1,3,5-TRIAZINE-2,4,6-TRIAMINE, N,N',N''-TRIS(4-((1,4-DIMETHYLPENTYL)AMINO)PHENYL- (CAS #121246-28-4) GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: May 16, 2024

ToxServices Review Date: May 16, 2029[1]

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[1] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

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1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is an organic compound that belongs to the class of phenylalkylamines. It is not explosive or flammable. At standard temperature and pressure it is dark purple pastille or flake. Based on its moderate boiling point of 225°C, it may be considered semi-volatile. It has a negligible vapor pressure (0 mmHg) and is not soluble in water. 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- has a high log Kow greater than 6.5, but it is expected to have limited bioavailability according to Lipinski's Rule of Five. In aquatic species, the modeled bioaccumulation factor was low at < 400.

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemical of High Concern"). This score is based on the following hazard score combinations:

- Benchmark 1c – vPT = very High Persistence + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)
    - vH Persistence (P) + vH (Chronic Aquatic Toxicity)(CA)
    - vH Persistence (P) + H (Skin Sensitization) (SnS)
    - vH Persistence (P) + H (Respiratory Sensitization) (SnR)

Data gaps (DG) exist for carcinogenicity, reproductive toxicity, developmental toxicity, endocrine activity, systemic toxicity (single and repeated exposure), and neurotoxicity (single and repeated exposure). As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gaps, and filling the data gaps would not change the Benchmark score.

New Approach Methodologies (NAMs) used in this GreenScreen® include use of QSAR modeling and *in vitro* / *ex vivo* test methods. 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 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-'s NAMs dataset include reliance on numerous studies that are reported with limited details within the public literature, and their reliability cannot be determined (i.e., Klimisch 4 – not assignable). 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-'s Type II (extrapolation output) uncertainties include use of *in vitro* data that is insufficient in some cases to discern the specific GHS hazard rating (e.g., GHS Category 1A or 1B), and use of *in vitro* data that do not fully mimic *in vivo* metabolic conditions.

GreenScreen® Hazard Summary Table for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-

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	*M*	DG	DG	DG	*L*	DG	*L*	DG	DG	*H*	*H*	*L*	*L*	**vH**	*vH*	*vH*	*L*	**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 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

Method Version: GreenScreen® Version 1.4
Assessment Type[2]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Nancy Linde, M.S.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: March 13, 2024

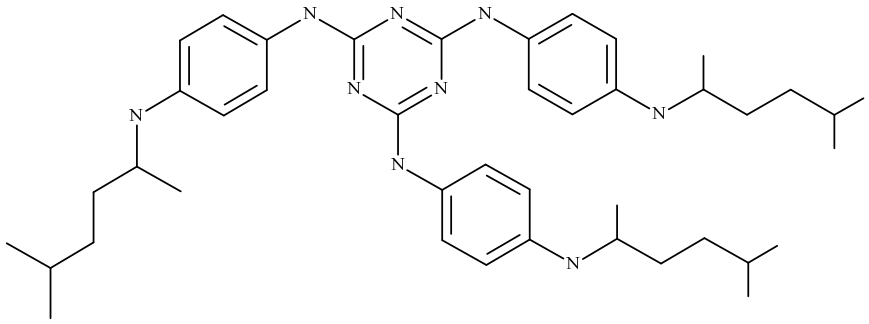
Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 16, 2024

ToxServices Review Date: May 16, 2029[3]

Chemical Name: 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)-phenyl-; N,N',N''-Tris[4-[(1,4-dimethylpentyl)amino]phenyl]-1,3,5-triazine-2,4,6-triamine

CAS Number: 121246-28-4

Chemical Structure(s):



(PubChem 2024)

Also called: 2-N,4-N,6-N-tris[4-(5-methylhexan-2-ylamino)phenyl]-1,3,5-triazine-2,4,6-triamine; EC 426-150-0, EC-601-761-7 (PubChem 2024); Durazone® 37 (SI Group 2019).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
No reasonable surrogates with data were identified. It may be noted that the target compound 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- has benzenediamine (CAS #106-50-3) and melamine (CAS #108-78-1) as structural components. Although these compounds are data rich, there are no indications that the target compound will hydrolyze or metabolize, in the environment and/or within the human body, to benzenediamine and/or melamine.

[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[3] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

Identify Applications/Functional Uses:
1. Antioxidant and antiozonant added to rubber compounds at 2-4 pph, including tires, technical rubber goods, and foams (SI Group 2024).

Known Impurities[4]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-[5,6 7,8]: 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemical of High Concern") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 1c – vPT = very High Persistence + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)
    - vH Persistence (P) + vH (Chronic Aquatic Toxicity)(CA)
    - vH Persistence (P) + H (Skin Sensitization (SnS)
    - vH Persistence (P) + H (Respiratory Sensitization (SnR)

Data gaps (DG) exist for carcinogenicity, reproductive toxicity, developmental toxicity, endocrine activity, systemic toxicity (single and repeated exposure), and neurotoxicity (single and repeated exposure). As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gaps, and filling the data gaps would not change the Benchmark score.

Figure 1: GreenScreen® Hazard Summary Table for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-

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

[4] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[5] 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.
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[8] 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.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not readily biodegradable, hydrolysable, and has no known metabolites, no transformation products have been identified. However, benzenediamine (CAS #106-50-3) and melamine (CAS #108-78-1) are structural components of 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-; it is theoretically possible they could result as transient breakdown products in some end-of-life processes, e.g., incineration. However, they would not be expected to persist longer than the parent compound under conditions of incineration, and are not considered relevant transformation products.

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[9,10]
End-of-life	Incineration	Benzenediamine	106-50-3	Y	N	LT-P1
End-of-life	Incineration	Melamine	108-78-1	Y	N	LT-1

Introduction

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is an antioxidant and antiozonant added to rubber compounds at 2-4 pph, including tires, technical rubber goods, and foams (SI Group 2024). No specific information was found regarding the manufacturing process for 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-; however, numerous other substituted 1,3,5-triazines have been manufactured starting with cyanuric chloride and successive, controlled nucleophilic substitution of each chloride with a nitrogen atom, followed by amino substitution at the 2, 4, or 6 position (Afonso et al. 2006). It is unclear if the branched alkyl diamino phenyl groups are added simultaneously or after the 2, 4, 6-substitution.

ToxServices assessed 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)-amino)phenyl- against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2024). 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',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not currently on the SCIL.

[9] 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 2024) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[10] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

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 2024) 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),[11] 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 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- can be found in Appendix C.

- 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not listed on the U.S. DOT list.

Hazard Statement and Occupational Control

Three EU harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-, as indicated in Table 2. Precautionary statement P280, as indicated in Table 3, is a general recommendation for personal protective equipment (PPE) that is applicable to most chemicals. No occupational exposure limits (OELs) specific to 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- were identified.

Table 2: GHS H Statements for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4) (Pharos 2024)

H Statement	H Statement Details
H317	May cause an allergic skin reaction (Skin Sens. 1)
H400	Very toxic to aquatic life (Aquatic Acute 1)
H410	Very toxic to aquatic life (Aquatic Chronic 1)

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
P280 - Wear protective gloves/protective clothing/eye protection/face protection	PubChem 2024	N/A	N/A

N/A – Not applicable.

Physicochemical Properties of 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is a solid at standard temperature and pressure. Based on its boiling point of 225°C, it may be considered semi-volatile; however, it has negligible vapor pressure (0 mmHg). It is not soluble in water and has a high partition coefficient (log K_{OW} > 6.5).

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

Table 4: Physical and Chemical Properties of 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)		
Property	**Value**	**Reference**
Molecular formula	$C_{42}H_{63}N_9$	PubChem 2024
SMILES Notation	CC(C)CCC(C)NC1=CC=C(C=C1)NC2=NC(=NC(=N2)NC3=CC=C(C=C3)NC(C)CCC(C)C)NC4=CC=C(C=C4)NC(C)CCC(C)C	PubChem 2024
Molecular weight	694.0 g/mol	PubChem 2024
Physical state	Solid	SI Group 2019
Appearance	Dark purple pastille or flake	SI Group 2019
Melting point	54°C (EU Method A.1)	ECHA, CAS #121246-28-4, 2024
Boiling point	225°C (EU Method A.2)	ECHA, CAS #121246-28-4, 2024
Vapor pressure	0 Pa (0 mmHg) at °C (EU Method A.4)	ECHA, CAS #121246-28-4, 2024
Water solubility	0 g/L at 20°C (EU Method A.6)	ECHA, CAS #121246-28-4, 2024
Dissociation constant	N/A	
Density/specific gravity	1.07 g/cm^3 at 20°C (EU Method A.3)	ECHA, CAS #121246-28-4, 2024
Partition coefficient	Log K_{OW} > 6.5 (EU Method A.8)	ECHA, CAS #121246-28-4, 2024

N/A – Not applicable

Toxicokinetics

No measured data were found regarding the absorption, distribution, metabolism, and/or excretion of 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-. The OECD QSAR Toolbox predicts it is not likely to be bioavailable based on Lipinski's Rule of Five. Furthermore, 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not predicted to hydrolyze under aqueous acidic, neutral, or basic conditions. Although seven possible metabolites are predicted with the *in vivo* rat metabolism simulator, the rates and specificities for each metabolite are not known, and none of the seven theoretical metabolites are affiliated with any of the chemical inventories (OECD 2023, Appendix D).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for carcinogenicity based on insufficient data. QSAR modeling was performed with a variety of programs. Toxtree (a rule based program) identified no structural alerts for genotoxic or nongenotoxic carcinogenicity. Results in VEGA were mixed with the rule-based methods, and the only statistical based method (CAESAR) could not provide a reliable prediction as the target compound was outside the applicability domain of the model. Results were also mixed in the Danish QSAR Database models for both in-domain and out-of-domain predictions. OncoLogic v8.0 and v9.0 could not evaluate

the compound. Accordingly, as there are no consistent and reliable predictions for both rule-based and statistical-based models, the weight of evidence is inconclusive and a Data Gap is assigned.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were found.
- Toxtree 2018
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- does not have any structural alerts for genotoxic or nongenotoxic carcinogenicity (Appendix E).
- VEGA 2023
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assessed for carcinogenicity with six models in the VEGA platform. 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). Predictions and the corresponding AD values are as follows:
    - CAESAR predicts it will be a non-carcinogen with low reliability based on a global ADI of 0.425.
    - ISS predicts it will be a **non-carcinogen** with moderate reliability based on a global ADI of 0.716.
    - IRFMN-ISSCAN-CGX predicts it will be a carcinogen with low reliability based on a global ADI of 0.693.
    - IRFMN-Antares predicts it will be a carcinogen with low reliability based on a global ADI of 0.
    - IRFMN oral classification model predicts it will be a carcinogen with low reliability based on a global ADI of 0.598.
    - IRFMN inhalation classification model predicts it will be a **carcinogen** with moderate reliability based on a global ADI of 0.703 (Appendix F).
- DTU 2021
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was modeled in the Danish QSAR Database.
    - For the E Ultra model, it was predicted to be negative for carcinogenicity and was within the applicability domain with 1 of 7 datasets (i.e., FDA RCA Cancer Male Mouse). For the remaining datasets, the compound was outside the applicability domain and the results were not considered in the weight of evidence.
    - For the Leadscope model, it was predicted to be negative for carcinogenicity and was within the applicability domain with 6 of 7 datasets (i.e., FDA RCA Cancer Male Rat, FDA RCA Cancer Female Rat, FDA RCA Cancer Rat, FDA RCA Cancer Male Mouse, FDA RCA Cancer Female Mouse, and FDA RCA Cancer Mouse). With the FDA RCA Cancer Rodent dataset, the compound was outside the applicability domain and the results were not considered in the weight of evidence.
    - The Battery, CASE Ultra, Leadscope, and SciQSAR models predicted it would be positive, and was within the applicability domain, with the Liver Specific Cancer in Rat or Mouse dataset (DTU-developed). The CASE Ultra model predicted it would be noncarcinogenic, but the compound was outside the applicability domain, and the result is not included in the weight of evidence (Appendix G).

