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TRIETHYLAMINE

(CAS #121-44-8)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: August 1, 2023

Expiration Date: August 1, 2028

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GreenScreen® Executive Summary for Triethylamine (TEA) (CAS #121-44-8)

Triethylamine (TEA, IUPAC name: *N*,*N*-diethylethanamine) belongs to the chemical class of tertiary aliphatic amines, with a central amino-group substituted with three ethyl groups. TEA is used as a chemical intermediate in the production of pesticides, textile treatment agents, dyestuffs, and quaternary ammonium compounds, as a catalyst for epoxy resins and polyurethane systems, as a stabilizer for amino resins in coating systems, as an accelerator activator for rubbers, as a wetting, waterproofing, and penetrating agent of quaternary ammonium compounds, as a corrosion inhibitor, as a curing and hardening agent for polymers, and as a propellant.

In the cosmetics industry, TEA is used as an emulsion stabilizing agent. Although TEA is a trialkylamine, it is no longer listed under Annex III, Section 62 of EC Regulation No. 1223/2009 with its delisting published in 2010. TEA is approved by the United States Food Drug Administration (U.S. FDA) for indirect food additives uses as a component in adhesives and polycarbonate resins under 21 CFR §175.105 and §177.1580.

Based on its boiling point of 90°C, it is a volatile organic compound (VOC). TEA is very soluble in water (68,600 – 112,400 mg/L). TEA is not explosive or oxidizing, but it is highly flammable.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (reproductive toxicity-R)
- Benchmark 2f
    - Very High Group II Human Toxicity (neurotoxicity (single dose)-Ns, skin irritation-IrS, and eye irritation-IrE)
    - High Group II* Human Toxicity (systemic toxicity (repeated dose)-STr*)
- Benchmark 2g
    - High flammability-F

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

The GreenScreen® Benchmark Score for TEA has not changed over time. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria, and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017, and the current version 1.4 update. The most recent update re-classified the scores and confidence levels for several endpoints, without affecting the overall benchmark score.

New Alternative Methods (NAMs) used in this assessment include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, and persistence, and *in vitro* testing for genotoxicity and endocrine activity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

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Type I (input data) uncertainties in TEA's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. TEA's Type II (extrapolation output) uncertainties include lack of defined applicability domains of Toxtree and OECD QSAR Toolbox in examination of structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and *in vitro* receptor binding activity assays, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization.

GreenScreen® Hazard Summary Table for TEA

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

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.

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GreenScreen® Chemical Assessment for Triethylamine (TEA) (CAS #121-44-8)

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

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Date: August 18, 2014

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Date: August 15, 2017

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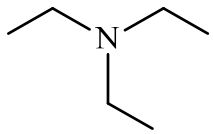
Organization: ToxServices LLC
Date: July 20, 2023; August 1, 2023

Expiration Date: August 1, 2028[2]

Chemical Name: Triethylamine

CAS Number: 121-44-8

Chemical Structure(s):



Also called:
(Diethylamino)ethane; (diethylamino)ethane; Ethanamine, N,N-diethyl- (9CI); N,N-Diethylethanamine; TAMINCO N.V., TEA; TRIETHYLAMINE; Triethylamin; Triethylamine; Triethylamine (7CI, 8CI); ethanamine, N,N-diethyl- (ECHA 2023a). Triethylamine, BioUltra, ≥ 99.5% (GC); Triethylamine, SAJ first grade, ≥ 98.0%; Triethylamine, United States Pharmacopeia (USP) Reference Standard (PubChem 2023a).

