N,N'-BIS(2,2,6,6-TETRAMETHYL-4-PIPERIDYL)-N,N'-DIFORMYLHEXAMETHYLENEDIAMINE

(CAS #124172-53-8)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: August 28, 2023

Expiration Date: August 28, 2028

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1526 New Hampshire Ave., N.W., Suite 350
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is a UV stabilizer in plastics at typical use concentrations of 0.5-0.8%. In the United States, it is approved as a food contact substance at levels up to 0.25% when used as a UV stabilizer in polystyrene, styrene block copolymers, acrylonitrile copolymers and resins, and polypropylene.

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is a white powder that is highly soluble in water. It is not volatile, non-reactive, and non-flammable.

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified Due to Insufficient Data"). Prior to data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c (lowered to U due to data gaps)
    - Very High Persistence-P + Moderate Group I Human Toxicity (developmental toxicity-D)
    - Very High P + Moderate Group II Human Toxicity (single dose systemic toxicity-ST)
    - Very High P + High Group II Human Toxicity (eye irritation-IrE)
    - Very High P + Moderate Ecotoxicity (acute aquatic-AA)
- Benchmark 2e (lowered to U due to data gaps)
    - Moderate Group I Human Toxicity (D)

Data gaps (DG) exist for carcinogenicity-C, reproductive toxicity-R, endocrine activity-E, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine does not meet the requirements for a GreenScreen Benchmark™ Score of 2 due to the hazard data gaps. In a worst-case scenario, if N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine were assigned a High score for the data gaps C, R, E or Nr*, it would be categorized as a Benchmark 1 Chemical.

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

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

Type I (input data) uncertainties in N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformyl hexamethylenediamine's NAMs dataset include lack of, or insufficient, experimental data for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, and persistence, and the lack of validated test methods for respiratory sensitization. N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine's Type II (extrapolation output) uncertainties include certain *in silico* models not defining the applicability domain, conflicting model predictions with similar reliability, inability of certain models in producing reliable predictions, limitations of *in vitro* genotoxicity tests in mimicking mammalian metabolism and their focusing on a few events in the process of mutagenicity, uncertain *in vivo* relevance of *in silico* modeling on endocrine receptor binding activities due to lack of toxicokinetic considerations, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-

diformylhexamethylenediamine'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 N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine

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*	*	*								
DG	**L**	DG	*M*	DG	**L**	*M*	*L*	*L*	DG	**L**	*L*	**L**	**H**	**M**	*L*	*vH*	**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 N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: July 13, 2023

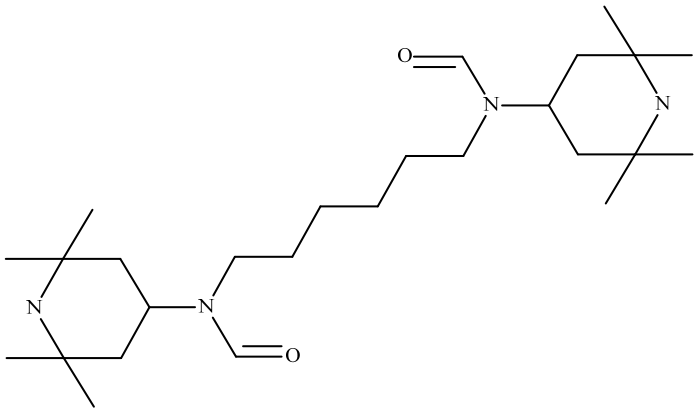
Quality Control Performed By:
Name: Mouna Zachary, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 28, 2023

Expiration Date: August 28, 2028[2]

Chemical Name: N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine

CAS Number: 124172-53-8[3]

Chemical Structure(s):

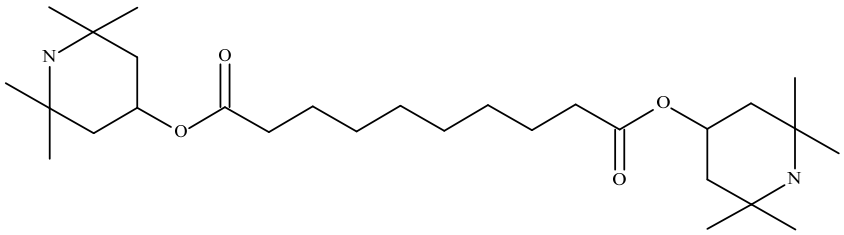


(PubChem 2023)

Also called:
N,N'-(Hexane-1,6-diyl)bis(N-(2,2,6,6-tetramethylpiperidin-4-yl)formamide); Formamide, N,N'-1,6-hexanediylbis[N-(2,2,6,6-tetramethyl-4-piperidinyl)-; N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide; N-[6-[formyl-(2,2,6,6-tetramethylpiperidin-4-yl)amino]hexyl]-N-(2,2,6,6-tetramethylpiperidin-4-yl)formamide; N,N'-bis-[2,2,6,6-tetra-methylpiperidin-4-yl]-N,N'-bisformyl-1,6-diaminohexane, Uvinul 4050H (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).
[3] The CAS number 124172-53-8 is associated with two EC numbers in ECHA: 602-984-2, formamide, N,N'-1,6-hexanediylbis[N-(2,2,6,6-tetramethyl-4-piperidinyl)-, and 413-610-0, N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide. The chemical names appear to refer to the same chemical. See: https://echa.europa.eu/search-for-chemicals?p_p_id=disssimplesearch_WAR_disssearchportlet&p_p_lifecycle=0&_disssimplesearch_WAR_disssearchportlet_searchOccurred=true&_disssimplesearch_WAR_disssearchportlet_sessionCriteriaId=dissSimpleSearchSessionParam101401689854675608

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine has a limited toxicological dataset. ToxServices identified bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9), also a hindered amine light/UV stabilizer, as a surrogate. It differs from the parent compound by having two ester groups instead of two formamide groups, and having a slightly longer alkyl chain (by two carbons) in the middle. As the surrogate does not adequately address the toxicities of the formamide moieties, ToxServices included the reproductive toxicity and neurotoxicity data on the surrogate to represent the toxicities of the piperidine moieties.



Surrogate: Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9)

Identify Applications/Functional Uses:
Light/ultra violet (UV) stabilizer in plastics at typical concentrations of 0.5-0.8% (PubChem 2023).

Known Impurities:
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine (tradename: UVINUL 4050H) has a purity of > 99.5%, and have three impurities: formamide (CAS #75-12-7) 0.05% by weight, and two unknowns at 0.04% and 0.05% each (NICNAS 1997). Impurities are not evaluated in this assessment. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine[4,5 6,7]: N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified Due to Insufficient Data") (CPA 2018b). Prior to data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c (lowered to U due to data gaps)
  - Very High Persistence-P + Moderate Group I Human Toxicity (developmental toxicity-D)
  - Very High P + Moderate Group II Human Toxicity (single dose systemic toxicity-ST)
  - Very High P + High Group II Human Toxicity (eye irritation-IrE)
  - Very High P + Moderate Ecotoxicity (acute aquatic-AA)
- Benchmark 2e (lowered to U due to data gaps)
  - Moderate Group I Human Toxicity (D)

[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.

Data gaps (DG) exist for carcinogenicity-C, reproductive toxicity-R, endocrine activity-E, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis) (CPA 2018b), N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformyl hexamethylenediamine does not meet the requirements for a GreenScreen Benchmark™ Score of 2 due to the hazard data gaps. In a worst-case scenario, if N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine were assigned a High score for the data gaps C, R, E or Nr*, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is hydrolytically stable and is not readily or inherently biodegradable (see persistence section). OECD Toolbox predicts stepwise oxidation of the two formamide functional groups as autooxidation products in alkaline medium (Appendix E), as shown in Table 1, below. Due to lack of additional data, ToxServices conservatively assumes that these predicted autoxidation products are relevant and feasible. These chemicals are not in the Pharos database, which is equivalent to an LT-UNK, and hence do not impact the benchmark score of the parent compound.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[8,9]
Any	Autooxidation in alkaline medium	6-[Carboxy-(2,2,6,6-tetramethyl-4-piperidyl)amino]hexyl-(2,2,6,6-tetramethyl-4-piperidyl)carbamic acid	N/A	Yes	Yes	Not in Pharos
Any	Autooxidation in alkaline medium	6-[Formyl-(2,2,6,6-tetramethyl-4-piperidyl)amino]hexyl-(2,2,6,6-tetramethyl-4-piperidyl)carbamic acid	N/A	Yes	Yes	Not in Pharos

[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).

Introduction

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is a low molecular weight hindered amine light stabilizer (HALS) that is commonly used as a thermal/light stabilizing agent of polymeric materials at typical use concentrations of 0.5-0.8% (PubChem 2023). In the United States, it is approved as a food contact substance at levels up to 0.25% when used as a UV stabilizer in polystyrene, styrene block copolymers, acrylonitrile copolymers and resins, and polypropylene (U.S. FDA 2023). No information on methods of manufacturing was found.

ToxServices assessed N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine 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 (SCIL)

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).

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 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 N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine can be found in Appendix C.

- N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not listed on the U.S. DOT list.
- N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is on the following lists for multiple endpoints.
    - GHS New Zealand: Hazardous to the aquatic environment – chronic category 3
    - GHS Australia: H412 – Harmful to aquatic life with long lasting effects [hazardous to the aquatic environment (chronic) – Category 3]
    - EU GHS (H Statements) Annex 6 Table 3-1: H412 – Harmful to aquatic life with long lasting effects [hazardous to the aquatic environment (chronic) – Category 3]
    - German FEA Substances Hazardous to Waters: Class 1 – Low Hazard to Waters
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

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

Hazard Statement and Occupational Control

Two Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements that were harmonized across the European Union (EU) were identified for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine, as indicated 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 N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8) (ECHA 2023a)

H Statement	H Statement Details
H319	Causes serious eye irritation
H412	Harmful to aquatic life with long lasting effects

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, safety glasses, and protective clothing	ECHA 2023b	None identified	N/A

N/A: Not applicable.

Physicochemical Properties of N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is a white crystalline powder with a small fraction within the respiratory range (i.e., diameter < 10 µm). It is not volatile based on the low vapor pressure and high boiling point. It is highly soluble in water (13 g/L), and the partition coefficient is pH dependent with the value of 2 reported under neutral conditions, and 0.8 under basic conditions.

Table 4: Physical and Chemical Properties of N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

Property	Value	Reference
Molecular formula	C26H50N4O2	PubChem 2023
SMILES Notation	CC1(CC(CC(N1)(C)C)N(CCCCCCN(C=O)C2CC(NC(C2)(C)C)(C)C)C=O)C	PubChem 2023
Molecular weight	450.7	PubChem 2023
Physical state	Solid	PubChem 2023
Appearance	Dry powder, white	PubChem 2023, ECHA 2023b
Melting point	157.3°C at 1,013 hPa (EU Method A.1)	ECHA 2023b
Boiling point	> 400°C at 1,013 hPa (exp.)	ECHA 2023c
Vapor pressure	0 Pa at 100.6°C (EU Method A.4) 0 Pa at 20°C (est.)	ECHA 2023b
Water solubility	13,000 mg/L at 25°C and pH of 11 (EU Method A.6)	ECHA 2023b
Dissociation constant	pKa = 9.35 at 22°C (OECD Guideline 112)	ECHA 2023c

Table 4: Physical and Chemical Properties of N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)		
Property	**Value**	**Reference**
Density/specific gravity	1.08at 20°C (EU Method A.3)	ECHA 2023b
Partition coefficient	Log K_{ow} = 0.8 at 25°C, and pH of 9 Log K_{ow} = -2 at 25°C and pH of 7 (EU Method. A.8)	ECHA 2023b
Particle size	D10 = 3.56 µm D50 = 26.56 µm (mass median diameter, MMD) D90 = 101.00 µm D100 = 288.7 µm	ECHA 2023b
Structure	Crystalline	NICNAS 1997
Bioavailability	Limited, see toxicokinetic section below	

Toxicokinetics

No experimental toxicokinetics data were identified for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine. Authors of its REACH dossier estimated its toxicokinetic behavior using the European Chemical Agency (ECHA)'s guidance, as shown below (ECHA 2023d).