- U.S. EPA 2021
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- does not fall into any of the chemical classes evaluated by OncoLogic v8.0.
- U.S. EPA 2023
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- could not be modeled with OncoLogic v9.0 as the molecular structure is outside the scope of v9.0.

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Moderate for mutagenicity/genotoxicity based on positive results in a bacterial reverse mutation assay (OECD 471) and an *in vitro* mammalian cell gene mutation test (OECD 476), which meets the criteria for GHS Category 2 classification. Although it was positive in an *in vitro* chromosome aberration assay, negative results in an *in vivo* micronucleus assay alleviate concerns for clastogenicity *in vivo*; however, there are no *in vivo* data to rule out the potential for gene mutations. GreenScreen® criteria classify chemicals as a Moderate hazard for mutagenicity/genotoxicity when data meet the criteria for GHS Category 2 classification (CPA 2018b). The confidence in the score is low as all publicly available study summaries are very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable).

- 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, CAS #121246-28-4, 2024
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was evaluated in a bacterial reverse mutation assay performed according to OECD TG 471 and EU Method B.13/14 (GLP compliance not specified). *Salmonella typhimurium* TA1535, TA1537, TA98, and TA100, and *Escherichia coli* WP2 were exposed to the test substance with and without activation. Results were **positive in TA98 with activation**. Results were negative in TA98 without activation, and in the remaining *S. typhimurium* and *E. coli* strains exposed with and without activation. There were no observations of cytotoxicity in any strain with or without activation. Results for the vehicle and positive controls were reported as valid (no further details provided) (Unnamed 1996 study report).
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vitro* mammalian cell gene mutation test performed according to OECD TG 476 (GLP compliance not specified). Mouse lymphomas L5178Y cells were exposed to the test substance. **Results were positive with and without activation and no cytotoxicity was observed.** Results for the vehicle and positive controls were reported as valid (no further details provided) (Unnamed 1997 study report).
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vitro* chromosome aberration study in mammalian cells performed according to OECD TG 473 (GLP compliance not specified). Chinese hamster lung fibroblasts (V79) were exposed to the test substance. **Results were positive with activation at cytotoxic concentrations.** Results were negative without activation, and no cytotoxicity was observed. Results for the vehicle and positive controls were reported as valid (no further details provided) (Unnamed 1997 study report).
    - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vivo* micronucleus test performed according to OECD TG 474 and EU Method B.12 (GLP compliance not specified). Male

and female mice were exposed to the test substance. **Results were negative** . Results for the vehicle and positive controls were reported as valid (no further details provided) (Unnamed 1997 study report).

Reproductive Toxicity (R) Score (H, M, or L): DG
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for reproductive toxicity based on lack of data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): DG
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for developmental toxicity based on based on lack of data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Endocrine Activity (E) Score (H, M, or L): DG
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for endocrine activity based on based on lack of data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

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*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values > 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are > 2,000 mg/kg (CPA 2018b). The confidence in the score is low because all publicly available study summaries are very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable). 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, CAS #121246-28-4, 2024

  Oral
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in an acute toxicity study using a standard acute method (guideline and GLP compliance not specified). The rat oral LD_{50} (gavage) was > 5,000 mg/kg in males and females (no further details provided) (Unnamed 1987 study

report).

Dermal

- 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in an acute toxicity study performed according to OECD TG 402 and EU Method B.3 (GLP compliance not specified). Male and female rats were exposed under semi-occlusive conditions, and the LD_{50} was > 2,000 mg/kg (no further details provided) (Unnamed 1996 study report).

Inhalation

- No data found.

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for systemic toxicity (single dose) based on lack of data. The above summarized acute oral and dermal toxicity studies did not report the observed clinical observations, or gross necropsy findings, and therefore are insufficient to fill this data gap.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for systemic toxicity (repeated dose) based on a 28-day oral NOAEL of 400 mg/kg/day in rats. This NOAEL exceeds the GHS duration-adjusted guidance value of 300 mg/kg/day for a 28-day study, and therefore, exceeds the criteria for GHS classification. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when data exceed the criteria for GHS classification (CPA 2018b). The confidence in the score is low because all publicly available study summaries are very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable).

- 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, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was evaluated in short-term repeated dose toxicity study performed according to EU Method B.7 (GLP compliance not specified). The rat oral (gavage) NOAEL was 400 mg/kg/day in males and females (no further details provided) (Unnamed 1997 study report).

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for neurotoxicity (single dose) based on lack of data. The above summarized acute oral and dermal toxicity studies did not report the observed clinical observations, or gross necropsy findings, and therefore are insufficient to fill this data gap.

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

  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was assigned a score of Data Gap for neurotoxicity (repeated dose) based on lack of data. The above summarized 28-day repeated dose oral exposure study did not report if a functional observational battery was performed, and it is unclear if neurotoxicity was assessed. Therefore, this study is insufficient to fill the data gap.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *H*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl1,4-dimethylpentyl)amino)phenyl- was conservatively assigned a score of High for skin sensitization based on a high occurrence of skin sensitization in an *in vivo* study in guinea pigs, which ToxServices conservatively assumes meets the criteria for GHS Category 1A. GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when data meet the criteria for GHS Category 1A (CPA 2018b). The confidence in the score is low because the only publicly available study summary is very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable), and is insufficient to discern between Category 1A and 1B because induction concentrations were not reported (and Category 1B would support a Moderate hazard rating). Additionally, the EU harmonized classification to H317 - May cause an allergic skin reaction (Skin sensitization – Category 1) does not discern between Category 1A and 1B.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS Annex 6, Table 3-1 – H317 – May cause an allergic skin reaction (Skin sensitization – Category 1)
  - *Screening:* GHS – Australia - H317 – May cause an allergic skin reaction (Skin sensitization – Category 1)
- ECHA, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vivo* skin sensitization study performed according to OECD TG 406 and EU Method B.6 (GLP compliance not specified). Female Dunkin-Hartley guinea pigs were induced with intradermal injection and epicutaneous administration under occlusion. Animals were challenged via epicutaneous administration under occlusion. Positive results were reported for 10/10 animals at 24 hours, 8/10 animals at 48 hours, and 9/10 animals at 72 hours. There were no positive reactions in any of the five negative control animals at 24 or 48 hours (no further details provided) (Unnamed 1996 study report).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *H*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was conservatively assigned a score of High for respiratory sensitization based on extrapolation from positive skin sensitization data, and a structural alert for respiratory sensitization, in accordance with guidance from ECHA (2071). GreenScreen® criteria classify chemicals as a High hazard for respiratory sensitization when data meet the criteria for GHS Category 1A (CPA 2018b). The confidence in the score is low because no data specific to respiratory sensitization are available, and, as noted above, the skin sensitization data as presented in the public literature are very brief, corresponding with unknown

reliability (i.e., Klimisch 4 – not assignable), and are insufficient to discern between Category 1A and 1B.

- 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
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- has one structural alert for respiratory sensitization – pro-Michael addition (Appendix D)
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- according to ECHA's guideline (ECHA 2017), which states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommends that if a chemical is a dermal sensitizer (GHS Category 1A or 1B), is not a diisocyanate or protein, and has a structural alert for respiratory sensitization (e.g., Michael addition), then classification as a respiratory sensitizer should be considered (ECHA 2017).

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for skin irritation/corrosivity based on tissue viability ≥ 100% in an *in vitro* / *ex vivo* skin study using reconstructed human epidermis (OECD TG 439). Tissue viability > 50% meets the criteria for GHS not classified. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when available data exceed the criteria for GHS classification (CPA 2018b). The confidence in the score is low because the publicly available study summary is very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable).

- 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, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vitro* / *ex vivo* skin irritation study performed according to OECD TG 439 and EU Method B.46, using the Reconstructed Human Epidermis Model (GLP compliance not specified). Tissue viability was 119% (no further details provided) (Unnamed 2015 study report). *ToxServices notes that OECD TG 439 identifies substances with > 50% tissue viability as not irritating to the skin (OECD 2021).*

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *L*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for eye irritation/corrosivity based on an *in vitro* irritation score (IVIS) of 0.2 in a Bovine Corneal Opacity and Permeability Test (OECD TG 437). An IVIS score ≤ 3 meets the criteria for GHS not classified. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when data meet the criteria for GHS not classified (CPA 2018b). The confidence in the score is low because the publicly available study summary is very brief, corresponding with unknown reliability (i.e., Klimisch 4 – not assignable).

- 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, CAS #121246-28-4, 2024

- 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was evaluated in an *in vitro* / *ex vivo* eye irritation study performed according to OECD TG 437 and EU Method B.47, using the Bovine Corneal Opacity and Permeability Test Method for identifying ocular corrosives and severe irritants (GLP compliance not specified). The *in vitro* irritation score (IVIS) was 0.2, and the positive and vehicle control were reported as valid (no further details provided) (Unnamed 2013 study report). *ToxServices notes that OECD TG 437 identifies substances with IVIS ≤ 3 as not requiring GHS classification for eye irritation or serious eye damage (OECD 2020a).*

Ecotoxicity (Ecotox)

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Very High for acute aquatic toxicity based on EU harmonized classification H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1]. This corresponds with data for the fish, invertebrate, and algae, which have a L/EC_{50} values as low as 0.014 mg/L (96-hour), 0,35 mg/L (96-hour),and 0.056 mg/L (96-hour biomass)/0.062 mg/L (24-hour growth). GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when they have the H400 EU harmonized classification, and when the most sensitive trophic level has acute toxicity values ≤ 1 (CPA 2018b). The confidence in the score is high based on EU harmonized classification.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS Annex 6, Table 3-1 – H400 – Very toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 1]
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #121246-28-4, 2024

  Fish
  - 96-hour LC_{50} in *Oncorhynchus mykiss* (Rainbow trout) was > 2 mg/L (nominal) under semi-static conditions, and the validity criteria were fulfilled (OECD TG 203 and EU Method C.1) (no further details provided) (Unnamed 1996 study report).

  Crustacea
  - 48-hour NOEC and EC_{50} based on mobility, in *Daphnia magna,* were each reported at > 2 mg/L (nominal), under static conditions, and the validity criteria were fulfilled (OECD TG 202 and EU Method C.2) (no further details provided) (Unnamed 1996 study report). *ToxServices notes the database likely has a typo, and it should read that the 48-hour NOEC and EC_{50} were 2 and > 2 mg/L, respectively.*

  Algae
  - *Desmodesmus subspicatus* (green algae) was exposed to the test substance for 72 hours (OECD TG 201 and EU Method C.3). The 72-hour NOEC was 0.02 mg/L (nominal) (growth rate or biomass not specified), the 72-hour EC_{50} based on biomass was 0.056 mg/L, the 24 hour EC_{50} based on growth rate was 0.062 mg/L, and the validity criteria were fulfilled (no further details provided) (Unnamed 1996 study report).
- USGS 2015

  Fish
  - 96-hour LC_{50} in *Oncorhynchus mykiss* (rainbow trout) was 34.0 µg/L (equivalent to 0.034 mg/L) when exposed at 13°C, pH 7.1, hardness 44, under static conditions (no further details provided).
  - 96-hour LC_{50} in *Oncorhynchus mykiss* (rainbow trout) was 32.0 µg/L (equivalent to 0.032 mg/L) when exposed at 13°C, pH 7.4, hardness 272, under static conditions (no further

details provided).
- 96-hour LC_{50} in *Lepomis macrochirus* (bluegill) was 14.0 µg/L (equivalent to 0.014 mg/L) when exposed at 18°C, pH 7.1, hardness 44, under static conditions (no further details provided).

