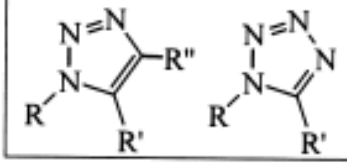
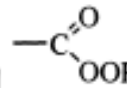
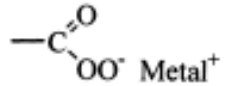
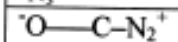
Explosivity – Full List

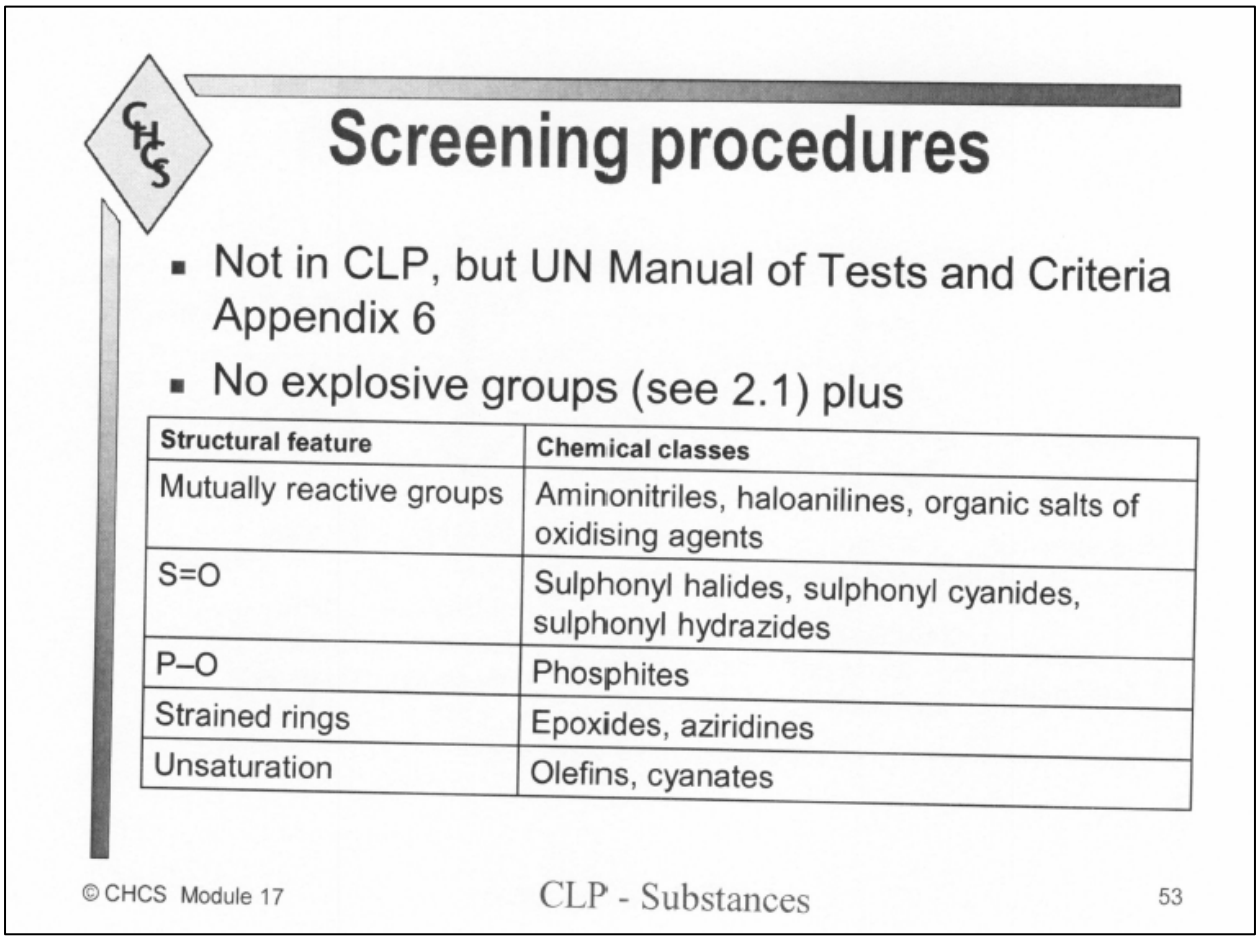
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



APPENDIX M: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for trimethyl pentanyl diisobutyrate. The GreenScreen® Benchmark Score for trimethyl pentanyl diisobutyrate has not changed over time. The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2016 and with this 2023 version 1.4 update.

Table 6: Change in GreenScreen® Benchmark™ for Trimethyl pentanyl diisobutyrate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
November 10, 2015	BM-2	v. 1.2	New GreenScreen® assessment.
April 22, 2016	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template.
November 20, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.

Licensed GreenScreen® Profilers

Trimethyl Pentanyl Diisobutyrate GreenScreen® Evaluation (v1.2) Prepared by:

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ToxServices LLC

2,2,4-Trimethyl-1,3-Pentanediol Diisobutyrate GreenScreen® Evaluation (v1.2) QC'd by:

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