- *Absorption:*
  - *Oral:* N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine has some potential for oral absorption based on its relatively small molecular weight, high hydrophilicity, and moderate log K_{ow} (between -1 and 4). Limited evidence of toxicities observed in a subacute toxicity study in rats suggests a low oral absorption potential.
  - *Dermal:* The molecular weight of > 100, the water solubility of > 10 g/L, and the low log K_{ow} of < 0 indicates a low dermal absorption potential.
  - *Inhalation:* N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is expected to have limited inhalation absorption, as a non-volatile particulate. The low log K_{ow} does not favor direct absorption across the respiratory tract epithelium by passive diffusion.
- *Distribution:* The high water solubility favors wide systemic distribution, but the low log K_{ow} suggests that it is unlikely to distribute into cells.
- *Metabolism:* The lack of genotoxicity in *in vitro* and *in vivo* studies indicates that N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not likely to be metabolized to genotoxic compounds.
- *Elimination:* Due to the high water solubility and low log K_{ow}, accumulation of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in the fatty tissues in the unchanged form is unlikely. Urine excretion is likely the main route of elimination of unchanged N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine.

In summary, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine has limited oral and inhalation absorption, and low dermal absorption potential. It may distribute widely in the body but is not expected to accumulate in cells or fatty tissues. No genotoxic metabolites are expected to form. Elimination is expected to occur mainly via the urine for the unchanged compound.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): DG
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Data Gap for carcinogenicity based on insufficient data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2019, 2021
  - ToxServices attempted to evaluate the carcinogenic potential of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine using OncoLogic, but version 9 could not evaluate its structural class (Appendix D). While version 8.0 can evaluate aldehydes, it does not allow the evaluation of the aldehyde moiety within a formamide group as in the target compound. Therefore, OncoLogic could not evaluate this chemical.
- OECD 2023
  - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (Appendix E).
- VEGA 2023
  - ToxServices used six VEGA models to predict the carcinogenicity of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine (Appendix F). *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).*
    - The CAESAR model predicts it to be a non-carcinogen, with moderate reliability. The global ADI is 0.632, and therefore the results are not included in the weight of evidence.
    - The ISS model predicts it to be a non-carcinogen, with moderate reliability. The global ADI is 0.711, but the concordance index is < 0.7 (i.e., 0.481).
    - The IRFMN-ISSCAN-CGX model predicts it to be a carcinogen, with moderate reliability. The global ADI is 0.782. However, the accuracy index is < 0.7 (i.e., 0.669).
    - The IRFMN-Antares model predicts it to be a non-carcinogen, with moderate reliability. The global ADI is 0.688, and therefore the results are not included in the weight of evidence.
    - The IRFMN oral classification model predicts it to be a carcinogen, with moderate reliability. The global ADI is 0.708. However, the concordance index is < 0.7 (i.e., 0.508).
    - The IRFMN inhalation classification model predicts it to be a non-stabilizer, with moderate reliability. The global ADI is 0.713. All other indices are > 0.7.
  - Overall, there are no high reliability predictions from any of the 6 VEGA models. Predictions from two models (CAESAR and IRFMN-Antares) are excluded from the weight of evidence due to global ADIs < 0.7. The remaining four models produced conflicting predictions with moderate reliability, and three of the four predictions (two positive, one negative) have concordance indices, or accuracy indices < 0.7, indicating lower reliability. Only one of the four models (IRFMN inhalation classification) produced a prediction

(negative) with all indices >0.7, and therefore the overall weight of evidence slightly supports a low concern for carcinogenicity.

- DTU 2023
    - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is out of domain of all models in the Danish QSAR database (Appendix G).
- Based on the weight of evidence, a score of Data Gap was assigned. N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine has no structural alerts for genotoxic or non-genotoxic carcinogenesis. OncoLogic and Danish QSAR models could not evaluate the target compound. The 6 models in VEGA produced mixed results, but overall supports a low carcinogenic concern. However, the VEGA models that produced reliable prediction are all rule-based models, and there are no reliable predictions from statistical models. ToxServices attempted to look for experimental data or perform modeling using statistical based models for the moieties of concern for this compound, i.e., the piperidine and formamide moieties, but inadequate data were identified and/or no reliable predictions could be generated.

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for mutagenicity/genotoxicity based on negative results for bacterial reverse mutation, mammalian gene mutation and chromosome aberration *in vitro,* and mammalian micronucleus *in vivo*. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, (Note: the four ECHA dossiers have duplicate entries with limited details and confusing study dates for seemingly identical studies. ToxServices made the best effort in identifying the unique studies and glean study details from each of the dossiers)
    - *In vitro:* In a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471, *Salmonella typhimurium* strains TA98, TA100, TA1537 and TA1538 were exposed to N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in DMSO at concentrations of 20 – 5,000 µg/plate with and without metabolic activation. Cytotoxicity was observed with TA98 without metabolic activation at 5,000 µg/plate. Information on controls was not available. There were no increase in revertants (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Hoffmann 1992 according to NICNAS 1997).
    - *In vitro:* In a GLP-unspecified mammalian cell gene mutation assay conducted according to OECD Guideline 476, no genotoxicity was found. No additional details were provided (Klimisch 2, reliable with restrictions) (Unnamed study 2008)
    - *In vitro:* In a GLP-unspecified mammalian chromosomal aberration test conducted according to Safepharm Standard method Number JMOL 03, Chinese hamster lung (CHL) fibroblasts (V79) were exposed to N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine at 250 – 2,000 µg/mL for 6 (with metabolic activation) or 24 hours (without metabolic activation), or 62.5 – 2,000 µg/mL for 48 hours (without metabolic activation). The results were negative. No additional information was provided (Klimisch 2, reliable with restrictions) (Unnamed study 1997/ Wright 1996 according to NICNAS 1997).

- *In vivo:* In a GLP-unspecified *in vivo* micronucleus assay, NMRI mice (5/sex/dose) received N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine orally (unspecified) at 300, 600 or 1,200 mg/kg and sacrificed at 16, 24, or 48 hours afterwards. Toxicity was observed at > 300 mg/kg/day (no additional details). Information on control animals was not provided. Study authors concluded that the results were negative. No additional details were available (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Hoffmann 1992 according to NICNAS 1997).

Reproductive Toxicity (R) Score (H, M, or L): DG
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Data Gap for reproductive toxicity based on lack of sufficiently detailed data. One ECHA dossier reported a NOAEL of 1,000 mg/kg/day from a limit study to a one-generation reproductive toxicity study, but the information reported is too limited for evaluation. The surrogate bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate disrupted estrous cyclicity in an OECD Guideline 422 combined repeated dose toxicity study with reproductive/developmental toxicity screening, at 15,000 ppm in the diet, and decreased the number of implantation sites in an OECD Guideline 443 extended one generation study at 5,000 ppm in the diet. As the surrogate does not contain the formamide functional groups as the target chemical, and as the limited OECD Guideline 415 study on the target chemical do not suggest any significant reproductive effects as seen with the surrogate, ToxServices did not use the data for the surrogate to score this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023c
  - In a one-generation reproductive toxicity study (limit test) conducted according to OECD Guideline 415 in Wistar rats through dietary exposure, a NOAEL of 1,000 mg/kg/day was established. No additional details were provided (Klimisch score not available) (Unnamed study 2010).
- ECHA 2023e
  - *Surrogate: Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9):* In a GLP-compliant extended one-generation reproductive toxicity study conducted according to OECD Guideline 443, Wistar rats received bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate in the diet at 0, 500, 1,500, or 5,000 ppm. F0 animals were exposed from 10 weeks before mating for a total of 11-13 weeks (males) or up to 18 weeks (females). F0 animals were examined for mortality, clinical chemistry, thyroid hormones, urinalysis, gross pathology, sperm analysis, organ weights, and histopathology. F1 animals (Cohort 1A, 1B, 2A, 2B, 3, exposed 5 - 18 weeks) were examined for mortality, clinical signs body weight food consumption, vaginal patency, balenopreputial separation, day of first estrous, estrous cyclicity, functional observation battery, immunotoxicity, thyroid hormones, urinalysis, gross pathology, sperm analysis, splenic lymphocyte subpopulation analysis, organ weights, histopathology, neurohistopathology, and brain tissue morphometric analysis. In addition, F0 and F1 generations were examined for mating and fertility indices, precoital time, implantation sites, gestation index and duration, parturition, maternal care, sex ratio, and early postnatal pup development. Cohort 1B was extended to produce an F2 generation (Cohorts 2A and 2B) due to effects observed during the first paring. Additionally, Cohort 3 was included as a previously OECD Guideline 422 study identified effects on the thymus. Study authors identified a systemic toxicity NOAEL of 500 ppm for the F0 generation (36-41 mg/kg/day according to the ECHA record) and 1,500 ppm for the F1 generation (121-165

mg/kg/day according to the ECHA record) based on decreased body weight and food consumption, and a reproductive toxicity NOAEL of 1,500 ppm for both F0 and F1 generations (109-165 mg/kg/day according to the ECHA record) based on decreased number of implantation sites (Klimisch 1, reliable without restriction) (Unnamed study 2020).

- *Surrogate: Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9):* In a GLP-compliant OECD Guideline 422 combined repeated dose toxicity study with reproduction/developmental toxicity screening test, Wistar rats (10/sex/dose) received the test substance in the feed at 0, 1,500, 5,000, or 15,000 ppm from at least 14 days before mating to at least 28 days for males and up to 14 days after delivery for a total of 51-63 days for females. Study authors identified a systemic toxicity LOAEL of 1,500 ppm (221 mg/kg/day according to ECHA record) for parental systemic toxicity based on inflammatory infiltrates (mononuclear) in the heart and myofibers necrosis in males, a reproductive toxicity NOAEL of 5,000 ppm (894-1,113 mg/kg/day according to the ECHA record) based on disrupted estrous cycles leading to failure to get pregnant (Klimisch 1, reliable without restriction) (Unnamed study 2021).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Moderate for developmental toxicity based on reduced implantation and number of live pups/dam in a prenatal developmental toxicity study in rats in the presence of maternal toxicity. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited evidence of developmental toxicity (CPA 2018b). The confidence in the score is low as the effects may be secondary to maternal toxicity, or unrelated to treatment, and because skeletal examination results were not provided for this 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 2023c
  - In a prenatal developmental toxicity study conducted according to OECD Guideline 414 in Wistar rats by gavage, a NOAEL of 1,000 mg/kg/day was established for maternal toxicity and developmental toxicity. No additional details were provided (Klimisch score not available) (Unnamed study 2012).
    - ToxServices notes that this may be the same study described below (BASF 2011), but the information provided in ECHA is too limited to confirm.
- BASF 2011
  - In a prenatal developmental toxicity study (limit test) conducted according to OECD Guideline 414, pregnant Wistar rats (25/dose) were exposed to N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine at 0, 100, 300, or 1,000 mg/kg/day by gavage on gestational day (GD) 6 – 19. High dose dams exhibited statistically significant reduction in food consumption (87% compared to control) on GD 6-8, and body weight (5% reduction) on GD 20. Body weight gain also reduced (57% (presumably of control) on GD 8-10, 82% on GD 17-19, and 78% on GD 19-20) at this dose. In addition, there were statistically significant reductions in the number of implantation sites (8.8 vs 10.6 in control), and mean number of live fetuses/dam (8.1 vs 10.0 in control), and increase in pre-implantation loss (15.5% vs 1.9% in control) at the high dose. These animals had a 19% reduction in uterus weight. No effects were found at low or mid doses. Skeletal examinations were still ongoing at the time of the report.
    - *ToxServices notes reduced implantation, reduced number of live offspring, and*

increased implantation loss are potentially causally related effects. The dams were exposed after implantation (GD 5), and therefore the effects on pre-implantation loss are not treatment related.