Crustacea
- 96-hour LC_{50} in *Gammarus lacustris* (amphipod) was 350 µg/L (equivalent to 0.35 mg/L) when exposed at 21°C, pH 7.1, hardness 44, under static conditions (no further details provided).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *vH*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Very High for chronic aquatic toxicity based on data for the most sensitive trophic level, algae, which has a 72-hour NOEC of 0.02 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when the most sensitive trophic level has a chronic toxicity value ≤ 0.1 mg/L (CPA 2018b). Although there are no chronic data available for fish and invertebrates, the lowest acute L/EC_{50} values are below 0.1 mg/L, indicating that the chronic NOECs will also be below this value. Although the available data in the public literature have limited details, confidence in the score is high based on the corresponding EU harmonized classification H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1].

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS Annex 6, Table 3-1 – H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]
  - *Screening:* GHS – Australia - H410 – Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]
- ECHA, CAS #121246-28-4, 2024

  Algae
  - *Desmodesmus subspicatus* (green algae) was exposed to the test substance for 72 hours (OECD TG 201 and EU Method C.3). The 72-hour NOEC was 0.02 mg/L (nominal) (growth rate or biomass not specified), the 72-hour EC_{50} based on biomass was 0.056 mg/L, the 24 hour EC_{50} based on growth rate was 0.062 mg/L, and the validity criteria were fulfilled (no further details provided) (Unnamed 1996 study report).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Very High for persistence based on predicted partitioning to soil and sediment with half-lives of 360 and 1,621 days, respectively. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when the dominant medium is soil or sediment and the half-life is > 180 days (CPA 2018b). The confidence in the score is low as it is based on modeling, and the available measured data have limited reporting.

- 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, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was evaluated in a ready biodegradability, CO_2 evolution test performed according to OECD TG 301B and EU Method C.4-C (GLP compliance not specified). The test substance was added

to domestic, adapted, activated sludge at an initial concentration of 28.6 mg/L, under aerobic conditions. Biodegradation, based CO_2 evolution, reached 18% in 28 days (no further details provided). *ToxServices notes the test substance was not readily or ultimately biodegradable based on <60% degradation in 28 days. Additionally, the 301 series ready biodegradability tests do not allow pre-adaptation (OECD 1992).*

  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- has a log Koc of > 4.53 at 23°C in soil (unspecified HPLC estimation method) (no further details provided) (Unnamed 1997 study report). *ToxServices notes that a log Koc ≥ 4.5 indicates very strong sorption to soil and sediment, and negligible migration potential to groundwater (U.S. EPA 2023).*

- OECD 2023
  - The OECD QSAR Toolbox predicts that 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- will not hydrolyze under acidic, neutral, or basic conditions (Appendix D).
- U.S. EPA 2017a/b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 52.1% will partition to soil with a half-life of 360 days, 47.4% will partition to sediment with a half-life of 1,621 days, 0.548% will partition to water with a half-life of <1 day of 360 days, and a negligible amount (2.19E-015%) will partition to air where it will rapidly degrade in < 1 hour (Appendix H).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for bioaccumulation based on a predicted BAF of 339.8. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when the BAF is in the range of >100 to 500 (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.
- U.S. EPA 2017
  - BCFBAF predicts a BAF of 339.8 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration, and a log K_{OW} of 6.50 (Appendix H).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L
1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for reactivity based on measured data indicating it is not explosive or self-heating, and based on its molecular structure which indicates it is not a peroxide, and that it lacks reactive functional groups associated with oxidizing potential and self-reactivity. As it is not explosive, it inherently does not require desensitization. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the substance does not require GHS classification for any of the reactivity endpoints (CPA 2018b). The confidence in the score is high based on measured data and physico-chemical properties. It may be noted that no data were found regarding corrosivity to metals, and the substance is not known to emit flammable gases on contact with water.

- 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, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was not explosive (EU Method A.10). It was not sensitive to impact at 40 J, to friction at 360 N, or to heat under defined confinement (Unnamed 1996 study report).
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- has a measured auto-ignition temperature > 400°C (EU Method A.15) (Unnamed 1996 study report).
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was oxidizing (EU Method A.17). When the test substance was mixed with powdered cellulose, the maximum burning rate was 1.471 mm/s, compared to the reference substance (not specified) which had a burning rate of 0.678 mm/s (no further details provided) (Unnamed 1996 study report). *ToxServices calculates that the test substance burned faster than the reference substance by a factor of 2.16 (1.471mm/s / 0.678 mm/s); therefore it was oxidizing under the conditions of the test. However, Section 2.14.4.2.3 of the GHS labeling rules for oxidizing solids excludes compounds that do not contain oxygen or halogens in the molecular structure (OECD 2023).*
- No measured data were identified for self-reactivity. Therefore, screening procedures based on the molecular structure were used, in accordance with GHS (UN 2023).
  - Based on it molecular structure, 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- is not considered self-reactive due to lack of functional groups associated with self-reactive properties (See Appendix I).

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

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- was assigned a score of Low for flammability based on lack of ignition when tested according to EU Method A.10. This meets the criteria for GHS not classified. GreenScreen® criteria classify chemicals as a Low hazard for flammability when data meet the criteria for GHS not classified (CPA 2018b). The confidence in the score is high based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #121246-28-4, 2024
  - 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- did not ignite and propagate combustion either by burning with flame or smoldering along 200 mm of the powder train within the 2 minute test period (EU Method A.10) (Unnamed 1996 study report).

Use of New Approach Methodologies (NAMs)[12] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 5, Type I (input data) uncertainties in 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-'s NAMs dataset include reliance on numerous studies that are reported with limited details within the public literature, and their reliability cannot be determined (i.e., Klimisch 4 – not assignable). 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)-amino)phenyl-'s Type II (extrapolation output) uncertainties include use of *in vitro* data that is insufficient in some cases to discern the specific GHS hazard rating (e.g., GHS Category 1A or 1B), and use of *in vitro* data that do not fully mimic *in vivo* metabolic conditions. Some of 1,3,5-triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl-'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 2020b)	
Type I Uncertainty: Data/Model Input	**Genotoxicity:** All available data are reported with limited details and reliability cannot be determined (i.e., Klimisch 4 – not assignable). **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Skin irritation**: Only one *in vitro* study is available (OECD 439), and it is reported with limited details and the reliability cannot be determined (i.e., Klimisch 4 – not assignable). **Eye irritation**: Only one *in vitro* study is available (OECD 437), and it is reported with limited details and the reliability cannot be determined (i.e., Klimisch 4 – not assignable).
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). VEGA tool

[12] 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).

	and Danish (Q)SAR database provided mixed results, with no apparent weight of evidence. **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[13]. 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).[14] 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[15]. **Skin irritation**: The OECD Guideline 439 test is only used to identify irritating substances (GHS Category 2) and non-irritating substances (no category), and does not allow the classification as a mild skin irritant (GHS Category 3)[16]. **Eye irritation**: The BCOP (OECD Guideline 437) test is not recommended for identifying GHS Category 2A or 2B irritants[17]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OECD Toolbox/Danish QSAR

[13] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[14] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[15] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[16] https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1614097324&id=id&accname=guest&checksum=D664A7EDCDE297919BE9A478941EBEC6
[17] https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1614095760&id=id&accname=guest&checksum=1613168F64BDB3558225572BDD75FC8D

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	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	Y	*In vitro* tests: OECD Guideline 439 Reconstructed Human Epidemis Model
Eye irritation	Y	*In vitro* tests: OECD Guideline 437 Bovine Corneal Opacity and Permeability Test Method
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301 B Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for 1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-((1,4-**	**121246-28-4**	DG	*M*	DG	DG	DG	*L*	DG	*L*	DG	DG	*H*	*H*	*L*	*L*	**vH**	*vH*	*vH*	*L*	**L**	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-	1

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

Table 6

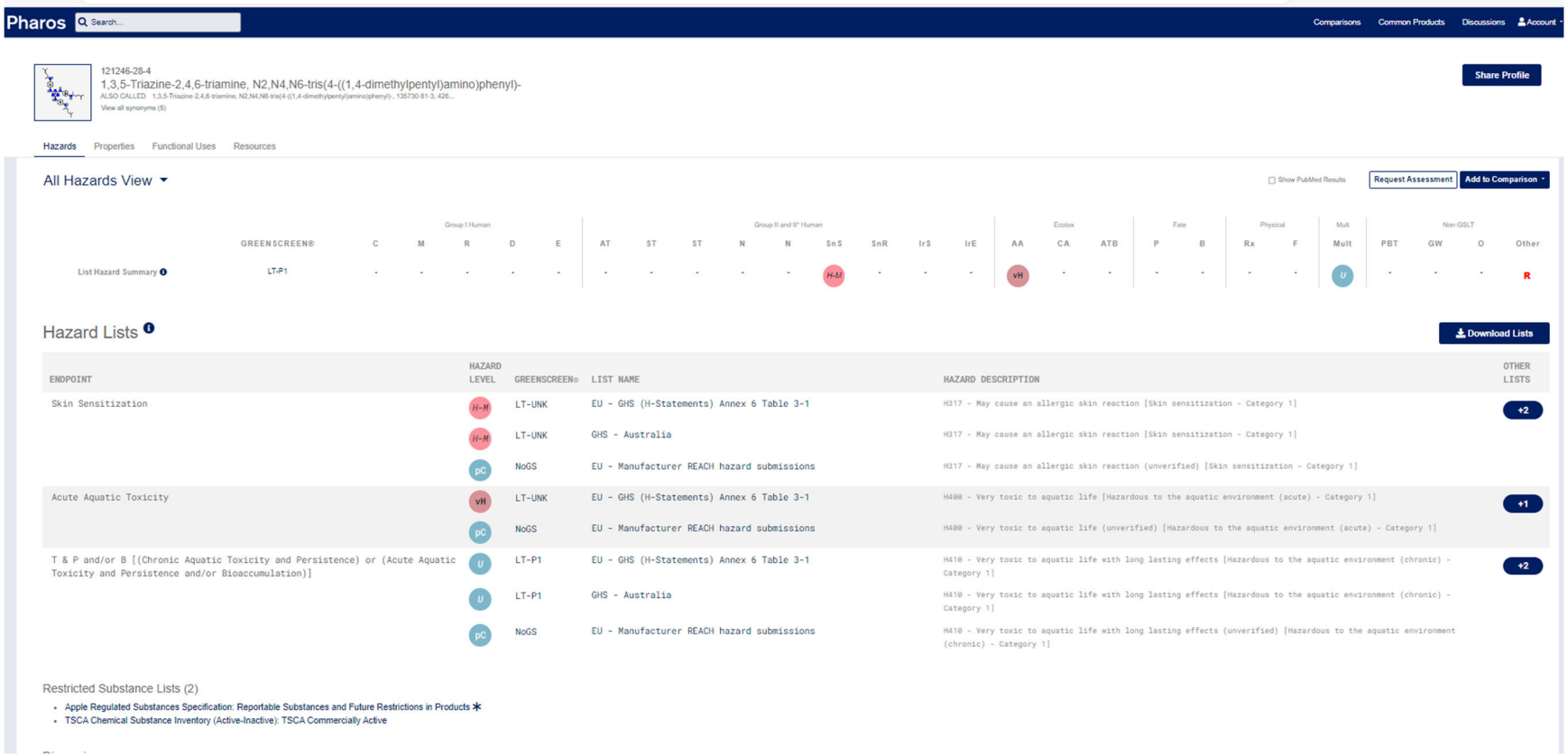
Chemical Name	Final GreenScreen® Benchmark Score
1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-	1

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												1
2												
3												
4												

APPENDIX C: Pharos Output for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)