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

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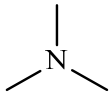
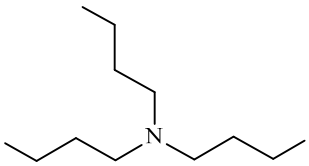
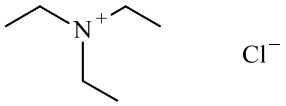
Suitable surrogates or moieties of chemicals used in this assessment (CAS #s):
For some endpoints, insufficient reliable data are available for TEA. Toxicokinetic studies in humans exposed to TEA via oral and inhalation routes and intravenous injection demonstrated that 24% of the intravenously administered TEA was metabolized via oxidation to form triethylamine oxide (TEAO), and the remaining TEA is excreted. No evidence in humans was found supporting metabolism of TEA to diethylamine (DEA) (ECHA 2023a). However, no data were identified for TEAO. ToxServices did not use DEA or TEAO as surrogates, but used trimethylamine (TMA) (CAS #75-50-3) and tributylamine (TBA, CAS #102-82-9) as surrogates to fill data gaps where feasible. These surrogates have been used to support the safety of TEA by the Organisation for Economic and Community Development (OECD), Australia, European Chemicals Agency (ECHA), and the authors of the ECHA dossier for TEA (OECD 2012, ECHA 2021, AICIS 2016, ECHA 2023a). TMA (C1) and TBA (C4) are tertiary amines with alkyl chain lengths one carbon shorter or two carbons longer than the target chemical, and sharing maximum common substructure (MCS) Tanimoto coefficients of 0.5714 and 0.5385, respectively, with the target chemical (ChemMine 2023, Appendix C). Additionally, TEA hydrochloride (CAS #554-68-7), the chloride salt of TEA, and trimethylammonium chloride (CAS #593-81-7), the chloride salt of TMA, were used to fill data gaps in carcinogenicity, reproductive toxicity, and repeated exposure systemic toxicity. Overall, ToxServices considered TMA and TMA chloride to be conservative surrogates and TBA a weak surrogate due to differences in molecule sizes.



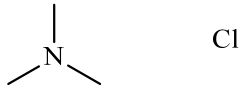
Surrogate #1: Trimethylamine (TMA, CAS #75-50-3) (Pubchem 2023b)



Surrogate #2: Tributylamine (TBA, CAS #102-82-9) (Pubchem 2023c)



Surrogate #3: TEA hydrochloride (CAS #554-68-7) (PubChem 2023d)



Surrogate #3: TMA chloride (CAS #593-81-7) (Pubchem 2023e)

Identify Applications/Functional Uses (HSDB 2016, EC 2023)**:**
1. Chemical intermediate in the production of pesticides, textile treatment agents, dyestuffs, and quaternary ammonium compounds,
2. Catalyst for epoxy resins and polyurethane systems,
3. Stabilizer for amino resins in coating systems,
4. Accelerator activator for rubbers,

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5. Wetting, waterproofing, and penetrating agent of quaternary ammonium compounds,
6. Corrosion inhibitor,
7. Curing and hardening agent for polymers,
8. Propellant,
9. Emulsion stabilizing agent in cosmetics formulations.

Known Impurities[3]:
Common impurities of TEA include diethylamine (DEA) <1%, triethylamine oxide (TEAO) < 0.1%, ammonia < 0.2%, and formaldehyde < 0.3% (ECHA 2021, NTP 2018, HSDB 2016). American Chemical Society (ACS) Standards report impurity limits of not more than 0.2% by weight ammonia and not more than 0.3% by weight formaldehyde (HSDB 2016). According to GreenScreen® Guidance, impurities present at < 100 ppm requires a List Translator screening, while those present at > 100 ppm require separate full GreenScreen® evaluations. Ammonia (CAS #7664-41-7) is an LT-P1 chemical, and formaldehyde (CAS #50-00-0) is a BM-1 chemical. Impurities are not evaluated in this assessment. Instead, they are evaluated at the product level, should they be present at > 100 ppm.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive toxicity-R)
- Benchmark 2f
  - Very High Group II Human Toxicity (neurotoxicity (single dose)-Ns, skin irritation-IrS, and eye irritation-IrE)
  - High Group II* Human Toxicity (systemic toxicity (repeated dose)-STr*)
- Benchmark 2g
  - High flammability-F

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis),), TEA meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if TEA were assigned a High score for the data gaps E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for TEA

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

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). Furthermore, OECD QSAR Toolbox predicted no possible hydrolysis products under neutral, basic, and acidic conditions (OECD 2023, Appendix D). TEA is readily biodegradable and, therefore, it is not expected to have relevant transformation products.