Endocrine Activity (E) Score (H, M, or L): DG
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Data Gap for endocrine activity based on the lack of sufficient data. ToxCast and Danish QSAR models predicted it to be in active for estrogen activity and androgen inhibition, but no *in vivo* data were identified, and there were no data on other endocrine pathways, such as thyroid pathways, and androgen agonism.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
  - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was predicted to be inactive for estrogen receptor agonism, antagonism, and binding (Appendix H).
- DTU 2023
  - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was predicted to be negative and in domain for model battery for androgen receptor inhibition (human *in vitro*) based on the negative and in domain predictions by CASE Ultra, Leadscope, and SciQSAR models. It is out of the domains of the remaining endocrine models (Appendix G).

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
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for acute toxicity based on an oral LD_{50} of > 2,200 mg/kg and a 4-hour dust inhalation LC_{50} of > 5 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values > 2,000 mg/kg, and 4-hour dust inhalation LC_{50} values > 5 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - *Oral* LD_{50} > 2,200 mg/kg (Wistar rats, GLP, Guideline: Acute Toxic Class (ATC)-Method, similar to OECD guidelines) (Klimisch 2, reliable with restrictions) (Unnamed 1992 study/Gelbke 1992)
  - *Inhalation:* LC_{50} (4h) > 5 mg/L (Wistar rats, GLP, OECD Guideline 403) (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gamer 1992)

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Moderate for systemic toxicity (single dose) based on signs of respiratory irritation (transient accelerated breathing and bloody nasal crust) observed in an acute inhalation toxicity study, that warrants classification to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation (CPA 2018b). The confidence in the score is low as the signs of respiratory irritation appeared to be mild.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - *Oral:* In the previously described acute oral toxicity study performed under GLP according to ATC-Method (similar to OECD guidelines), Wistar rats (3/sex) received N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in olive oil by gavage at 2,200 mg/kg followed by an observation period of 14 days. There were no clinical signs, no unscheduled mortality, and no gross pathological findings (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gelbke 1992).
  - *Inhalation:* In the previously describe acute inhalation toxicity study performed under GLP according to OECD Guideline 403, Wistar rats (5/sex) were exposed to the fine powder of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine (mass median aerodynamic diameter of 2.9 μm) via head-nose inhalation at 5 mg/L for 4 hours, followed by a 14-day observation period. There were no unscheduled mortalities or treatment related gross pathological abnormalities. Clinical observations included accelerated respiration and bloody nasal crust that were reversible after 4 days (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gamer 1992).

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for systemic toxicity (repeated dose) based on a NOAEL of 714 mg/kg/day from a 28-day oral study in rats, which is higher than the duration-adjusted GHS guidance value of 300 mg/kg/day for a 28-day study. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is low as some toxicities were reported in subacute and subchronic inhalation toxicity studies, but study details are too limited for full evaluations.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - *Oral:* In a GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407, Wistar rats (5/sex/dose) received N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine by gavage at 0, 100, 300, or 1,000 mg/kg/day 5 days per week for 28 days. There were no treatment related effects on food consumption, body weight, and clinical observations. High dose females exhibited a slight decrease in serum total protein and albumin, while high dose males had a slight decrease in serum total protein (statistical significance not reported). There were no significant treatment related effects on organ weights, gross pathology, or histopathology. ECHA dossier authors identified a NOEL of 300 mg/kg/day based on the marginal effects on serum total protein, and a

NOAEL of 1,000 mg/kg/day based on a lack of adverse effects in this study (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Kirsch 1992).
    - *The NOAEL of 1,000 mg/kg/day is equivalent to a daily dose of 1,000 mg/kg/day * 5 days / 7 days = 714 mg/kg/day*.
- ECHA 2023c
    - *Inhalation:* In a GLP-unspecified subacute inhalation study conducted according to OECD Guideline 412, Wistar rats were exposed nose only to N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine aerosol for 28 days. ECHA dossier authors identified a LOAEC of 75 mg/m^3 (0.075 mg/L). No additional details were available (No Klimisch score assigned) (Unnamed 2009 study).
    - *Inhalation:* In a GLP-unspecified subchronic inhalation study conducted according to OECD Guideline 413, Wistar rats were exposed nose/head only to N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine dust for 90 days. ECHA dossier authors identified two NOAECs: 3.12 mg/m^3 and 102 mg/m^3. No additional details were available (No Klimisch score assigned) (Unnamed study 2011).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for neurotoxicity (single dose) based on lack of clinical signs and gross pathology findings indicative of neurotoxicity in acute oral and inhalation studies at doses above GHS classification. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and negative and when they are not classified under GHS (CPA 2018b). The confidence in the score is low because it is based on studies with limited neurotoxicity examination.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
    - *Oral:* In the previously described acute oral toxicity study performed under GLP according to ATC-Method (similar to OECD guidelines), Wistar rats (3/sex) received N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in olive oil by gavage at 2,200 mg/kg followed by an observation period of 14 days. There were no clinical signs of neurotoxicity, no unscheduled mortality, and no gross pathological findings (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gelbke 1992). *Clinical signs of neurotoxicity often evaluated in animal studies include: drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness, lethargy, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure. As animals in this study did not show any of these signs, ToxServices concluded that the test substance was not neurotoxic in this study*.
    - *Inhalation:* In the previously describe acute inhalation toxicity study performed under GLP according to OECD Guideline 403, Wistar rats (5/sex) were exposed to the fine powder of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine (mass median aerodynamic diameter of 2.9 µm) via head-nose inhalation at 5 mg/L for 4 hours, followed by a 14-day observation period. There were no unscheduled mortalities, treatment related gross pathological abnormalities, or clinical signs indicative of neurotoxicity (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gamer 1992).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of sufficient data identified. An OECD Guideline 422 study on the surrogate did not find neurobehavioral effects at up to the highest dose tested, 2,337-5,061 mg/kg/day, in rats. However, it reduced noradrenaline levels in the superior cervical ganglion in a 28-day gavage study. The significance of this effect is unclear. Further, the potential neurotoxicity from the formamide moiety in the target compound could not be represented by the surrogate. Therefore there are insufficient data for score this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023e
  - *Surrogate: Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9):* In the previously described GLP-compliant OECD Guideline 422 combined repeated dose toxicity study with reproduction/developmental toxicity screening test, Wistar rats (10/sex/dose) received the test substance in the feed at 0, 1,500, 5,000, or 15,000 ppm from at least 14 days before mating to at least 28 days for males and up to 14 days after delivery for a total of 51-63 days for females. Neurobehavioral examinations were performed on 5/sex/dose during week 4 of treatment for males and last week of lactation for females, including hearing ability, fore- and hind-limb grip strength, locomotor activity, total movements and ambulation. Therefore, were no treatment related effects on these parameters (Klimisch 1, reliable without restriction) (Unnamed study 2021).
    - *ToxServices identified a NOAEL of 15,000 ppm for neurotoxicity for this study based on lack of effects identified, which is equivalent to 2,337 mg/kg/day and 5,061 mg/kg/day for males and females, respectively, according to the study authors.*
  - *Surrogate: Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9):* In a non-GLP, non-guideline study, Tif:RAI rats (5/sex/dose) were exposed to the test substance by gavage at 0, 600, 1,000, or 2,000 mg/kg/day for 28 days. Study authors measured the noradrenaline levels of neurons in the iris, the superior cervical ganglion, and the vas deferens, and the dopamine levels of neurons in the striatum using the formaldehyde-fluorescence method. The results indicated that treated animals had "distinctly" lower average noradrenaline levels in the principal perikaryal of the superior cervical ganglion compared to controls (Klimisch 2, reliable with restrictions) (Unnamed study 1976).
    - *ToxServices notes that the toxicological significance of the measured changes in the noradrenaline content in the cervical ganglion is of unclear toxicological significance.*

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for skin sensitization based on negative results in a guinea pig maximization study performed according to an established guideline. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NICNAS 1997, ECHA 2023b

- In a GLP-compliant guinea pig maximization test conducted according to EU Method B.6, female Pirbright White Dunkin Hartley guinea pigs (5 control, 10 treated) were intradermally induced with 5% N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in olive oil and epicutaneously induced with 25% in olive oil. Fourteen days afterwards the animals were challenged with 10% test compound (the maximum non-irritating concentration in a preliminary test) in olive oil and scored at 24 and 48 hours. During the induction phase, there were indications of skin irritation, including significant skin redness and weak edema after intradermal treatment, and significant redness, weak edema, incrustation, and partially open skin after epicutaneous treatment. There were no positive reactions upon challenge, and the study authors concluded that the chemical was not sensitizing to the skin of guinea pigs (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gelbke 1992).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for respiratory sensitization based on a lack of structural alerts and extrapolation from negative skin sensitization data according to ECHA guidance (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not classified under GHS (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine does not contain any structural alerts for respiratory sensitization (Appendix E).
- 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 N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine 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 N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine, and as it does not contain any structural alerts for respiratory sensitization (OECD 2023), N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for skin irritation/corrosivity based on negative results in a study in rabbits for the undiluted compound conducted according to an established guideline. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - In a GLP-compliant acute dermal irritation study performed according to OECD Guideline 404, three Vienna White rabbits (2 male, 1 female) were exposed to 0.5 g N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine moistened with water on the intact skin under semiocclusion for 4 hours. The Draize scores were 0 for erythema and edema at 2,4, 48 and 72 hours. The study authors concluded that the test compound was not irritating to the skin of rabbits (Klimisch 2, reliable with restrictions) (Unnamed study 1992/Gelbke 1992).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): H
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of High for eye irritation/corrosivity based on reactions in a rabbit study that warrant GHS Category 2A classification, along with the harmonized Category 2A classification in the EU. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A (CPA 2018b). The confidence in the score is high as it is based on an authoritative A list and reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* EU GHS (H Statements) Annex 6 Table 3-1: H319 – Causes serious eye irritation – Category 2A.
  - *Screening:* GHS Australia: H319 – Causes serious eye irritation – Category 2A.
  - *Screening:* GHS New Zealand: Eye irritation Category 2.
- ECHA 2023b, NICNAS 1997
  - In a GLP-compliant acute eye irritation study conducted according to OECD Guideline 405, Vienna White rabbits (1 male, 2 female) were exposed to 24 mg N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine in the eye and observed for 15 days. The mean scores across 24, 48, and 72 hours for each animal were 0.33, 1, and 1 for corneal opacity, 1, 1, and 1 for iritis, 2, 2, and 1.7 for conjunctival redness, and 1, 0.7, and 1.7 for chemosis. Conjunctival discharge was also observed in all three animals. Some effects were not reversible within 8 days, but all effects were reversible within 15 days. Study authors concluded that the test article was moderately irritating to the eyes (Klimisch 2, reliable with restrictions) (Unnamed study 1992 / Gelbke 1992).
    - *According to GHS criteria, the mean 24, 48, and 72 hours scores for corneal opacity ≥ 1, for iritis ≥ 1, for conjunctival redness ≥ 2, and/or for chemosis ≥ 2 in at least 2 out of 3 animals warrant classification to GHS Category 2A when the effects are reversible within 21 days, and to Category 2B when the effects are reversible within 7 days. The corneal opacity and conjunctival redness scores, along with reversibility within 21 days in this study warrant classification to GHS Category 2A.*

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Moderate for acute aquatic toxicity based on a 48-hour EC_{50} of 92.1 mg/L in daphnia. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute L/EC_{50} values are

between 10 and 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - 96-hour LC_{50} > 100 mg/L in *Danio rerio* (zebra fish) (GLP, EU Method C.1) (Klimisch 2, reliable with restrictions) (Unnamed 1992 study).
  - 48-hour EC_{50} = 92.1 mg/L in *Daphnia magna* (GLP, EU Method C.2) (Klimisch 2, reliable with restrictions) (Unnamed 1992 study).
- NICNAS 1997
  - 96-hour LC_{50} > 100 mg/L in *Ieuciscus idus* (ide fish).
- ECHA 2023d
  - 72-hour EC_{50} = 298 mg/L (nominal) for growth rate, and 181 mg/L (nominal) for biomass in *Desmodesmus subspicatus* (green algae) (GLP, EU Method C.3) (Klimisch 1, reliable without restriction) (Unnamed study 2011).
- ECHA 2023c
  - 72-hour EC_{50} > 108 mg/L in algae (unspecified) for growth rate (GLP unspecified, OECD Guideline 201) (Klimisch score not assigned) (Unnamed study 2005).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for chronic aquatic toxicity based on experimental and modeled chronic values of at least 11.8 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic values are greater than 10 mg/L (CPA 2018b). The confidence in the score is low as it is in part based on modeled data (for fish).