Pharos Search... Comparisons Common Products Discussions Account

121246-28-4
1,3,5-Triazine-2,4,6-triamine, N2,N4,N6-tris(4-((1,4-dimethylpentyl)amino)phenyl)-
ALSO CALLED 1,3,5-Triazine-2,4,6-triamine, N2,N4,N6-tris(4-((1,4-dimethylpentyl)amino)phenyl) , 136730-81-3, 426...
View all synonyms (5)

Share Profile

Hazards Properties Functional Uses Resources

All Hazards View

Show PubMed Results Request Assessment Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GREENSCREEN®	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
List Hazard Summary	LT-P1	-	-	-	-	-	-	-	-	-	-	H-M	-	-	-	vH	-	-	-	-	-	-	U	-	-	-	R

Hazard Lists

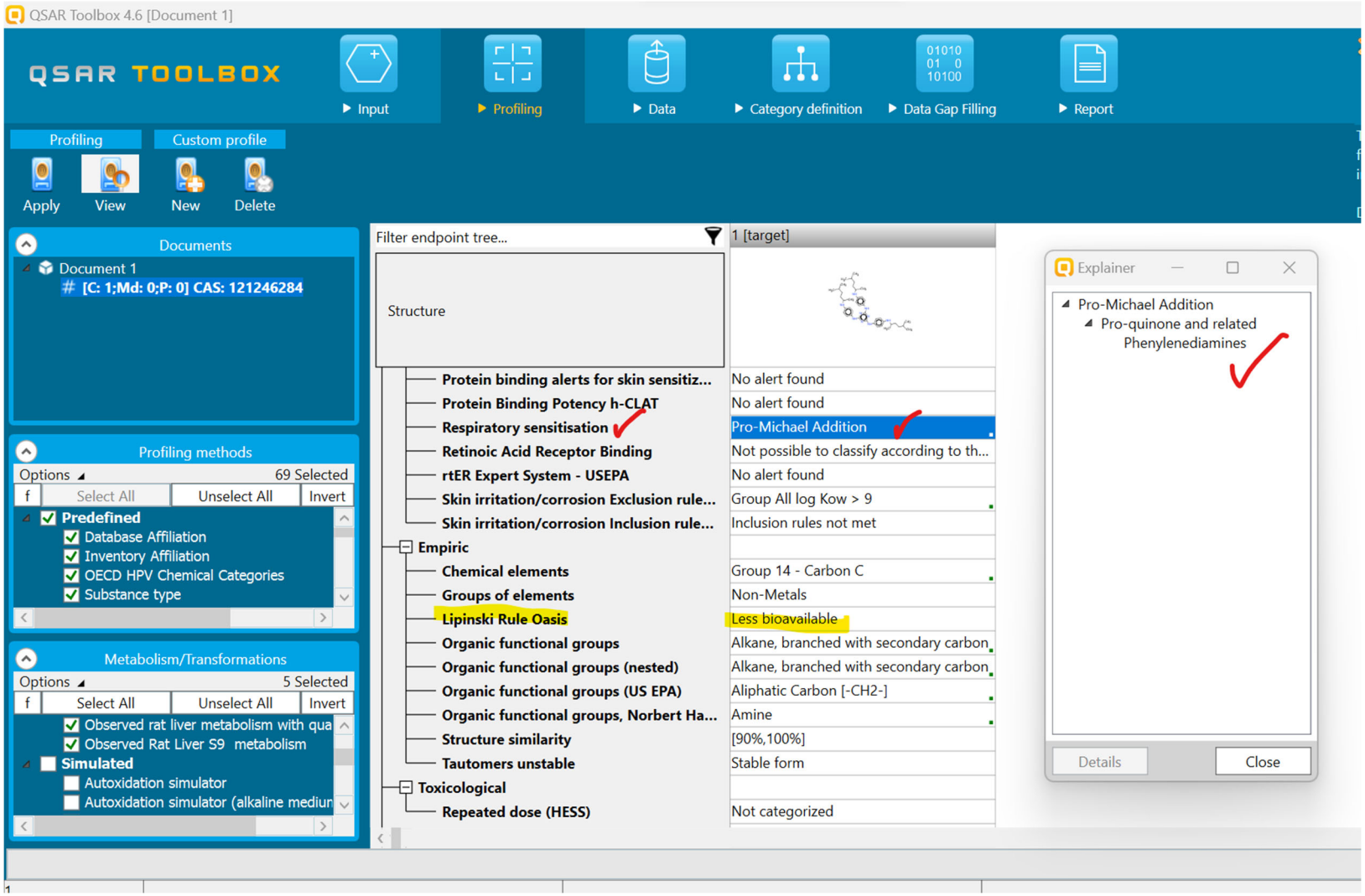
Download Lists

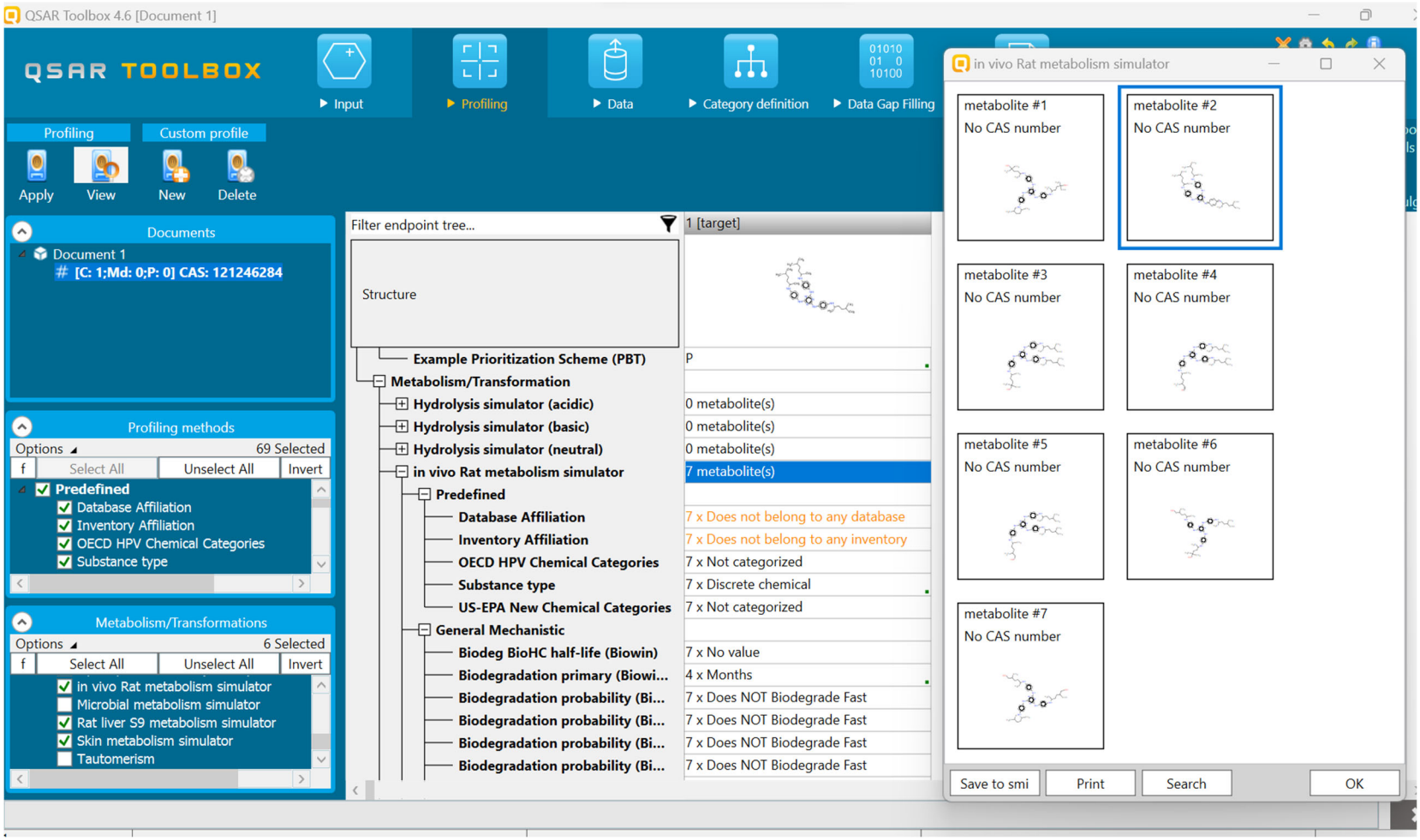
ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Skin Sensitization	H-M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	+2
	H-M	LT-UNK	GHS - Australia	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Acute Aquatic Toxicity	vH	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified) [Hazardous to the aquatic environment (acute) - Category 1]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-P1	EU - GHS (H-Statements) Annex 6 Table 3-1	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	+2
	U	LT-P1	GHS - Australia	H410 - Very toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 1]	

Restricted Substance Lists (2)

- Apple Regulated Substances Specification: Reportable Substances and Future Restrictions in Products ✱
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Commercially Active

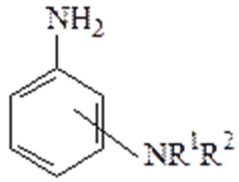
APPENDIX D: OECD Toolbox Profiling Results for 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)





ortho- and *para*-Phenylenediamines

The general structure of mono- and dialkylated *ortho*- and *para*-phenylenediamine isomers can be presented as follows:



N-Alkylated-*ortho*- and *para*-phenylenediamines could be divided into 2 subgroups according to their substituents:

Subgroup 1: *o*-PhDs and *p*-PhDs containing secondary and tertiary amino groups (NR^1R^2), where at R^1 = H and R^2 = Csp^3(acy) *sec*-amino group and $R^1 = R^2$ = Csp^3(acy) *tert*-amino group.

Subgroup 2: *p*-Substituted anilines in which the substituents are saturated cycloalkylamine residues, i.e. R^1 and R^2 = Csp^3(scy).

The presented subgroups of *N*-alkylated phenylenediamines are based on the selected chemicals containing at least one primary amino group.

The phenylenediamines have a wide application in practice in the preparation of various polymers, as antiozonants in production of rubber products, in hair colouring products, as a corrosion inhibitor for steel, as a component of dyes for leather and textiles, etc. [1,2]. The main components of permanent oxidant dyes are *para*-phenylenediamine, 2,5-diaminotoluene, 2,4-diaminoanisole, 2-amino-4-nitrophenol, and *ortho*-phenylenediamine [3].

More recent investigations for acute toxicity yielded oral or parenteral LD_{50} values for *o*-phenylenediamine in rodents between 500 and 1300 mg/kg body weight and for *o*-phenylenediamine dihydrochloride between 300 and 1600 mg/kg body weight [4], which classifies them as harmful if swallowed. The LD_{50} values for *p*-phenylenediamines vary in the range from 50 to 2000 mg/kg indicating

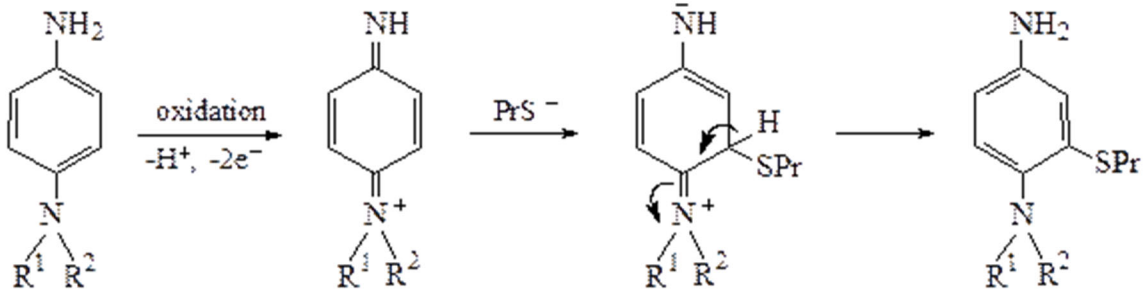
that they can be accepted as toxic or harmful if swallowed according to GHS classification. Thus, the *o*-phenylenediamines were found to be less toxic than the respective *p*-isomers.