Introduction

TEA is produced via the vapor phase alkylation of ammonia with ethanol, reaction of N,N-diethylacetamide with lithium aluminum hydride, reaction of ethyl chloride and ammonia with pressure and heat, or via the reaction of ammonia, hydrogen, and acetaldehyde in the presence of a hydrogenation catalyst (HSDB 2016).

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

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

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

TEA is not listed on the SCIL.

Hazard Statement and Occupational Control

A harmonized EU classification is available for TEA (ECHA 2023b), as shown in Table 1. The EU has classified this chemical as a GHS Category 2 flammable liquid (H225), GHS Category 4 acute toxicant (oral, dermal, and inhalation), and GHS Category 1A skin corrosive substance. Recommended personal protective equipment (PPE) and identified occupational exposure limits (OEL) are summarized below in Table 2.

Table 1: GHS H Statements for TEA (CAS #121-44-8) (ECHA 2023b)

H Statement	H Statement Details
H225	Flammable liquid
H302	Harmful if swallowed
H312	Harmful in contact with the skin
H314	Causes severe skin burns and eye damage
H332	Harmful if inhaled

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Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for TEA (CAS #121-44-8)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Tightly fitted safety goggles/work under hood, gloves, flame retardant antistatic protective clothing, filtering respirator when vapors/aerosols are generated.	Millipore Sigma 2023	ACGIH TLV: 8h TWA: 0.5 ppm	Millipore Sigma 2023, OSHA 2021
		ACGIH TLV: 8h STEL: 1 ppm	Millipore Sigma 2023, OSHA 2021
		CAL/OSHA: PEL-C: 1 ppm (4.1 mg/m^3)	Millipore Sigma 2023, OSHA 2021
		OSHA PEL: 8h TWA: 25 ppm (100 mg/m^3) (29 CFR 1910.1000 Table Z-1)	OSHA 2021
		NIOSH IDLH: 200 ppm	OSHA 2021

ACGIH: American Conference of Governmental Industrial Hygienists
IDLH: Immediately Dangerous to Life or Health
NIOSH: National Institute for Occupational Safety and Health
OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limit
PEL-C: Permissible Exposure Limit Ceiling
STEL: Short-term Exposure Limit
TLV: Threshold Limit Value
TWA: Time Weighted Average

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for TEA can be found in Appendix C.

- TEA is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- TEA is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group II, and label code 3.
- TEA is on the following list for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - GHS – Japan – H412 – Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 3].
    - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters.

Physicochemical Properties of TEA

Triethylamine is a colorless liquid at standard temperature and pressure. It has a high vapor pressure (54 mm Hg) indicating that it will exist in the liquid and vapor phases. It is very soluble in water (68,600-

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

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112,400 mg/L). It is more soluble in octanol than water (log K_{ow} of 1.45) at basic pH, indicating that it is not likely to bioaccumulate in aquatic biota.

Table 3: Physical and Chemical Properties of TEA (CAS #121-44-8)		
Property	**Value**	**Reference**
Molecular formula	$C_6H_{15}N$ or $(C_2H_5)_3N$	PubChem 2023a
SMILES Notation	CCN(CC)CC	PubChem 2023a
Molecular weight	101.19 g/mol	PubChem 2023a
Physical state	Liquid	ECHA 2023a
Appearance	Colorless with strong ammonia odor	ECHA 2023a
Melting point	-115 to -114.7ºC	ECHA 2023a
Boiling point	90ºC	ECHA 2023a
Vapor pressure	54 mmHg	OSHA 2021
Water solubility	68,600 mg/L @ 25ºC; 112,400 mg/L @ 25ºC	PubChem 2023a; ECHA 2023a
Dissociation constant	pKa of 11.43 @ 0ºC, pKa = 10.75 @ 25ºC, and pKa = 10.45 @ 35ºC	ECHA 2023a
Density/specific gravity	0.73 g/cm^3	ECHA 2023a
Partition coefficient	1.45 at pH 13 (calculated)	ECHA 2023a