- 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 2023c
  - 21-day NOEC = 12.5 mg/L (nominal) and 11.8 mg/L (analytical) and LOEC = 25 mg/L (nominal) and 23.6 mg/L (analytical) for reproduction in aquatic invertebrates (unspecified species) (GLP unspecified, OECD Guideline 211) (Klimisch score not assigned) (Unnamed study 2006).
  - 72-hour NOEC = 41.8 mg/L, LOEC = 108 mg/L for growth rate in algae (unspecified) (GLP unspecified, OECD Guideline 201) (Klimisch score not assigned) (Unnamed study 2005)
- ECHA 2023d
  - 72-hour NOEC = 100 mg/L (estimated), EC_{10} = 164 mg/L (nominal), and LOEC = 200 mg/L (estimated) for growth rate; and EC_{10} = 116 mg/L (nominal), NOEC = 100 mg/L (estimated), and LOEC = 200 mg/L (estimated) for biomass in *D. subspicatus* (green algae) (GLP, EU Method C.3) (Klimisch 1, reliable without restriction) (Unnamed study 2011)
- U.S. EPA 2017a
  - N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine belongs to the Aliphatic Amines and Amides ECOSAR chemical classes. The most conservative predicted chronic values (ChVs) are 376 mg/L in fish, 144 mg/L in daphnia, and 513 mg/L in green algae (Appendix I).

Environmental Fate (Fate)

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Very High for persistence based on a modeled half-life of 360 days in the predicted dominant environmental compartment of soil. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when the half-life is > 180 days in soil (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - In a GLP-compliant preliminary hydrolysis study performed according to EU C.7 and OECD Guideline 111, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was hydrolytically stable, with no hydrolysis observed under normal pH conditions, and a hydrolysis half-life of > 560 days at 50°C and Ph of 4.3-9.3 (Klimisch 2, reliable with restrictions) (Unnamed study 1992).
- ECHA 2023b, c
  - In a GLP-compliant ready biodegradability study conducted according to EU Method C.4-B (modified OECD screening test), N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine reached 10% degradation at 28 days with non-adapted activated sludge. The positive control sodium benzoate degraded by 85% in 3 days. Study authors concluded that the test substance was not readily biodegradable (Klimisch 1, reliable without restriction according to ECHA 2023c, and Klimisch 2, reliable with restrictions according to ECHA 2023b) (Unnamed study 1992).
- ECHA 2023c
  - In a GLP-unspecified OECD Guideline 301 F (manometric respirometry test) using domestic activated sludge (adaptation unspecified), less than 10% degradation was observed on day 28 at the initial concentration of 100 mg/L for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine. No additional details were reported (Klimisch score not assigned) (Unnamed study 2005).
  - In a GLP-unspecified OECD Guideline 301 E (modified OECD screening test) using domestic non-adapted activated sludge, less than 20% degradation based on dissolved organic carbon (DOC) was observed on day 28 at the initial concentration of 29 mg/L for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine. No additional details were reported (Klimisch score not assigned) (Unnamed study 1992).
- ECHA 2023c
  - In a GLP-unspecified inherent biodegradation study performed according to OECD Guideline 302B (Zahn-Wellens/EMPA test), 0% degradation was observed on day 24 for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine at the initial concentration of 297 mg/L, using domestic activated sludge (adaptation unspecified). No additional details were reported (Klimisch score not assigned) (Unnamed study 1992).
- NICNAS 1997
  - In a GLP-unspecified inherent biodegradability study performed according to OECD Guideline 302B, less than 20% reduction in DOC was measured. No additional details were provided.
- U.S. EPA 2017b

  - The BIOWIN modeling Ready Biodegradable Predictor indicates that N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 94.7% will partition to soil with a half-life of 360 days (8.64e+003 hours / 24 hours), 4.39% will partition to water with a half-life of 180 days (4.32e+003 hours / 24 hours), and 0.896% will partition to sediment with a half-life of 1,621 days (Appendix J).
- Based on the weight of evidence, a score of Very High was assigned. N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not readily or inherently biodegradable when tested in ready and inherent biodegradability studies with limited details. The degree of degradation in these studies varied from 0 to less than 20%. Therefore, ToxServices relied on modeled data to score this endpoint. The modeled half-life of 360 days in the predicted dominant environmental compartment of soil warrants a Very High score (> 180 days).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Very Low for bioaccumulation based on an experimental log K_{ow} of -2 at the neutral pH of 7, supported by modeled BCF values of up to 3.162. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when low K_{ow} values ≤ 4 (CPA 2018b). The confidence in the score is high as it is based on an experimental partition coefficient value for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, NICNAS 1997
  - N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine has an experimental partition coefficient (log K_{ow}) of 0.8 at pH of 9 and -2 at pH of 7, at 25°C, as determined by gas chromatography in a GLP-compliant study conducted according to EU Method A.8 (Klimisch 2, reliable with restrictions) (Unnamed 1992 study).
- U.S. EPA 2017b
  - BCFBAF predicts a BCF of 3.162 L/kg wet-wt using the regression-based model based on a measured log K_{ow} of -2, and a BCF of 0.8932 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix J).

<u>Physical Hazards (Physical)</u>

Reactivity (Rx) Score (vH, H, M, or L): *L*
N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for reactivity based on the lack of structural features with reactivity concerns. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not classified for any of the reactivity sub endpoints under GHS (CPA 2018b). The confidence in the score is low due to a lack of experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NICNAS 1997
  - The structure of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine does not indicate concerns for explosiveness.
  - Dust explosion may occur as with any organic powders.

  - The compound does not have oxidizing properties and does not degrade or decompose under normal conditions.
  - Overall, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not reactive.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix K).
  - Based on the structure of its components or moieties, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine 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.

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was assigned a score of Low for flammability based on negative flammability (solid) tests. GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not flammable according to GHS (CPA 2018b). The confidence in the score is high as it is based on experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - In a GLP-compliant flammability (solids) test performed according to EU Method A.10, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine was not highly flammable (Klimisch 2, reliable with restrictions) (Unnamed study 1992).
  - In a GLP-compliant self-ignition test performed according to EU Method A.16, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine did not self-ignite at up to the melting point of 157.3°C.
  - Based on experience in handling and use, N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine does not ignite on contact with air, is not pyrophoric, and does not liberate highly flammable gases upon contact with water (Klimisch 2, reliable with restrictions).

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

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

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

As shown in Table 5, Type I (input data) uncertainties in N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine's NAMs dataset include lack of, or insufficient, experimental data for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, and persistence, and the lack of validated test methods for respiratory sensitization. N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine's Type II (extrapolation output) uncertainties include certain *in silico* models not defining the applicability domain, conflicting model predictions with similar reliability, inability of certain models in producing reliable predictions, limitations of *in vitro* genotoxicity tests in mimicking mammalian metabolism and their focusing on a few events in the process of mutagenicity, uncertain *in vivo* relevance of *in silico* modeling on endocrine receptor binding activities due to lack of toxicokinetic considerations, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine'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:** No *in vivo* or *in vitro* data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Chronic aquatic toxicity:** No experimental data are available for the fish trophic level. **Persistence**: No experimental environmental partitioning data or soil half-life data are available.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: OECD Toolbox only identifies structural alerts (SAs), and no applicability domain can be defined. VEGA models produced mixed predictions with similar global ADIs. OncoLogic

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

	could not evaluate the target compound. Danish QSAR did not produce any in domain predictions. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12]. 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).[13] 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[14]. **Endocrine activity:** ToxCast models don't define applicability domain; the *in vivo* relevance of *in silico* modeling of receptor binding activity is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/ OncoLogic™/OECD Toolbox/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: /ToxCast models/ Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	

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

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	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301 and 302 Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

References

BASF. 2011. Declassification of the chemical identity previously claimed as CBI in submission (88080000212s) with N,N-1,6 hexanediylbis (N-(2,2,6,6-tetramethyl- piperdin-4-yl)formamide). OTS0602103. DCN: 8EHQ-08-17169. Available: https://ntrl.ntis.gov/NTRL/

Clean Production Action (CPA). 2018a. GreenScreen® Assessment Expiration Policy. October 2, 2018.

Clean Production Action (CPA). 2018b. The GreenScreen® for Safer Chemicals Guidance. Version 1.4 Guidance. Dated January, 2018. Available: https://www.greenscreenchemicals.org/static/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf

Danish Technical University (DTU). 2023. National Food Institute. Danish QSAR Database. Available: http://qsar.food.dtu.dk/.

European Chemicals Agency (ECHA). 2017. Guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 6.0. Dated: July 2017. Available: https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f?t=1500286622893

European Chemicals Agency (ECHA). 2023a. Summary of Classification and Labeling for N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)-formamide (CAS # 124172-53-8). Available: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/91207

European Chemicals Agency (ECHA). 2023b. REACH registration dossier for N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide (CAS #124172-523-8). Full dossier, Active, total tonnage band ≥ 10 to < 100 tonnes. Last Updated 30-03-2014. Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/6030/9

European Chemicals Agency (ECHA). 2023c. REACH registration dossier for N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide (CAS #124172-523-8). Full dossier, Active, total tonnage band ≥ 100 tonnes. Last Updated 31-07-2019. Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/5678/4/4/?documentUUID=ed65c1e2-137c-4851-b29b-be4487827c94

European Chemicals Agency (ECHA). 2023d. REACH registration dossier for N,N'-1,6-hexanediylbis(N-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide (CAS #124172-523-8). Full dossier, Active, total tonnage band ≥ 10 to < 100 tonnes. Last Updated 22-08-2011. Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/8312/7/2/1

European Chemicals Agency (ECHA). 2023e. REACH registration dossier for bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (CAS #52829-07-9). Available: https://echa.europa.eu/registration-dossier/-/registered-dossier/14267/7/9/3/?documentUUID=c7ec5b86-1dbf-4d1f-ab9b-ee1a9b852e6d

European Food Safety Authority (EFSA). 2018. Guidance on uncertainty analysis in scientific assessments. *EFSA J.* 16(1): e05123. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7009727/

Gad, S. 2016. QSAR Tools for Drug Safety. Chapter 10. In, Drug Safety Evaluation. Third Edition. New York: Wiley. 209-224.