Substituted *para*- and *ortho*-phenylenediamines are susceptible toward abiotic and biotic oxidation yielding the corresponding benzoquinone diimines [5,6]. The rate of their oxidation was shown to increase when pH of the medium increased from 6 to 8 [7].

1. Subgroup 1: *para*- and *ortho*-Phenylenediamines containing secondary (monoalkyl) and tertiary (dialkyl) amino groups

If one of the amino groups in benzene ring is tertiary, the corresponding diamine can be oxidized to a charged analogue as in the case of *N,N*-dialkyl-*p*-phenylenediamines. This derivative is expected to be more reactive as a Michael acceptor than the uncharged oxidized products [5]. The overall mechanism for the interaction of this type of *p*-phenylenediamines with protein thiols is summarized as shown in Scheme 1. The nucleophilic binding of protein thiolate (mainly Cys-S^-) to *N,N*-dialkyl-*p*-benzoquinone-diiminium cation proceeds as an A_N2 Michael-type addition reaction.

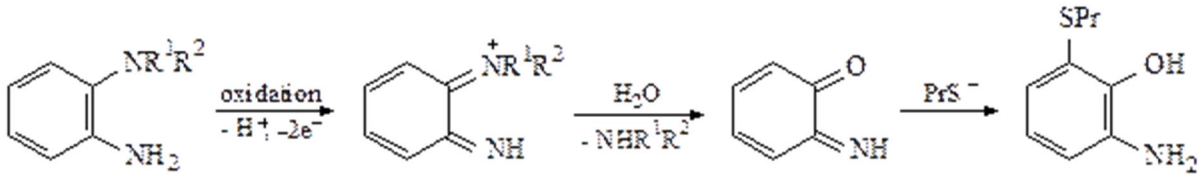
Scheme 1



ortho-Phenylenediamine salts such as *o*-phenylenediamine dihydrochloride are stable to oxidation in the solid state but the *free base o*-phenylenediamine is unstable in the solid state and even more so as the liquid and in solution. In the presence of oxygen or oxidants, brown-coloured oxidation products are formed, particularly in the light [4]. As this substance is a methaemoglobin-producer in analogy with other aromatic amines, it may be assumed that *o*-phenylenediamine forms *N*-oxidized metabolites. Likewise, the

monooxygenase-dependent formation of genotoxic reaction products observed in *Salmonella* mutagenicity tests indicates the formation of *N*-oxidized or ring-hydrolyzed metabolites [4]. The proposed mechanism of the reaction involving *N,N*-dialkyl-*o*-quinonediamines and protein thiolates is shown in Scheme 2.

Scheme 2



where $R^1 = R^2 =$ H or Csp^3(acy); $R^1 =$ H and $R^2 =$ Csp^3(acy)

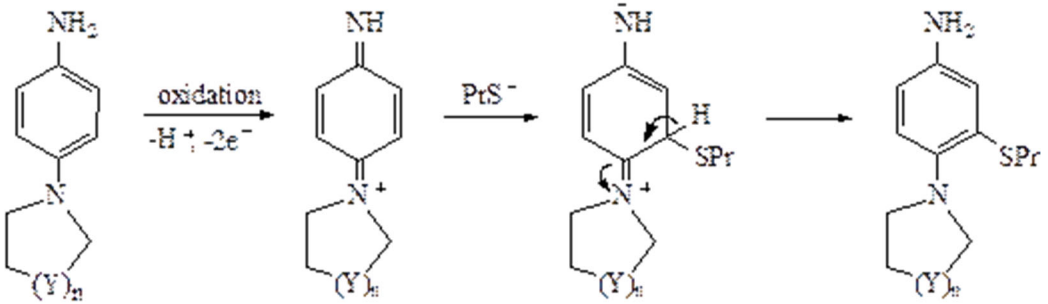
For phenylenediamines with a comparable degree of methylation has been found that the sequence of *in vitro* citotoxicity correlates to their *in vitro* autoxidation rates, namely: ring-methylated *p*-PhD > *N*-methylated *p*-PhD >> *N*-methylated *o*-PhD > *N*-methylated *m*-PhD [8]. According to Babich *et al*. [8], the established decreasing order of cytotoxicity could serve as a strong predictor of *in vivo* acute toxicity.

In addition, it should be taken in mind that orally administered phenylenediamines may be detoxified by first-pass effects (extraction/metabolism) by liver. The principal metabolic pathway of detoxification of aromatic amines given orally will largely depend on the activity of *N*-acetyltransferase-2 (NAT2) found in the liver and responsible for the transformation of primary and secondary phenylenediamines to acetylated metabolites [3].

2. Subgroup 2: *p*-Substituted anilines in which the substituents are saturated cycloalkylamine residues

The possible mechanism of the acute oral toxicity of *p*-substituted anilines containing a saturated cycloaliphatic moiety is presented in Scheme 3. The formation of a charged *p*-benzoquinone diiminium metabolite in analogy with tertiary *p*-phenylenediamines is assumed to be responsible for their reaction with proteins.

Scheme 3



where Y = Csp^3 (scy) or N(scy); n = 0 2

However, the toxic potency of chemicals of subgroup 2 is expected to be lower as compared to the chemicals of subgroup 1 due to steric reasons during the formation of reactive benzoquinone diiminium intermediate, i.e. $reactivity_{subgroup2} \leq reactivity_{subgroup1}$.

Many authors have been found that phenylenediamines can produce different types of toxic effects after oral ingestion. For example, *p*-PhD may cause rapid developmental of severe oedema of the face, neck, pharynx, tongue and larynx with respiratory distress, often requiring tracheotomy. In addition to *p*-PhD dyeing properties, it was also used to kill wild animals when added to food [9]. Short-term acute exposure to high levels of *p*-PhD may cause severe dermatitis, eye irritation and tearing, asthma, gastritis, renal failure, vertigo, tremors, convulsions, and coma in humans. Renal lesions associated with *p*-PhD intoxication received much attention, together with a damage of the nervous system. According to Waggas [9], the presence of the active metabolite *p*-benzoquinone diimine may cause kidney injury. At the same time, *p*-PhD neurotoxicity is able to be due to the formation of reactive oxygen species in the course of its transformation into a quinone diimine [9-11].

The acute toxicity of *o*-PhD affected predominantly central nervous system. The symptoms of acute poisoning in animals were excitement, tremor, convulsions, salivation and respiratory depression. Oral administration in rats produced irritation of the stomach. Death occurs within the first 24 h after ingestion [4,12]. Of particular interest is the observation that *ortho*-phenylenediamines are less toxic than *para*-isomers, reflecting the instability of the corresponding radical cations (semiquinone-imines). [8]. Both *para*- and

ortho-PhDs can cause methemoglobinemia [13,14] as a result of oxidation of the ferrous form (Fe^{2+}) of hemoglobin to the ferric (Fe^{3+}) form [15].

Conclusions

1. *N*-Alkylated-*ortho*- and *para*-phenylenediamines have been found to exhibit acute oral toxicity as a result of the formation of reactive benzoquinone-diimine metabolites that can bind to nucleophilic sites of proteins.
2. It has been demonstrated that acute oral exposure of rats to *o*- and *p*-phenylenediamines is able to cause a variety of toxic effects. *ortho*- and *para*-Phenylenediamines intoxication leads within few hours after exposure to severe syndromes such as vomiting, gastritis, hypertension, vertigo, tremors and convulsions. Renal and liver lesions associated with phenylenediamines intoxication received much attention, together with damage of the nervous system.

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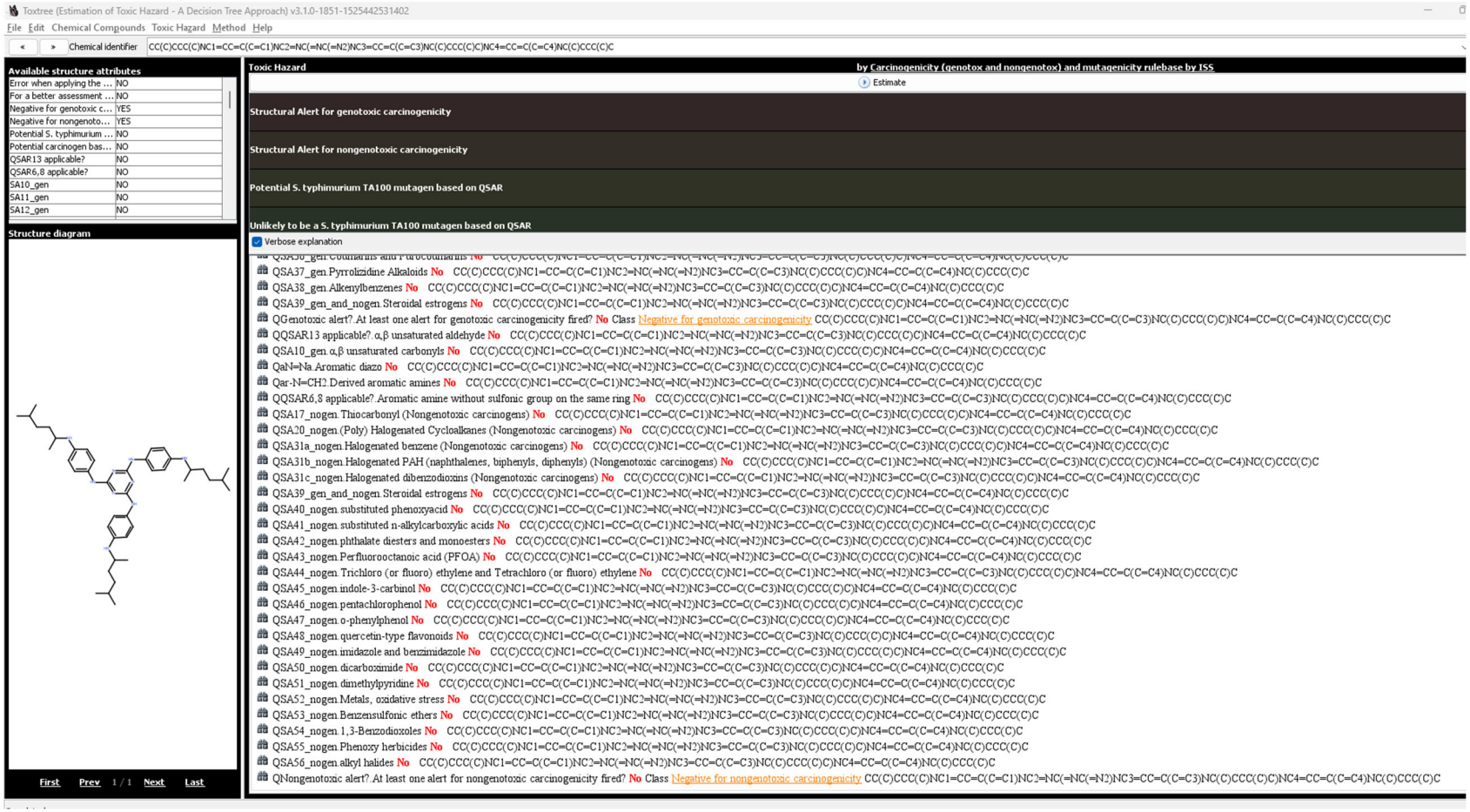
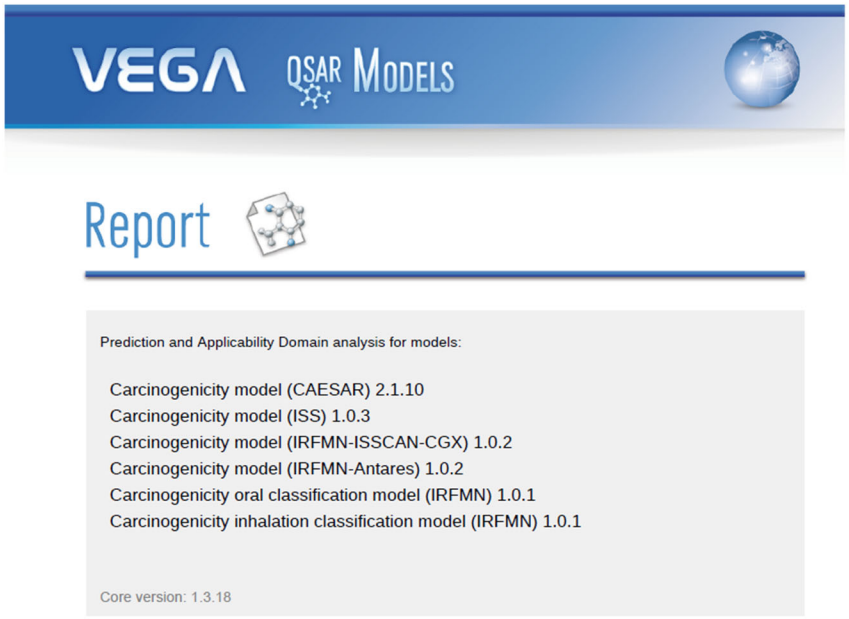
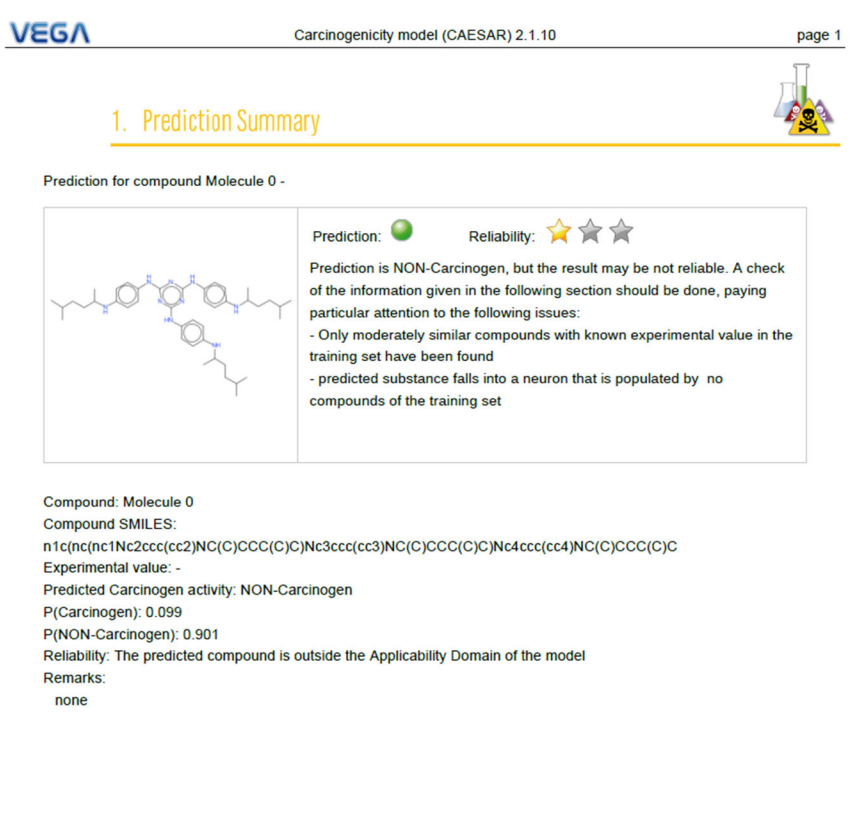
APPENDIX E: Toxtree Carcinogenicity Modeling Results for 1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