Toxicokinetics

- *Absorption*: TEA is rapidly and well absorbed by all routes (oral, dermal and inhalation) with near 100% absorption.
    - *Oral:* Sufficient evidence in humans found that TEA is readily and extensively absorbed following ingestion (OECD 2012, AICIS 2016), and bioavailability via the oral route was almost complete (ECHA 2023a).
    - *Dermal:* Absorption via the dermal route is likely due to the physiochemical properties of the chemical including high water solubility and a log K_{ow} of 0.354, and it is known to rapidly absorb through the skin (AICIS 2016).
    - *Inhalation:* Absorption via the inhalation route occurs readily in humans (80% with an additional 20% unabsorbed dead space). Humans exposed for 8 hours to 20 – 50 mg/m^3 (equivalent to 0.02 – 0.05 mg/L) TEA vapor reported visual disturbances; however, no visual issues were reported for subjects exposed to 10 mg/m^3 (equivalent to 0.01 mg/L) (Klimisch 2, reliable with restrictions) (ECHA 2023a).
- *Distribution:* TEA is rapidly and widely distributed throughout the body via the blood stream. Pharmacokinetic studies in humans found no potential for bioaccumulation as it was readily released with average plasma and urine half-lives of 3 – 4 hours (ECHA 2023a).
- *Metabolism:* TEA (24%) is metabolized via N-oxidation into triethylamine-N-oxide (TEAO). Furthermore, a pharmacokinetic *in vivo* study in rats found that less than 0.3% TEA metabolized into diethylamine (DEA), indicating DEA, a known toxicant, is not a major metabolite of TEA (ECHA 2023a).
- *Excretion:* Pharmacokinetic studies in humans found that elimination rapidly takes place with a half-life of 3.2 hours into the urine with a minimal amount via exhalation. TEA is excreted unchanged (90-97%) or metabolized into TEAO and excreted in urine. Limited excretion is expected via exhalation (ECHA 2023a, OECD 2012, AICIS 2016).

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In summary, TEA is readily and extensively absorbed via oral, dermal, and inhalation exposure, rapidly and widely distributed, metabolized to a limited extent, and/or excreted without bioaccumulation.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
TEA was assigned a score of Low for carcinogenicity based on negative and in domain predictions from both statistical-based models (Danish (Q)SAR database), and rule-based models (two VEGA models, Oncologic and Toxtree) for the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available, and they are not GHS classified (CPA 2018b). The confidence in the score is low based on modeling due to lack of reliable, 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.
- NTP 1998, AICIS 2016, ECHA 2023a
  - *Oral: Surrogate: TEA hydrochloride (CAS #554-68-7)*: A carcinogenicity study was performed with female SIV50 rats (sex and number not specified) administered diets containing 0.5% TEA hydrochloride and 0.5% nitrite for 1 year. No tumors were identified with treatment. The authors concluded that despite the large dose, the nitrosamine production is insufficient to be tumorigenic. It should be noted that TEA was not administered as a single compound tested in these rats (Klimisch 3, not reliable, as it does not meet criteria of current guidelines, and a mixture was tested).
- Toxtree 2018
  - ToxServices evaluated TEA using Toxtree (Toxtree 2018); no structural alerts for genotoxic or nongenotoxic carcinogenicity were found (Appendix F).
- VEGA 2023
  - ToxServices predicted the carcinogenicity potential of TEA using the following six VEGA v1.3.18 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/Antares v1.0.2, IRFMN/ISSCAN-CGX v1.0.2, IRFMN Oral Classification 1.0.1, and IRFMN Inhalation Classification 1.0.1 models. If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
  - The global ADI was < 0.70 for four out of the six models: CAESAR v2.1.10, carcinogen (ADI = 0.385), IRFMN/ISSCAN-CGX v1.0.2, possible non-carcinogen (ADI = 0.603), IRFMN/Antares v1.0.0, possible non-carcinogen (ADI = 0.616), and IRFMN Oral Classification 1.0.1, non-carcinogen (ADI = 0); therefore, the results of these models are not suitable for a weight of the evidence evaluation. The global ADI was > 0.70 for two of the six models: ISS v.1.0.3, non-carcinogen (ADI = 0.743), and IRFMN Inhalation Classification 1.0.1, non-carcinogen (ADI = 1); therefore, the result of these models are suitable for a weight of the evidence evaluation. TEA was also identified as non-carcinogenic in the IRFMN Oral and Inhalation Classification 1.0.1 models based on experimental data; however, the only oral study ToxServices identified is unreliable and not

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sufficient for classification (see data summary above), and no data are identified for the inhalation route (Appendix G).