Madden, J.C., S.J. Enoch, A. Paini, and M.T.D. Cronin. 2020. A review of *in silico* tools as alternatives to animal testing: principles, resources, and applications. *Alt. Lab. Animals.* 1-27. Available: https://journals.sagepub.com/doi/pdf/10.1177/0261192920965977

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). 1997. Full public report. UVINUL 4050H. File No. NA/518. December 1997. Available: https://www.industrialchemicals.gov.au/sites/default/files/NA518%20Public%20Report%20PDF.pdf

Organisation for Economic Co-operation and Development (OECD). 2020. Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA), Series on Testing and Assessment, No. 329, Environment, Health and Safety, Environment Directorate. Available: https://www.oecd.org/chemicalsafety/risk-assessment/concepts-and-available-guidance-related-to-integrated-approaches-to-testing-and-assessment.pdf

Organisation for Economic Co-operation and Development (OECD). 2023. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 4.6. Available: https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm#Download_qsar_application_toolbox

Pharos. 2023. Pharos chemical and material library entry for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine (CAS #124172-53-8). Available: http://www.pharosproject.net/material/.

PubChem. 2023. Formamide, N,N'-1,6-hexanediylbis[N-(2,2,6,6-tetramethyl-4-piperidinyl)- (CAS #124172-53-8). United States National Library of Medicine. Available: https://pubchem.ncbi.nlm.nih.gov/compound/14419064

Sahigara, F. 2007. Defining the Applicability Domain of QSAR models: An overview. Available: http://www.moleculardescriptors.eu/tutorials/T7_moleculardescriptors_ad.pdf

ToxServices. 2021. SOP 1.37: GreenScreen® Hazard Assessments. Dated: May 24, 2021.

United Nations (UN). 2021. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Ninth revised edition.

United States Department of Transportation (U.S. DOT). 2008a. Chemicals Listed with Classification. 49 CFR § 172.101. Available: http://www.gpo.gov/fdsys/pkg/CFR-2008-title49-vol2/pdf/CFR-2008-title49-vol2-sec172-101.pdf.

United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl

United States Environmental Protection Agency (U.S. EPA). 2015. Safer Choice Standard. Available: https://www.epa.gov/saferchoice/standard

United States Environmental Protection Agency (U.S. EPA). 2017a. ECOSAR 2.0. Washington, DC, USA. Available: http://www.epa.gov/oppt/newchems/tools/21ecosar.htm/.

United States Environmental Protection Agency (U.S. EPA). 2017b. Estimation Programs Interface (EPI) Suite™ Web, v4.11, Washington, DC, USA. Available: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm.

United States Environmental Protection Agency (U.S. EPA). 2019. OncoLogic™. Version 8.0.16 Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2020. New Approach Methods Workplan. Office of Research and Development. Office of Chemical Safety and Pollution Prevention. EPA 615B20001. June 2020. Available: https://www.epa.gov/sites/default/files/2020-06/documents/epa_nam_work_plan.pdf

United States Environmental Protection Agency (U.S. EPA). 2021. OncoLogic™. Version 9.0 Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2023a. Safer Chemical Ingredients List (SCIL). Available: https://www.epa.gov/saferchoice/safer-ingredients

United States Environmental Protection Agency (U.S. EPA). 2023b. CompTox Dashboard. Available: https://comptox.epa.gov/dashboard

United States Food and Drug Administration (U.S. FDA). 2023. FCN No. 647: BASF Aktiengesellschaft. Available: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=fcn&id=647

Virtual Models for Evaluating the Properties of Chemicals within a Global Architecture (VEGA). 2023. Predictive Model Platform version 1.2.3. Available: https://www.vegahub.eu/portfolio-item/vega-qsar/

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 N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

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	N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine	**124172-53-8**	DG	**L**	DG	*M*	DG	**L**	**M**	*L*	*L*	DG	**L**	*L*	**L**	**H**	**M**	*L*	*vH*	**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	Yes	No	Yes	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-	2

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

Table 6

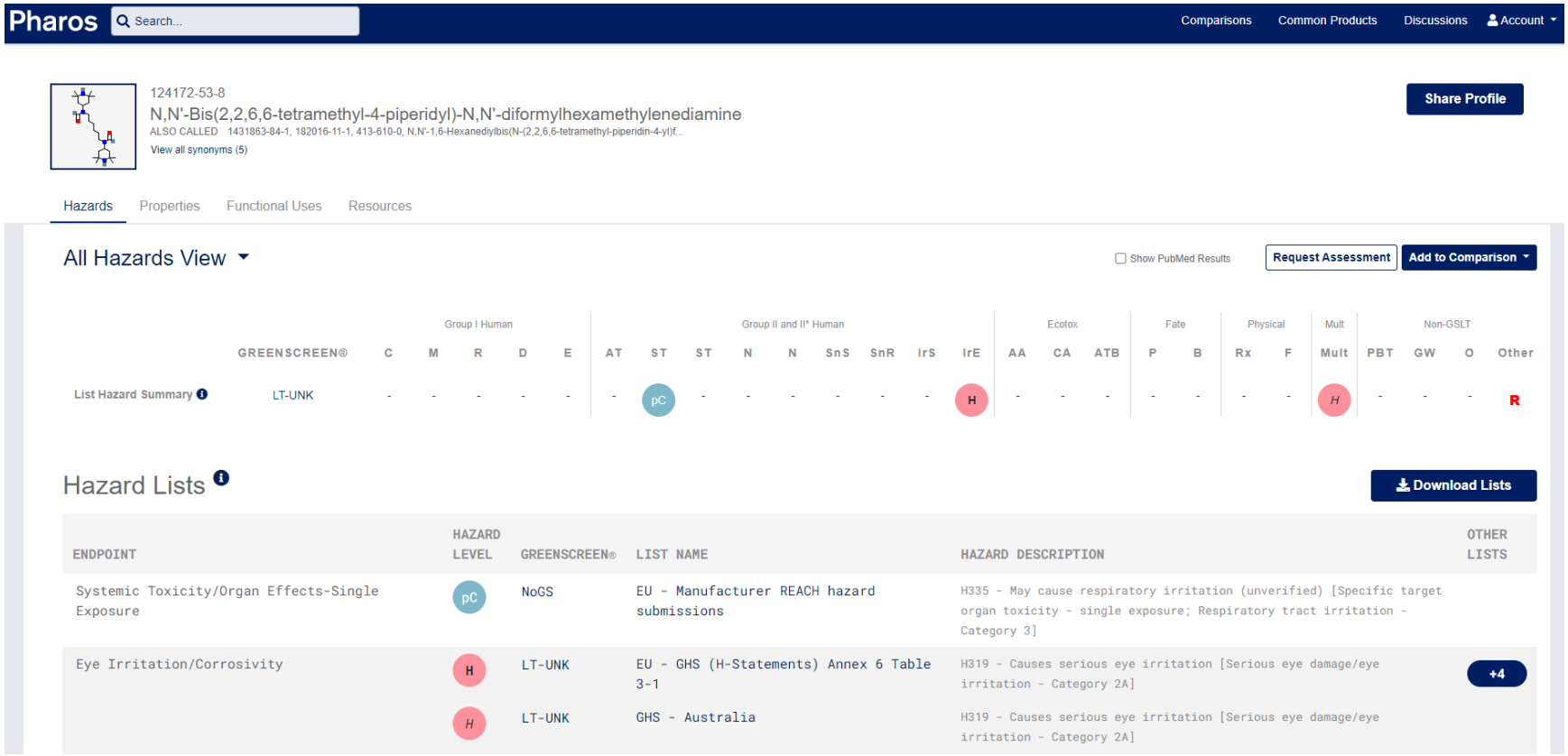
Chemical Name	Final GreenScreen® Benchmark Score
N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-	U

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	No	Yes	Yes	Yes	Yes							U
3												
4												

APPENDIX C: Pharos Output for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)



	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified) [Serious eye damage/eye irritation - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	H	LT-UNK	GHS - New Zealand	Hazardous to the aquatic environment - chronic category 3	+3
	M	LT-UNK	GHS - Australia	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]	
	U	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

Restricted Substance Lists (2)

- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

Positive Lists (1)

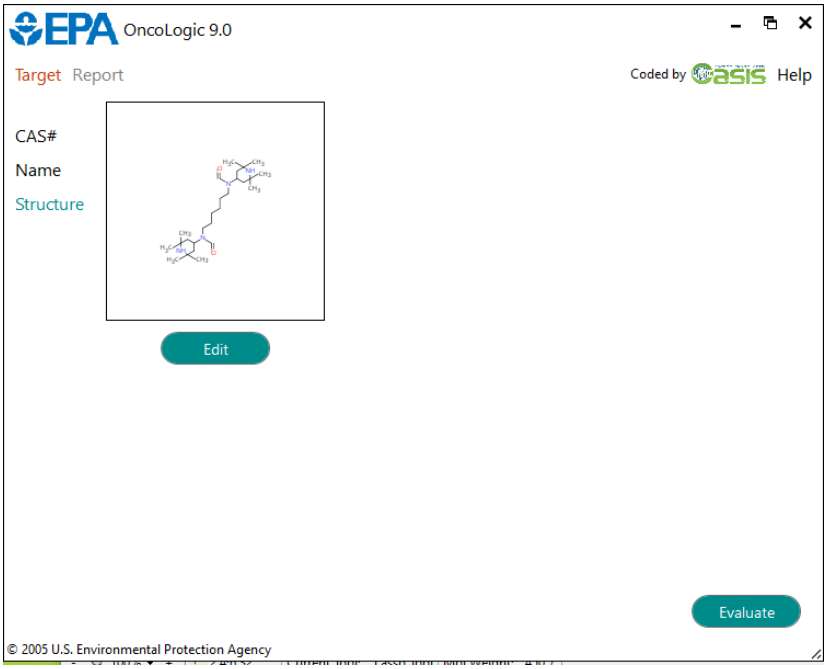
- GB 9685 National Food Safety Standard (2016): GB 9685 National Food Safety Standard (2016)

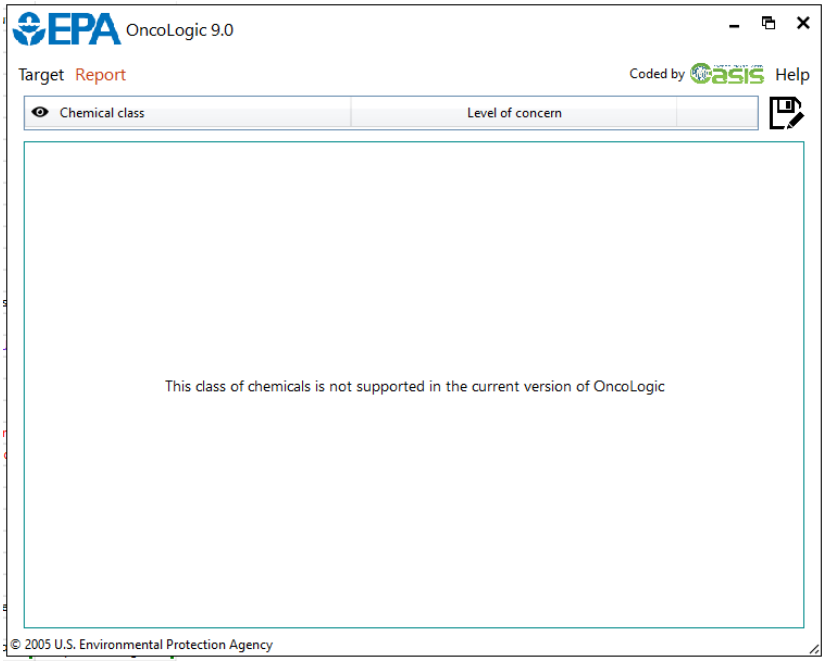
Discussions

No discussions have been posted yet.