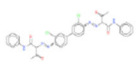


APPENDIX F: VEGA Carcinogenicity Results for 1,3,5-Triazine-2,4,6-triamine, N,N’,N’’-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)



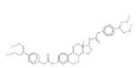


3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



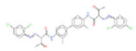
Compound #1

CAS: 6358-85-6
Dataset id:802 (Training Set)
SMILES:
O=C(Nc1ccccc1)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3ccccc3)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.725
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



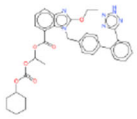
Compound #2

CAS: 22966-79-6
Dataset id:297 (Training Set)
SMILES:
O=C(Oc1ccc2c(c1)CCC4C2CCC5(C)(C(OC(=O)Cc3ccc(cc3)N(CCCl)CCCl)CCC45))Cc6ccc(cc6)N(CCCl)CCCl
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



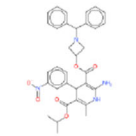
Compound #3

CAS: 5979-28-2
Dataset id:803 (Test Set)
SMILES:
O=C(Nc1ccc(cc1C)c3ccc(NC(=O)C(N=Nc2ccc(cc2Cl)Cl)C(=O)C)c(c3)C)C(N=Nc4ccc(cc4Cl)Cl)C(=O)C
Similarity: 0.715
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #4

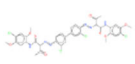
CAS: 145040-37-5
Dataset id:123 (Training Set)
SMILES:
O=C(OC(OC(=O)c2cccc1nc(OCC)n(c12)Cc3ccc(cc3)c5ccccc5(c4nn[nH]n4))C)OC6CCCCC6
Similarity: 0.692
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 123524-52-7
Dataset id:67 (Training Set)
SMILES:
O=C(OC(C)C)C5=C(NC(N)=C(C(=O)OC1CN(C1)C(c2ccccc2)c3ccccc3)C5(c4cccc(c4)[N+](=O)[O-]))C
Similarity: 0.691
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

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



Compound #6

CAS: 5567-15-7
Dataset id:804 (Test Set)
SMILES:
O=C(Nc1cc(OC)c(cc1(OC))Cl)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3cc(OC)c(cc3(OC))Cl)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.689
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

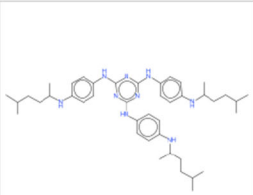
✖	Global AD Index AD index = 0.425 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.723 Explanation: Only moderately similar compounds with known experimental value in the training set have been 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 = 0.801 Explanation: model class assignment is well defined..
✖	Neural map neurons concordance Neurons concordance = 0.5 Explanation: predicted substance falls into a neuron that is populated by no compounds of the training set..

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0 -

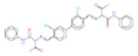


Prediction: Reliability:

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

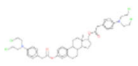
Compound: Molecule 0
Compound SMILES:
n1c(nc(nc1Nc2ccc(cc2)NC(C)CCC(C)C)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)NC(C)CCC(C)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



Compound #1

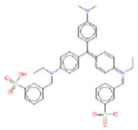
CAS: 6358-85-6
Dataset id:719 (Training Set)
SMILES:
O=C(Nc1ccccc1)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3ccccc3)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.725
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #2

CAS: 22966-79-6
Dataset id:731 (Training Set)
SMILES:
O=C(Oc1ccc2c(c1)CCC4C2CCC5(C)(C(OC(=O)Cc3ccc(cc3)N(CCCl)CCCl)CCC45))Cc6ccc(cc6)N(CCCl)CCCl
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

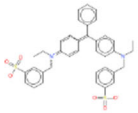
Alerts (not found also in the target): SA5 S or N mustard



Compound #3

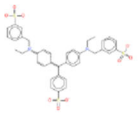
CAS: 1694-09-3
Dataset id:411 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)C[N+](=C2C=CC(C=C2)=C(c3ccc(cc3)N(C)C)c4ccc(cc4)N(Cc5cccc(c5)S(=O)(=O)O)CC)CC
Similarity: 0.701
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA28bis Aromatic mono- and dialkylamine



Compound #4

CAS: 4680-78-8
Dataset id:426 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)C(c3ccccc3)=C4C=CC(C=C4)=[N+](Cc5cccc(c5)S(=O)(=O)[O-])CC)CC
Similarity: 0.688
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

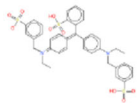


Compound #5

CAS: 5141-20-8
Dataset id:421 (Training Set)
SMILES: O=S(=O)([O-])c1ccc(cc1)C(c2ccc(cc2)N(Cc3cccc(c3)S(=O)(=O)[O-])CC)=C4C=CC(C=C4)=[N+](Cc5cccc(c5)S(=O)(=O)[O-])CC
Similarity: 0.676
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA53 Benzensulfonic ethers

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



Compound #6

CAS: 3844-45-9
Dataset id:806 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)C[N+](=C2C=CC(C=C2)=C(c3ccc(cc3)N(Cc4cccc(c4)S(=O)(=O)O)CC)c5ccccc5S(=O)(=O)O)CC
Similarity: 0.675
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.716
Explanation: The predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.723
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 = 0.502
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..

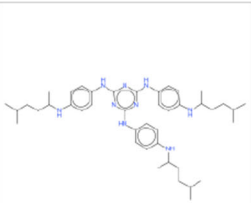
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

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 -

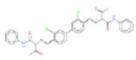


Prediction: Reliability:

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
- 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
The following relevant fragments have been found: Carcinogenity alert no. 42

Compound: Molecule 0
Compound SMILES:
n1c(nc(nc1Nc2ccc(cc2)NC(C)CCC(C)C)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)NC(C)CCC(C)C
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 42
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

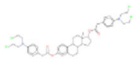
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 6358-85-6
Dataset id:565 (Training Set)
SMILES:
O=C(Nc1ccccc1)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3ccccc3)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.725
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

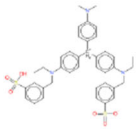


Compound #2

CAS: 22966-79-6
Dataset id:571 (Training Set)
SMILES:
O=C(Oc1ccc2c(c1)CCC4C2CCC5(C)C(C(OC(=O)Cc3ccc(cc3)N(CCCl)CCCl)CCC45))Cc6ccc(cc6)N(CCCl)CCCl
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 11; Carcinogenity alert no. 29; Carcinogenity alert no. 37; Carcinogenity alert no. 38; Carcinogenity alert no. 41

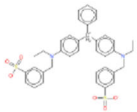


Compound #3

CAS: 1694-09-3
Dataset id:674 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)[CH2+](c3ccc(cc3)N(C)C)c4ccc(cc4)N(Cc5cccc(c5)S(=O)(=O)O)CC)CC
Similarity: 0.719
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 40; Carcinogenity alert no. 41



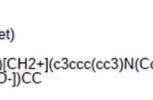
Compound #4

CAS: 4680-78-8
Dataset id:352 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)[CH2+](c3ccccc3)c4ccc(cc4)N(Cc5cccc(c5)S(=O)(=O)[O-])CC)CC
Similarity: 0.706
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 40; Carcinogenity alert no. 41

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

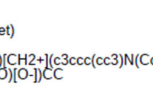


Compound #5

CAS: 3844-45-9
Dataset id:737 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)[CH2+](c3ccc(cc3)N(Cc4cccc(c4)S(=O)(=O)[O-])CC)c5ccccc5S(=O)(=O)[O-])CC
Similarity: 0.687
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 40; Carcinogenity alert no. 41



Compound #6

CAS: 2353-45-9
Dataset id:948 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)[CH2+](c3ccc(cc3)N(Cc4cccc(c4)S(=O)(=O)[O-])CC)c5ccc(O)cc5S(=O)(=O)[O-])CC
Similarity: 0.683
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 40; Carcinogenity alert no. 41

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.693 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.722 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.665 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
⚠	Concordance for similar molecules Concordance index = 0.665 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

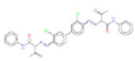
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 42

Structural alert for carcinogenity defined by the SMARTS:Nc1ccccc1

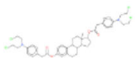
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 6358-85-6
Dataset id:565 (Training Set)
SMILES:
O=C(Nc1ccccc1)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3ccccc3)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.725

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

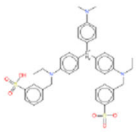


CAS: 22966-79-6
Dataset id:571 (Training Set)
SMILES:
O=C(Oc1ccc2c(c1)CCC4C2CCC5(C)(C(OC(=O)Cc3ccc(cc3)N(CCCl)CCCl)CCC45))Cc6ccc(cc6)N(CCCl)CCCl
Similarity: 0.722

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 11; Carcinogenity alert no. 29; Carcinogenity alert no. 37; Carcinogenity alert no. 38; Carcinogenity alert no. 41



CAS: 1694-09-3
Dataset id:674 (Training Set)
SMILES: O=S(=O)([O-])c1cccc(c1)CN(c2ccc(cc2)[CH2+](c3ccc(cc3)N(C)C)c4ccc(cc4)N(Cc5cccc(c5)S(=O)(=O)O)CC)CC
Similarity: 0.719

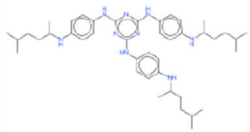
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found also in the target): Carcinogenity alert no. 40; Carcinogenity alert no. 41

1. Prediction Summary

Prediction for compound Molecule 0 -



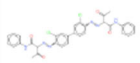
Prediction: Reliability:

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

The following relevant fragments have been found: Carcinogenity alert no. 36

Compound: Molecule 0
Compound SMILES:
n1c(nc(nc1Nc2ccc(cc2)NC(C)CCC(C)C)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)NC(C)CCC(C)C
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 36
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

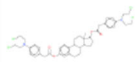
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 6358-85-6
Dataset id:802 (Training Set)
SMILES:
O=C(Nc1ccccc1)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3ccccc3)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.725
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

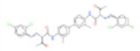
Alerts (not found also in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24



Compound #2

CAS: 22966-79-6
Dataset id:297 (Training Set)
SMILES:
O=C(Oc1ccc2c(c1)CCC4C2CCC5(C)(C(OC(=O)Cc3ccc(cc3)N(CCCl)CCCl)CCC45))Cc6ccc(cc6)N(CCCl)CCCl
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

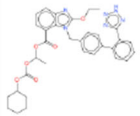
Alerts (not found also in the target): Carcinogenity alert no. 31; Carcinogenity alert no. 57; Carcinogenity alert no. 72; Carcinogenity alert no. 73; Carcinogenity alert no. 102



Compound #3

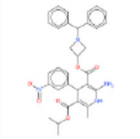
CAS: 5979-28-2
Dataset id:803 (Test Set)
SMILES:
O=C(Nc1ccc(cc1C)c3ccc(NC(=O)C(N=Nc2ccc(cc2Cl)Cl)C(=O)C)c(c3)C)C(N=Nc4ccc(cc4Cl)Cl)C(=O)C
Similarity: 0.715
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 28



Compound #4

CAS: 145040-37-5
Dataset id:123 (Training Set)
SMILES:
O=C(OC(OC(=O)c2cccc1nc(OCC)n(c12)Cc3ccc(cc3)c5ccccc5(c4nn[nH]n4))C)OC6CCCCC6
Similarity: 0.692
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

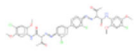


Compound #5

CAS: 123524-52-7
Dataset id:67 (Training Set)
SMILES:
O=C(OC(C)C)C5=C(NC(N)=C(C(=O)OC1CN(C1)C(c2ccccc2)c3ccccc3)C5(c4cccc(c4)[N+](=O)[O-])C
Similarity: 0.691
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 33; Carcinogenity alert no. 63; Carcinogenity alert no. 64; Carcinogenity alert no. 76; Carcinogenity alert no. 77

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



Compound #6

CAS: 5567-15-7
Dataset id:804 (Test Set)
SMILES:
O=C(Nc1cc(OC)c(cc1(OC))Cl)C(N=Nc2ccc(cc2Cl)c4ccc(N=NC(C(=O)Nc3cc(OC)c(cc3(OC))Cl)C(=O)C)c(c4)Cl)C(=O)C
Similarity: 0.689
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 37; Carcinogenity alert no. 38

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.721 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

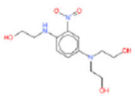
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 36

Structural alert for carcinogenity defined by the SMARTS: CNc1ccc(N)cc1

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

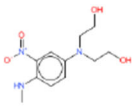


CAS: 33229-34-4
Dataset id:103 (Training Set)
SMILES: O=[N+]([O-])c1cc(ccc1(NCCO))N(CCO)CCO
Similarity: 0.599

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 36

Alerts (not found also in the target): Carcinogenity alert no. 63; Carcinogenity alert no. 64

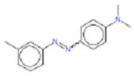


CAS: 2784-94-3
Dataset id:102 (Training Set)
SMILES: O=[N+]([O-])c1cc(ccc1(NC))N(CCO)CCO
Similarity: 0.582

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 36

Alerts (not found also in the target): Carcinogenity alert no. 63; Carcinogenity alert no. 64



CAS: 55-80-1
Dataset id:448 (Training Set)
SMILES: N(=Nc1cccc(c1)C)c2ccc(cc2)N(C)C
Similarity: 0.577

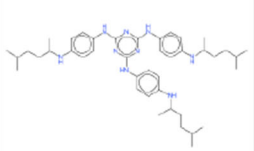
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 36

Alerts (not found also in the target): Carcinogenity alert no. 33; Carcinogenity alert no. 71

1. Prediction Summary

Prediction for compound Molecule 0 -

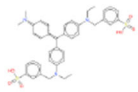


Prediction: Reliability:

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

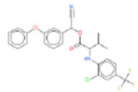
Compound: Molecule 0
Compound SMILES:
n1c(nc(nc1Nc2ccc(cc2)NC(C)CCC(C)C)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)NC(C)CCC(C)C
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



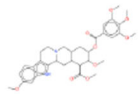
Compound #1

CAS: 1694-09-3
Dataset id:40 (Training Set)
SMILES:
O=S(=O)(O)c1cccc(c1)CN(c2ccc(cc2)C(c3ccc(cc3)N(Cc4cccc(c4)S(=O)(=O)O)CC)=C5C=CC(C=C5)=[N+](C)C)CC
Similarity: 0.705
Experimental value : Carcinogen
Predicted value : Carcinogen



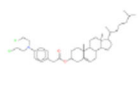
Compound #2

CAS: 69409-94-5
Dataset id:522 (Training Set)
SMILES: N#CC(OC(=O)C(Nc1ccc(cc1Cl)C(F)(F)F)C(C)C)c3cccc(Oc2ccccc2)c3
Similarity: 0.664
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



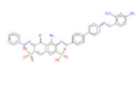
Compound #3

CAS: 50-55-5
Dataset id:272 (Training Set)
SMILES:
O=C(OC3CC4CN2CCc1c5ccc(OC)cc5([nH]c1C2CC4(C(C(=O)OC)C3(OC)))c6cc(OC)c(OC)c(OC)c6
Similarity: 0.658
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #4

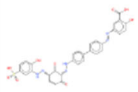
CAS: 3546-10-9
Dataset id:256 (Training Set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)(C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CCCl)CCCl
Similarity: 0.654
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 1937-37-7
Dataset id:136 (Training Set)
SMILES:
O=C5C(=NNc1ccccc1)C(=Cc6cc(c(N=Nc2ccc(cc2)c4ccc(N=Nc3ccc(N)cc3(N))cc4)c(N)c56)S(=O)(=O)O)S(=O)(=O)O
Similarity: 0.653
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #6

CAS: 16071-86-6
Dataset id:138 (Test Set)
SMILES:
O=C(O)c5cc(N=Nc1ccc(cc1)c2ccc(cc2)NN=C4C(=O)C=CC(=NNc3cc(ccc3(O))S(=O)(=O)O)C4(=O))ccc5(O)
Similarity: 0.642
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.598 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.683 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 = 0.524 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 = 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.

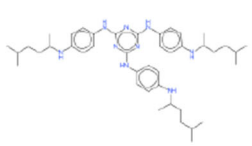
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(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: cNc
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -

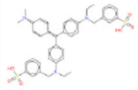


Prediction: Reliability:

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

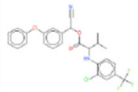
Compound: Molecule 0
Compound SMILES:
n1c(nc(nc1Nc2ccc(cc2)NC(C)CCC(C)C)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)NC(C)CCC(C)C
Experimental value: -
Predicted Inhalation Carcinogenic class: Carcinogen
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



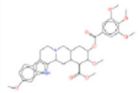
Compound #1

CAS: 1694-09-3
Dataset id:35 (Training Set)
SMILES:
O=S(=O)(O)c1cccc(c1)CN(c2ccc(cc2)C(c3ccc(cc3)N(Cc4cccc(c4)S(=O)(=O)O)CC)=C5C=CC(C=C5)=[N+](C)C)CC
Similarity: 0.705
Experimental value : Carcinogen
Predicted value : Carcinogen



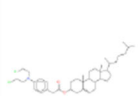
Compound #2

CAS: 69409-94-5
Dataset id:495 (Test Set)
SMILES: N#CC(OC(=O)C(Nc1ccc(cc1Cl)C(F)(F)F)C(C)C)c3cccc(Oc2ccccc2)c3
Similarity: 0.664
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



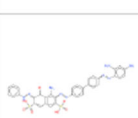
Compound #3

CAS: 50-55-5
Dataset id:231 (Training Set)
SMILES:
O=C(OC3CC4CN2CCc1c5ccc(OC)cc5([nH]c1C2CC4(C(C(=O)OC)C3(OC)))c6cc(OC)c(OC)c(OC)c6
Similarity: 0.658
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #4

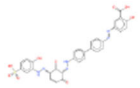
CAS: 3546-10-9
Dataset id:219 (Training Set)
SMILES:
O=C(OC4CC3=CCC1C(CCC2(C)(C(CCC12)C(C)CCCC(C)C))C3(C)CC4)Cc5ccc(cc5)N(CCCl)CCCl
Similarity: 0.654
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 1937-37-7
Dataset id:111 (Training Set)
SMILES:
O=C5C(=NNc1ccccc1)C(=Cc6cc(c(N=Nc2ccc(cc2)c4ccc(N=Nc3ccc(N)cc3(N))cc4)c(N)c56)S(=O)(=O)O)S(=O)(=O)O
Similarity: 0.653
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #6

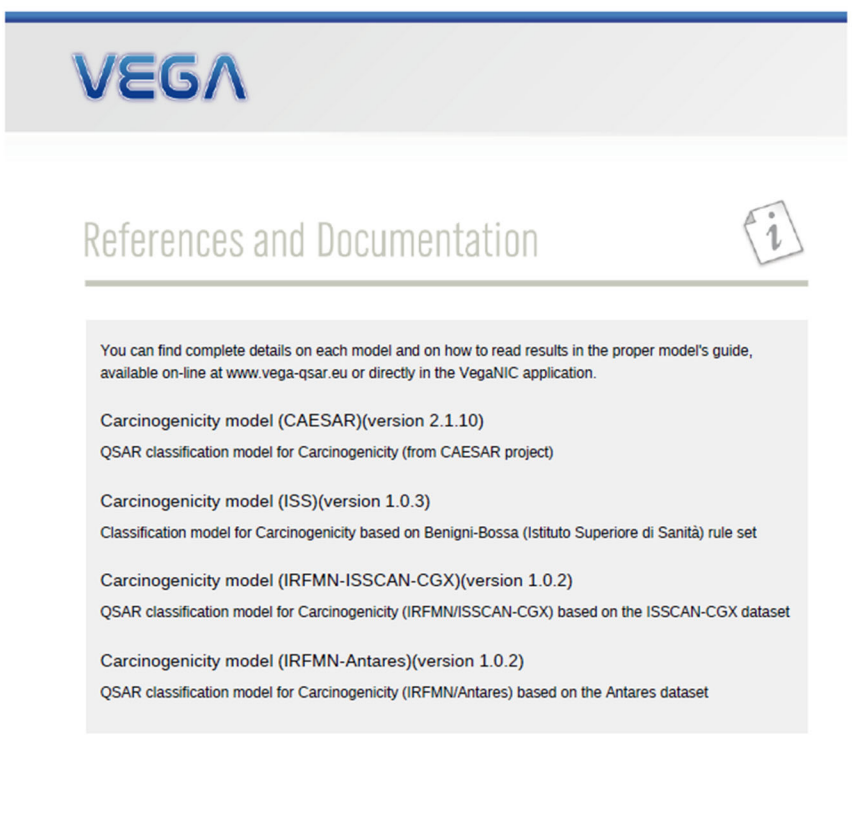
CAS: 16071-86-6
Dataset id:113 (Test Set)
SMILES:
O=C(O)c5cc(N=Nc1ccc(cc1)c2ccc(cc2)NN=C4C(=O)C=CC(=NNc3cc(ccc3(O))S(=O)(=O)O)C4(=O))ccc5(O)
Similarity: 0.642
Experimental value : Carcinogen
Predicted value : Carcinogen