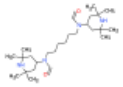
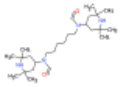
Ask a question about this chemical in the forums >

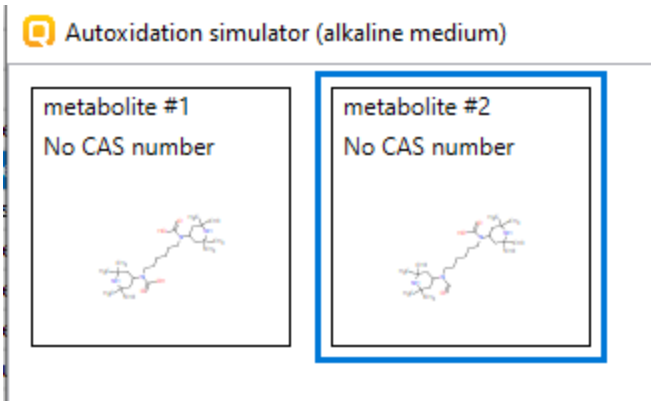
APPENDIX D: OncoLogic Output for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)





APPENDIX E: OECD Toolbox Profile for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

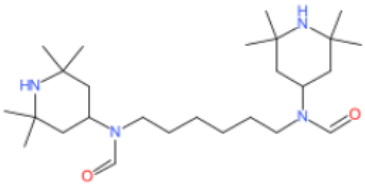
Filter endpoint tree...	1	2
Structure		
Bioaccumulation - metabolism alerts	-CH - [cyclic]	-CH - [cyclic]
Bioaccumulation - metabolism half-lives	Fast	Fast
Biodegradation fragments (BioWIN MITI)	-CH - [cyclic]	-CH - [cyclic]
Carcinogenicity (genotox and nongenotox) alerts by ISS	No alert found	No alert found
DART scheme	Not known precedent reproductiv...	Not known precedent reproductive a...
DNA alerts for AMES, CA and MNT by OASIS	No alert found	No alert found
Eye irritation/corrosion Exclusion rules by BfR	Group All Melting Point > 200 C	Group All Melting Point > 200 C
Eye irritation/corrosion Inclusion rules by BfR	Inclusion rules not met	Inclusion rules not met
in vitro mutagenicity (Ames test) alerts by ISS	No alert found	No alert found
in vivo mutagenicity (Micronucleus) alerts by ISS	No alert found	No alert found
Keratinocyte gene expression	Not possible to classify according...	Not possible to classify according to t...
Oncologic Primary Classification	Aldehyde Type Compounds	Aldehyde Type Compounds
Protein binding alerts for Chromosomal aberration by...	Radical mechanism	Radical mechanism
Protein binding alerts for skin sensitization according...	No alert found	No alert found
Protein binding alerts for skin sensitization by OASIS	No alert found	No alert found
Protein Binding Potency h-CLAT	No alert found	No alert found
Respiratory sensitisation	No alert found	No alert found
Retinoic Acid Receptor Binding	Not possible to classify according...	Not possible to classify according to t...
rtER Expert System - USEPA	No alert found	No alert found
Skin irritation/corrosion Exclusion rules by BfR	Group All Melting Point > 200 C	Group All Melting Point > 200 C
Skin irritation/corrosion Inclusion rules by BfR	Inclusion rules not met	Inclusion rules not met
Empiric		
Toxicological		
Custom		
Example Prioritization Scheme (PBT)	P	P
Metabolism/Transformation		
Autoxidation simulator	0 metabolite(s)	0 metabolite(s)
Autoxidation simulator (alkaline medium)	2 metabolite(s)	2 metabolite(s)
Dissociation simulator	0 dissociation product(s)	0 dissociation product(s)
Hydrolysis simulator (acidic)	0 metabolite(s)	0 metabolite(s)
Hydrolysis simulator (basic)	3 metabolite(s)	3 metabolite(s)
Hydrolysis simulator (neutral)	0 metabolite(s)	0 metabolite(s)
Tautomerism	0 tautomer(s)	0 tautomer(s)



APPENDIX F: VEGA Carcinogenicity Output for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

1. Prediction Summary

Prediction for compound Molecule 0 -

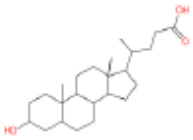


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- Only moderately similar compounds with known experimental value in the training set have been found
- predicted value disagrees with experimental values of training set compounds laying in the same neuron

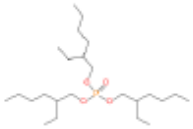
Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.398
P(NON-Carcinogen): 0.602
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



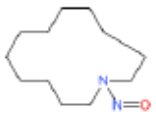
Compound #1

CAS: 434-13-9
Dataset id:413 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.711
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



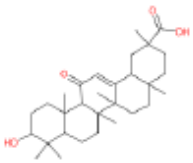
Compound #2

CAS: 78-42-2
Dataset id:784 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



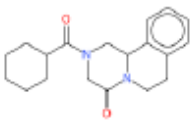
Compound #3

CAS: 40580-89-0
Dataset id:586 (Training Set)
SMILES: O=NN1CCCCCCCCCCCC1
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen



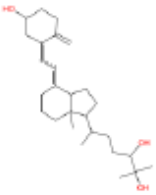
Compound #4

CAS: 471-53-4
Dataset id:353 (Training Set)
SMILES:
O=C(O)C4(C)(CCC5(C)(CCC2(C(=CC(=O)C1C3(C)(CCC(O)C(C)(C)C3(CCC12(C)))C5(C4)(C)))
Similarity: 0.707
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 55268-74-1
Dataset id:666 (Test Set)
SMILES: O=C4N2CCc1ccccc1C2CN(C(=O)C3CCCCC3)C4
Similarity: 0.696
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 55721-11-4
Dataset id:702 (Test Set)
SMILES: OC3CC(=CC=C1CCCC2(C)(C1CCC2(C(C)CCC(O)C(O)(C)C)))C(=C)CC3
Similarity: 0.694
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.632 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.71 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✓	Model class assignment reliability Pos/Non-Pos difference = 0.205 Explanation: model class assignment is well defined..
⚠	Neural map neurons concordance Neurons concordance = 0.75 Explanation: predicted value disagrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

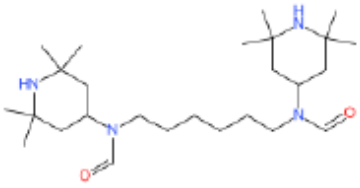
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

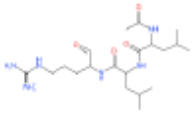


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

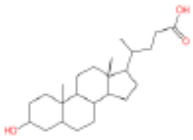
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

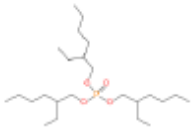
CAS: 24365-47-7
Dataset id:390 (Training Set)
SMILES: O=CC(NC(=O)C(NC(=O)C(NC(=O)C)CC(C)C)CC(C)C)CCCNC(N)=[NH2+]
Similarity: 0.748
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA11 Simple aldehyde



Compound #2

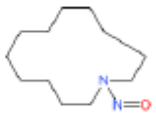
CAS: 434-13-9
Dataset id:117 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.711
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #3

CAS: 78-42-2
Dataset id:69 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : Carcinogen
Predicted value : Carcinogen

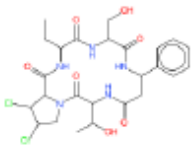
Alerts (not found also in the target): SA41 Substituted n-alkylcarboxylic acids



Compound #4

CAS: 40580-89-0
Dataset id:553 (Training Set)
SMILES: O=NN1CCCCCCCCCCCC1
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen

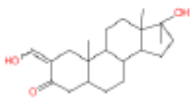
Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups



Compound #5

CAS: 12663-46-6
Dataset id:338 (Training Set)
SMILES:
O=C2NC(C(=O)N3CC(C(C3(C(=O)NC(C(=O)NC(C(=O)NC(c1ccccc1)C2)CO)CC))Cl)Cl)C(O)C
Similarity: 0.698
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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



Compound #6

CAS: 434-07-1
Dataset id:248 (Training Set)
SMILES: O=C1C(=CO)CC4(C)(C(C1)CCC3C4(CCC2(C)(C3(CCC2(O)(C)))))
Similarity: 0.685
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA10 alfa, beta unsaturated carbonyls

3.2 Applicability Domain:
Measured Applicability Domain Scores

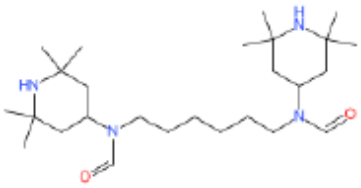
⚠	Global AD Index AD index = 0.711 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.729 Explanation: Only moderately similar compounds with known experimental value in the training set have 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 = 0.481 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 -



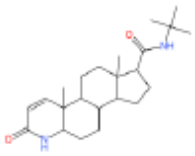
Prediction: Reliability:

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

The following relevant fragments have been found: Carcinogenity alert no. 7

Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 7
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

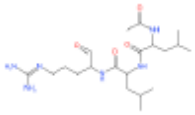
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

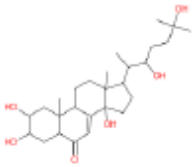
CAS: 98319-26-7
Dataset id:833 (Training Set)
SMILES: O=C1C=CC4(C)(C(N1)CCC2C4(CCC3(C)(C(C(=O)NC(C)(C)C)CCC23)))
Similarity: 0.792
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #2

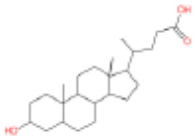
CAS: 24365-47-7
Dataset id:320 (Training Set)
SMILES: O=CC(NC(=O)C(NC(=O)C(NC(=O)C)CC(C)C)CC(C)C)CCCN=C(N)N
Similarity: 0.747
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

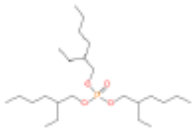
CAS: 3604-87-3
Dataset id:829 (Training Set)
SMILES:
O=C3C=C1C(CCC2(C)C(CCC12(O))C(C)C(O)CCC(O)(C)C))C4(C)(CC(O)C(O)CC34)
Similarity: 0.715
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #4

CAS: 434-13-9
Dataset id:93 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.711
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

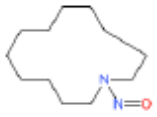


Compound #5

CAS: 78-42-2
Dataset id:59 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : Carcinogen
Predicted value : Carcinogen

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

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



Compound #6

CAS: 40580-89-0
Dataset id:464 (Training Set)
SMILES: O=NN1CCCCCCCCCCC1
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.782 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.747 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.669 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..
✓	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.

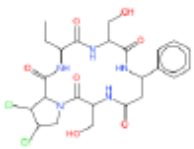
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 7

Structural alert for carcinogenity defined by the SMARTS:NCCCN

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

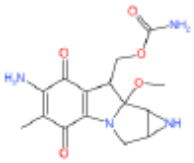


CAS: 12663-46-6
Dataset id:274 (Training Set)
SMILES:
O=C2NC(C(=O)N3CC(C(C3(C(=O)NC(C(=O)NC(C(=O)NC(c1ccccc1)C2)CO)CC))Cl)Cl)CO
Similarity: 0.691

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 11; Carcinogenity alert no. 25; Carcinogenity alert no. 40

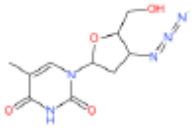


CAS: 50-07-7
Dataset id:296 (Training Set)
SMILES: O=C(OCC4C=1C(=O)C(N)=C(C(=O)C=1N3CC2NC2C34(OC))C)N
Similarity: 0.63

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 29; Carcinogenity alert no. 39



CAS: 30516-87-1
Dataset id:699 (Training Set)
SMILES: [N-]=[N+]=NC1CC(OC1(CO))N2C=C(C(=O)NC2(=O))C
Similarity: 0.607

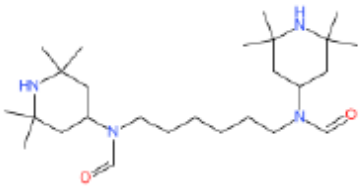
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

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

1. Prediction Summary

Prediction for compound Molecule 0 -

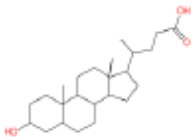


Prediction: Reliability:

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

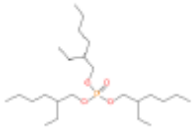
Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



Compound #1

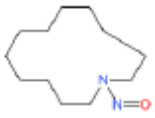
CAS: 434-13-9
Dataset id:413 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.711
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

CAS: 78-42-2
Dataset id:784 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

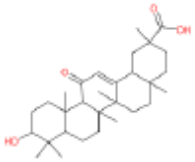
Alerts (not found also in the target): Carcinogenity alert no. 98



Compound #3

CAS: 40580-89-0
Dataset id:586 (Training Set)
SMILES: O=NN1CCCCCCCCCCCC1
Similarity: 0.708
Experimental value : Carcinogen
Predicted value : Carcinogen

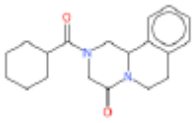
Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 5; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 53; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63



Compound #4

CAS: 471-53-4
Dataset id:353 (Training Set)
SMILES:
O=C(O)C4(C)(CCC5(C)(CCC2(C(=CC(=O)C1C3(C)(CCC(O)C(C)(C)C3(CCC12(C)))))C5(C4)(C)))
Similarity: 0.707
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

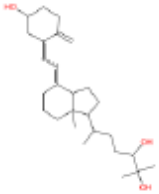
Alerts (not found also in the target): Carcinogenity alert no. 85



Compound #5

CAS: 55268-74-1
Dataset id:666 (Test Set)
SMILES: O=C4N2CCc1ccccc1C2CN(C(=O)C3CCCCC3)C4
Similarity: 0.696
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

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



Compound #6

CAS: 55721-11-4
Dataset id:702 (Test Set)
SMILES: OC3CC(=CC=C1CCCC2(C)(C1CCC2(C(C)CCC(O)C(O)(C)C)))C(=C)CC3
Similarity: 0.694
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

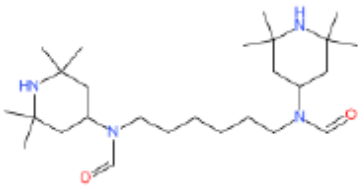
⚠	Global AD Index AD index = 0.688 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.71 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.666 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
⚠	Concordance for similar molecules Concordance index = 0.668 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0 -

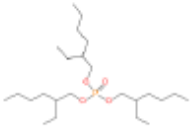


Prediction: Reliability:

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

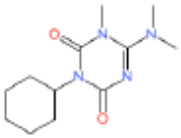
Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



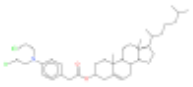
Compound #1

CAS: 78-42-2
Dataset id:313 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : Carcinogen
Predicted value : Carcinogen



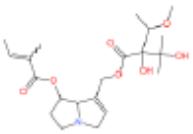
Compound #2

CAS: 51235-04-2
Dataset id:543 (Training Set)
SMILES: O=C1N=C(N(C(=O)N1C2CCCCC2)C)N(C)C
Similarity: 0.696
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



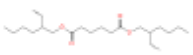
Compound #3

CAS: 3546-10-9
Dataset id:256 (Training Set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)(C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CCCl)CCCl
Similarity: 0.678
Experimental value : Carcinogen
Predicted value : Carcinogen



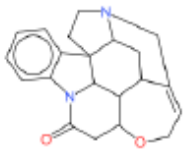
Compound #4

CAS: 303-34-4
Dataset id:186 (Training Set)
SMILES: O=C(OC2CCN1CC=C(COC(=O)C(O)(C(OC)C)C(O)(C)C)C12)C(=CC)C
Similarity: 0.677
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 103-23-1
Dataset id:94 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.676
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 57-24-9
Dataset id:675 (Training Set)
SMILES: O=C2N6c1ccccc1C57(CCN4CC3=CCOC(C2)C(C3CC45)C67)
Similarity: 0.676
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.708 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.703 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 = 0.508 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:

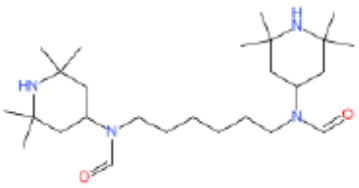
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ 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 -

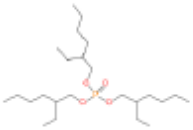


Prediction: Reliability:

Prediction is NON-Carcinogen, 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 atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

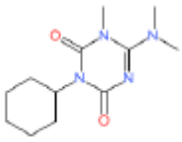
Compound: Molecule 0
Compound SMILES: O=CN(CCCCCCN(C=O)C1CC(NC(C)(C)C1)(C)C)C2CC(NC(C)(C)C2)(C)C
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



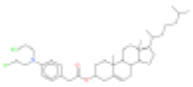
Compound #1

CAS: 78-42-2
Dataset id:741 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.71
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



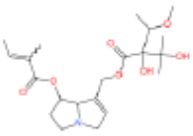
Compound #2

CAS: 51235-04-2
Dataset id:519 (Training Set)
SMILES: O=C1N=C(N(C(=O)N1C2CCCCC2)C)N(C)C
Similarity: 0.696
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #3

CAS: 3546-10-9
Dataset id:219 (Training Set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)(C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CC
C)CCCl
Similarity: 0.678
Experimental value : Carcinogen
Predicted value : Carcinogen

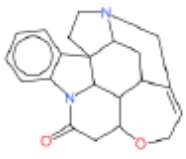


Compound #4

CAS: 303-34-4
Dataset id:155 (Training Set)
SMILES: O=C(OC2CCN1CC=C(COC(=O)C(O)(C(OC)C)C(O)(C)C)C12)C(=CC)C
Similarity: 0.677
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #5

CAS: 103-23-1
Dataset id:391 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.676
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 57-24-9
Dataset id:669 (Training Set)
SMILES: O=C2N6c1ccccc1C57(CCN4CC3=CCOC(C2)C(C3CC45)C67)
Similarity: 0.676
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.713 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.703 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
⚠	Atom Centered Fragments similarity check ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

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 rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

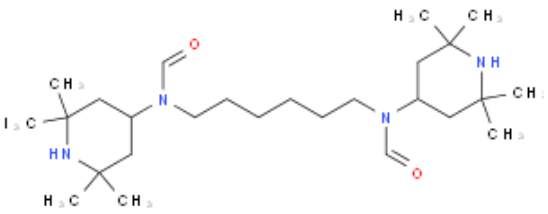
Fragment defined by the SMILES: NC=O
The fragment has less than 3 occurrences in the model's training set

APPENDIX G: Danish QSAR Database Results for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

Danish (Q)SAR Database, https://qsar.food.dtu.dk Date: 12-07-2023

(Q)SAR predicted profile

Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction):
C1(C)(C)CC(N(C=O)CCCCCCN(C2CC(C)(C)NC(C)(C)C2)C=O)CC(C)(C)N1

ID

Registry Number	124172-53-8	PubChem CID	
REACH EC Number (pre-registration, by 2013)	602-984-2	REACH EC Number (registration, 2019 or 2022)	413-610-0
REACH registration (2022)	Yes	REACH registration cumulated minimum annual tonnage (2022)	120
EU CLP Harmonized Classification*	Aquatic Chronic 3; Eye Irrit. 2	DK-EPA / DTU QSAR-based CLP Advisory Classification	
EU Biocide active substances		EU Pesticide active substances	
EU EFSA Botanical substances		US TSCA (Oct. 2021)	Yes
Tox21 (2019)		ToxCast (Oct. 2021)	
Molecular Formula	C26 H50 N4 O2	Molecular weight (g/mole)	450.71
Chemical Name	Formamide, N,N'-1,6-hexanediylbis[N-(2,2,6,6-tetramethyl-4-piperidinyl)-;Uvinul 4050H		

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

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_OUT	INC_OUT
FDA RCA Cancer Female Rat	NEG_OUT	INC_OUT
FDA RCA Cancer Rat	NEG_OUT	NEG_OUT
FDA RCA Cancer Male Mouse	NEG_OUT	INC_OUT
FDA RCA Cancer Female Mouse	NEG_OUT	INC_OUT
FDA RCA Cancer Mouse	NEG_OUT	NEG_OUT
FDA RCA Cancer Rodent	NEG_OUT	NEG_OUT

Commercial models from CASE Ultra and Leadscope

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

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:
- parent only
Oncologic Primary Classification, alerts in:
- parent only

OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	INC_OUT	POS_OUT	NEG_OUT
Estrogen Receptor α Activation (Human *in vitro*)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	INC_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	INC_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			72093.68	4283.682	36906.01
- µM			159955.8	9504.298	81884.16
- Positive for IC_{50} ≤ 10 µM					

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			14584.7	65.61864	14584.7
- µM			32359.38	145.5895	32359.38
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	INC_OUT	POS_OUT	NEG_OUT	POS_OUT
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	INC_OUT	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A

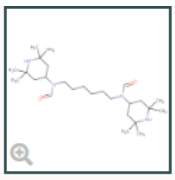
DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from *in vivo* Rat metabolism simulator only	
- metabolites from Rat liver S9 metabolism simulator only	Non binder, impaired OH or NH2 group; Non binder, without OH or NH2 group
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	
- 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 H: ToxCast Endocrine Model Prediction Results for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)



Formamide, N,N'-1,6-hexanediylbis[N-(2,2,...

124172-53-8 | DTXSID9073094

Searched by CASRN

Bioactivity - ToxCast: Models

ToxCast Model Predictions

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

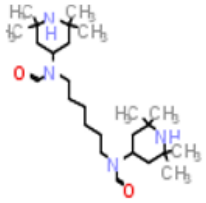
APPENDIX I: ECOSAR Modeling Results for N,N'-is(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

Created on Jul 13, 2023 9:22:07 AM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
		CC1(CC(CC(N1)(C)C)N(CCCCCCN(C=O)C2CC(NC(C2)(C)C)(C)C)C=O)C

Structure


Details	
Mol Wt	450.71
Selected LogKow	-2
Selected Water Solubility (mg/L)	13000
Selected Melting Point (°C)	157.3
Estimated LogKow	2.9
Estimated Water Solubility (mg/L)	1000000
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	

Class Results:	

Aliphatic Amines

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	36762.18	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	2752.34	5	
Green Algae	96h	EC50	5699.03	6.4	
Fish		ChV	8832.86	8	
Daphnid		ChV	143.85	8	
Green Algae		ChV	1353.01	8	

Amides

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	166571.67	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	296757.19	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	4702.2	6.4	
Fish		ChV	375.93	8	
Daphnid		ChV	11277.2	8	
Green Algae		ChV	512.98	8	
Fish (SW)	96h	LC50	82813.52	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid (SW)	96h	LC50	1482.86	5	
Mysid (SW)		ChV	5911.55	8	
Earthworm	14d	LC50	5709.54	6	

APPENDIX J: EPI Suite™ Modeling Results for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine (CAS #124172-53-8)

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

CAS Number: 127172-53-8
SMILES : CC1(CC(CC(N1)(C)C)N(CCCCCCN(C(=O))C2CC(NC(C2)(C)C)(C)C)C(=O))C
CHEM :
MOL FOR: C26 H50 N4 O2
MOL WT : 450.71
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): -2.00
Boiling Point (deg C) : ------
Melting Point (deg C) : 157.30
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 13000
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 2.90