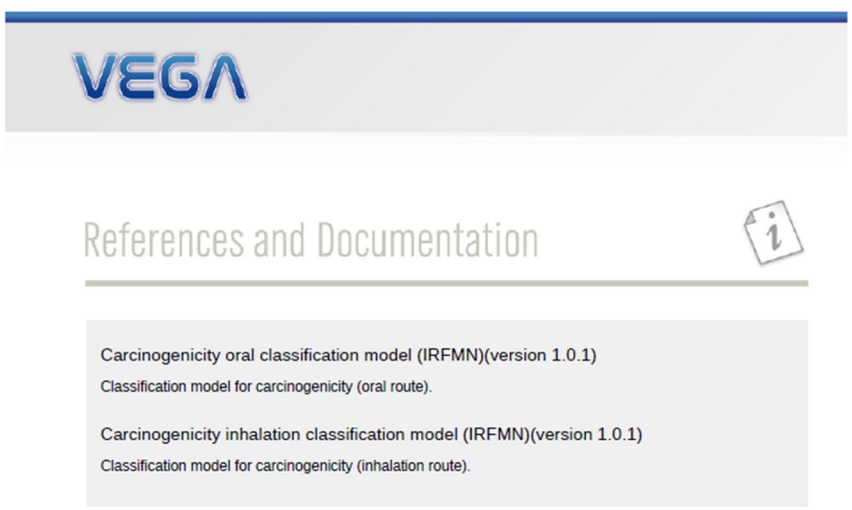
3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.703 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.683 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 = 0.524 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.





APPENDIX G: Danish QSAR Database Modeling Results for 1,3,5-Triazine-2,4,6-triamine, N,N,N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

Carcinogenicity

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

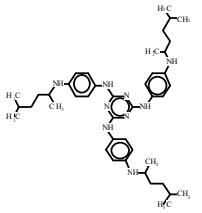
Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Aromatic Amine Type Compounds
OECD QSAR Toolbox v.4.2 profilers	
Profiler predictions are supporting information to be used together with the relevant QSAR predictions	

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		POS_IN	NEG_OUT	POS_IN	POS_IN
DTU-developed models					

APPENDIX H: EPI Suite™ Modeling Results for 1,3,5-Triazine-2,4,6-triamine, N,N,N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- (CAS #121246-28-4)

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

EPI Suite Results For CAS 121246-28-4



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SMILES :
CC(C)CCC(C)Nc1ccc(cc1)Nc2nc(nc(n2)Nc3ccc(cc3)NC(C)CCC(C)C)Nc4ccc(cc4)
NC(C)CCC(C)C
CHEM   : 1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)
amino)phenyl-
MOL FOR: C42 H63 N9
MOL WT : 694.03
Vapor Pressure (mm Hg) :   ------
Henry LC (atm-m3/mole) :   ------
Log Kow (octanol-water):   6.50
Physical Property Inputs:
------------------------------ EPI SUMMARY (v3.20) --------------------------
Water Solubility (mg/L):   ------
Boiling Point (deg C)  :   225.00
Melting Point (deg C)  :   54.00

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  11.90

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  787.12  (Adapted Stein & Brown method)
Melting Pt (deg C):  346.72  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  0.0512  (Modified Grain method)
VP (Pa, 25 deg C) :  6.83  (Modified Grain method)
Subcooled liquid VP: 0.0949 mm Hg (25 deg C, Mod-Grain method)
: 12.7 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  0.007052
log Kow used: 6.50 (user entered)
melt pt used: 54.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  6.9403e-007 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Melamines
```

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Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method :   2.43E-021  atm-m3/mole  (2.47E-016 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:  6.630E+000 atm-m3/mole  (6.718E+005 Pa-m3/mole)
VP:   0.0512 mm Hg (source: MPBPVP)
WS:   0.00705 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  6.50  (user entered)
Log Kaw used:  -19.003  (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):  25.503
Log Koa (experimental database):  None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :  -0.9758
Biowin2 (Non-Linear Model)     :   0.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   0.6099  (recalcitrant)
Biowin4 (Primary Survey Model) :   2.1386  (months      )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :  -0.9413
Biowin6 (MITI Non-Linear Model):   0.0000
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -3.6095
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):  12.7 Pa (0.0949 mm Hg)
Log Koa (Koawin est  ): 25.503
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  2.37E-007
Octanol/air (Koa) model:  7.82E+012
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  8.56E-006
Mackay model           :  1.9E-005
Octanol/air (Koa) model:  1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 283.7174 E-12 cm3/molecule-sec
Half-Life =     0.038 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =    27.144 Min
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1.38E-005 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
```

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Koc    :  1E+010  L/kg (MCI method)
Log Koc:  11.407      (MCI method)
Koc    :  1.941E+004  L/kg (Kow method)
Log Koc:  4.288       (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 = 3.439 (BCF = 2747 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.0520 days (HL = 1.127 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.453 (BCF = 283.7)
Log BAF Arnot-Gobas method (upper trophic) = 2.531 (BAF = 339.8)
log Kow used: 6.50 (user entered)

Volatilization from Water:
Henry LC:  2.43E-021 atm-m3/mole  (estimated by Bond SAR Method)
Half-Life from Model River: 6.347E+017  hours   (2.645E+016 days)
Half-Life from Model Lake : 6.924E+018  hours   (2.885E+017 days)

Removal In Wastewater Treatment:
Total removal:              93.43  percent
Total biodegradation:        0.78  percent
Total sludge adsorption:    92.66  percent
Total to Air:                0.00  percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       2.19e-015       0.905        1000
Water     0.548           4.32e+003    1000
Soil      52.1            8.64e+003    1000
Sediment  47.4            3.89e+004    0
Persistence Time: 1.51e+004 hr

Level III Fugacity Model: (MCI Method with Water percents)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       2.19e-015       0.905        1000
Water     0.548           4.32e+003    1000
water     (3.65e-005)
biota     (5.77e-006)
suspended sediment (0.548)
Soil      52.1            8.64e+003    1000
Sediment  47.4            3.89e+004    0
Persistence Time: 1.51e+004 hr

Level III Fugacity Model: (EQC Default)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       2.33e-015       0.905        1000
Water     0.807           4.32e+003    1000
water     (0.26)
biota     (0.0411)
suspended sediment (0.505)
Soil      55.5            8.64e+003    1000
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Sediment  43.7            3.89e+004    0
Persistence Time: 1.42e+004 hr
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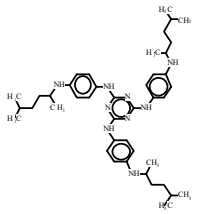

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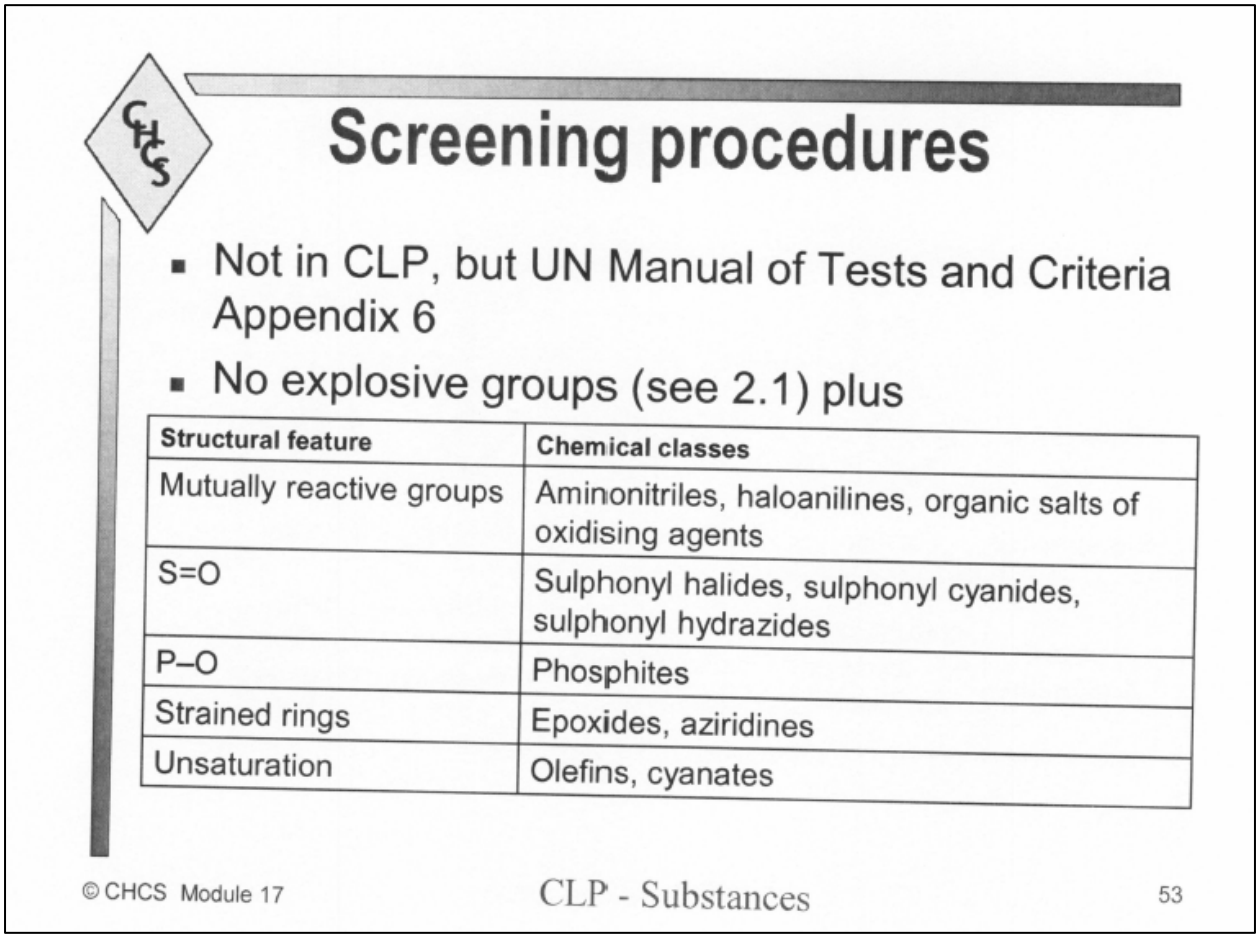
APPENDIX I: Known Structural Alerts for Reactivity

Self-Reactive Substances



Licensed GreenScreen® Profilers

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Nancy Linde, M.S.
Senior Toxicologist
ToxServices LLC

1,3,5-Triazine-2,4,6-triamine, N,N',N''-tris(4-((1,4-dimethylpentyl)amino)phenyl- GreenScreen® Evaluation QC'd by:

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Jennifer Rutkiewicz, Ph.D.
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