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 550.65 (Adapted Stein & Brown method)
Melting Pt (deg C): 236.26 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 6.2E-011 (Modified Grain method)
VP (Pa, 25 deg C) : 8.27E-009 (Modified Grain method)
Subcooled liquid VP: 1.4E-009 mm Hg (25 deg C, Mod-Grain method)
: 1.87E-007 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1e+006
log Kow used: -2.00 (user entered)
melt pt used: 157.30 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 4314.3 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Aliphatic Amines
Amides

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 2.53E-016 atm-m3/mole (2.57E-011 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 2.828E-015 atm-m3/mole (2.866E-010 Pa-m3/mole)
VP: 6.2E-011 mm Hg (source: MPBPVP)
WS: 1.3E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -2.00 (user entered)
Log Kaw used: -13.985 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 11.985
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.5252
Biowin2 (Non-Linear Model) : 0.0641
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 1.2951 (recalcitrant)
Biowin4 (Primary Survey Model) : 3.0811 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : -0.0657
Biowin6 (MITI Non-Linear Model): 0.0002
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -2.1638
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): 1.87E-007 Pa (1.4E-009 mm Hg)
Log Koa (Koawin est): 11.985
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 16.1
Octanol/air (Koa) model: 0.237
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.998
Mackay model : 0.999
Octanol/air (Koa) model: 0.95

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 244.6022 E-12 cm3/molecule-sec
Half-Life = 0.044 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.525 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.999 (Junge-Pankow, Mackay avg)
0.95 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 2182 L/kg (MCI method)
Log Koc: 3.339 (MCI method)
Koc : 0.1535 L/kg (Kow method)
Log Koc: -0.814 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.3620 days (HL = 0.004345 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.8932)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.8932)
log Kow used: -2.00 (user entered)

Volatilization from Water:
Henry LC: 2.53E-016 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 4.913E+012 hours (2.047E+011 days)
Half-Life from Model Lake : 5.36E+013 hours (2.233E+012 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.75 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**3.14e-007**	**1.05**	**1000**
Water	**4.39**	**4.32e+003**	**1000**
Soil	**94.7**	**8.64e+003**	**1000**
Sediment	**0.896**	**3.89e+004**	**0**

Persistence Time: 7.86e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.14e-007	1.05	1000
Water	4.39	4.32e+003	1000
water	(4.37)		
biota	(2.19e-009)		
suspended sediment	(0.0143)		
Soil	94.7	8.64e+003	1000
Sediment	0.896	3.89e+004	0

Persistence Time: 7.86e+003 hr

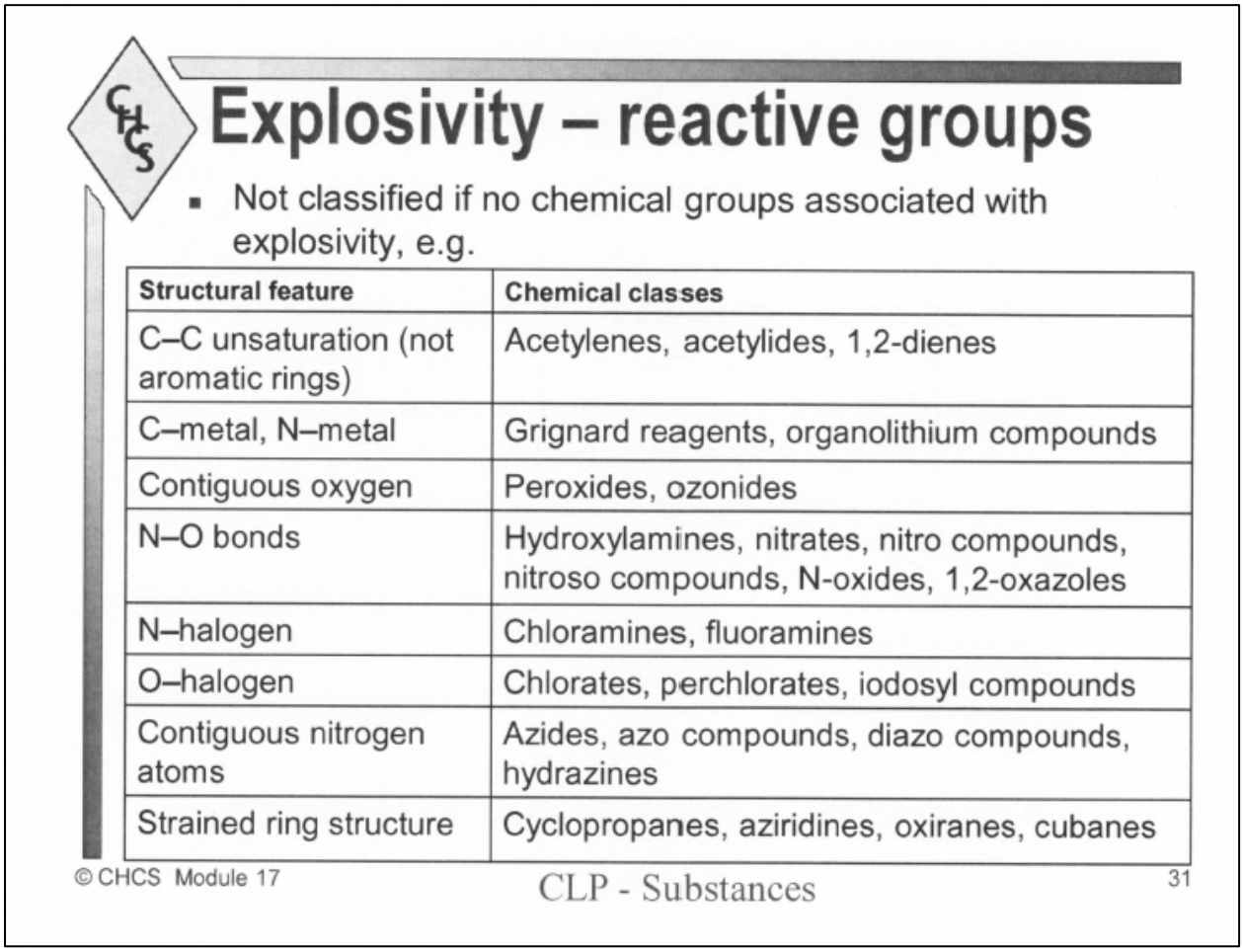
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.63e-006	1.05	1000
Water	53.9	4.32e+003	1000
water	(53.9)		
biota	(2.7e-008)		
suspended sediment	(3.32e-007)		
Soil	46	8.64e+003	1000
Sediment	0.106	3.89e+004	0

Persistence Time: 1.51e+003 hr

APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



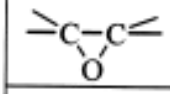
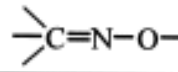
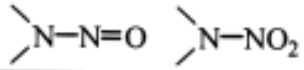
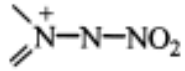
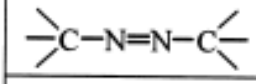
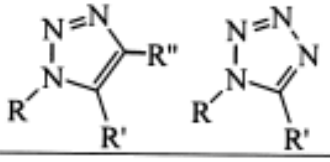
Explosivity – reactive groups

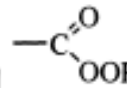
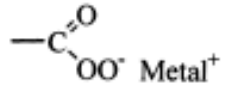
- Not classified if no chemical groups associated with explosivity, e.g.

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

Explosivity – Full List

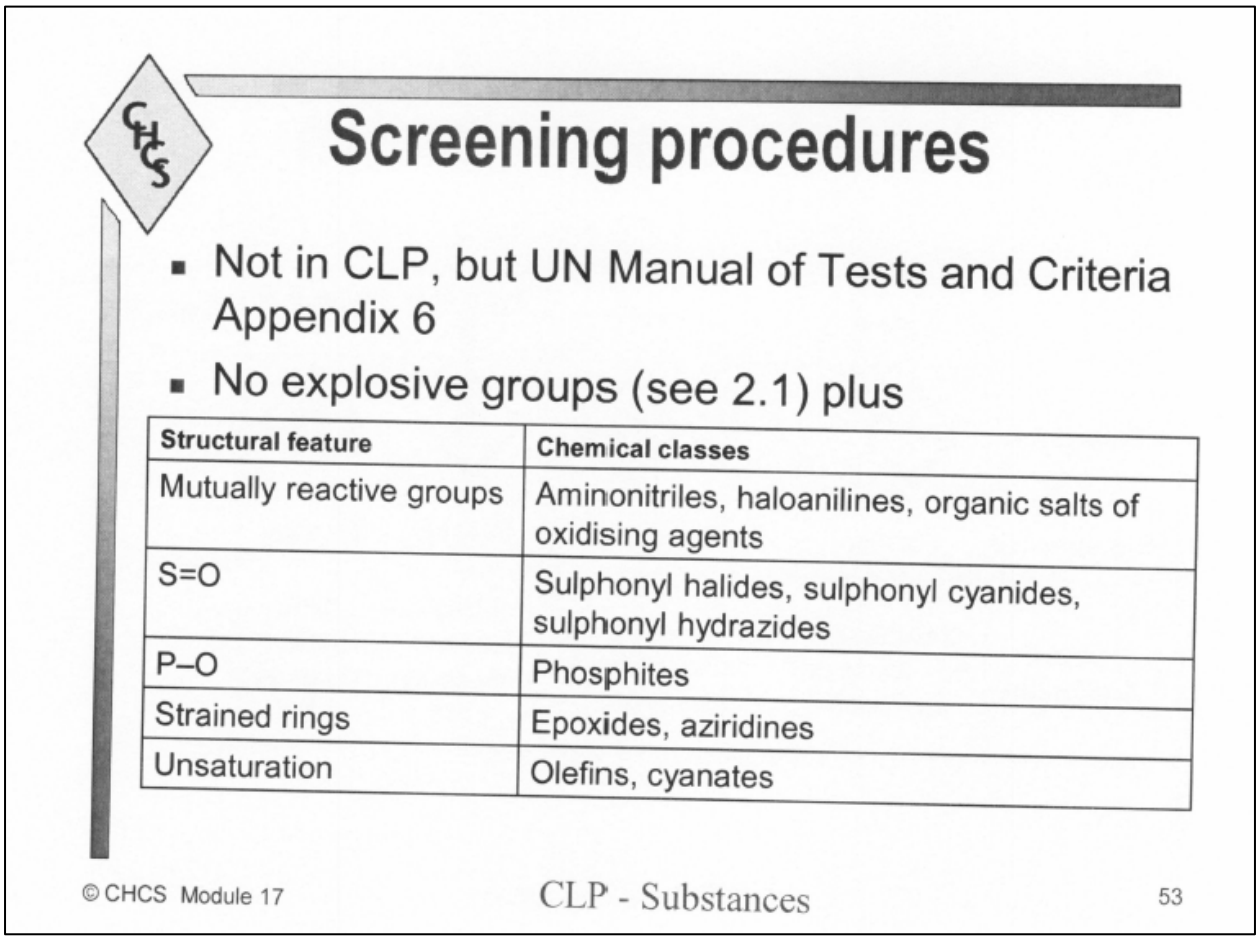
Table R.7.1-28 Chemical groups associated with explosive properties

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

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. NCl_3, $RNCl_2$	N-Halogen Compounds

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

Self-Reactive Substances



Screening procedures

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

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

APPENDIX L: Change in Benchmark Score

Table 6 provides a summary of changes to ToxServices' GreenScreen® Benchmark™ for N,N'-bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-diformylhexamethylenediamine. This is a new GreenScreen® assessment.

Table 6: Change in GreenScreen® Benchmark™ for N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
August 28, 2023	BM-U	v. 1.4	New assessment

Licensed GreenScreen® Profilers

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

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

N,N'-Bis(2,2,6,6-tetramethyl-4-piperidyl)-N,N'-Diformylhexamethylenediamine GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Mouna Zachary, Ph.D.
Senior Toxicologist
ToxServices LLC