- U.S. EPA 2019, 2021
    - ToxServices attempted to evaluate TEA using OncoLogic (v9.0) (U.S. EPA 2021). However, OncoLogic 9.0 could not evaluate TEA; therefore, ToxServices evaluated the carcinogenic potential of TEA as an aliphatic amine using Oncologic v8.0. According to OncoLogic, aliphatic amines are generally considered not to have significant carcinogenicity unless the alkyl group is small or specific functional groups are present. These include unhindered terminal double bonds, terminal mono-halogens, and N-hydroxylated amines. Since TEA does not contain any of the three specific functional groups identified above and is not diethanolamine or triethanolamine, the carcinogenic potential of TEA is low (Appendix H).
- DTU 2023
    - ToxServices evaluated TEA with the Danish (Q)SAR Database for carcinogenicity (DTU 2023, Appendix G). TEA is in the domains of all seven E Ultra FDA RCA cancer models and predicted to be negative in all models (i.e., male rat, female rat, rat, male mouse, female mouse, mouse, and rodent). TEA is outside the domains of all seven Leadscope FDA RCA cancer models. Regarding the liver specific cancer in rat or mouse model, Case Ultra, SciQSAR, and overall battery predictions are negative and the compound is within their applicability domains; TEA is outside the applicability domain of the Leadscope model (Appendix I).
- Based on the weight of evidence, a score of Low was assigned. A limited carcinogenicity study reported no tumor production following administration of diets containing 0.5% surrogate TEA hydrochloride and 0.5% nitrite for 1 year; however, the study is unreliable because it does not meet current guidelines and a mixture was tested. Based on the lack of reliable experimental data identified for the target chemical and surrogates, modeling with statistical based, and expert rule-based models (i.e., Toxtree, VEGA, Oncologic, and Danish QSAR) were used to evaluate the carcinogenicity of TEA. Two of the six carcinogenicity predictions in VEGA was within the applicability domain – and both predicted TEA to be non-carcinogenic. Toxtree did not identify structural alerts for non-genotoxic and genotoxic carcinogenicity. OncoLogic predicted it to be of low concern and Danish QSAR predicted the target chemical to be non-carcinogenic in all models within their applicability domains. Based on negative predictions from rule-based (VEGA, OncoLogic, and Toxtree) and statistical-based (Danish QSAR) models, TEA is not likely to be carcinogenic.

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

TEA was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in a combination of *in vitro* and *in vivo* tests in mice and rats. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). Confidence is low due to equivocal results reported in a more recent *in vivo* micronucleus study in mice.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- NTP 2018, ECHA 2023a
    - *In vitro*: In an Ames bacterial reverse mutation test conducted in a manner similar to OECD Guideline 471 (GLP unspecified), *Salmonella typhimurium* tester strains TA97, TA98,

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TA100, TA1535, and TA1537 were exposed to TEA (purity not specified; 95% ethanol vehicle) at 0, 100, 333, 1,000, 3,333, and 10,000 µg/plate with and without metabolic activation (Aroclor 1254-induced rat and hamster S9). No information on precipitation was provided, and cytotoxicity was reported at the highest dose. Positive (i.e., sodium azide, 9-aminoacridine, 4-nitro-o-phenylenediamine, and 2-aminoanthracene) and negative controls were valid. No increase in the frequency of revertants was observed in any strain at any dose in the presence or absence of metabolic activation (Klimisch 2, reliable with restrictions).

- ECHA 2023a (The authors of the ECHA dossier identified a few more studies for *in vitro* genotoxicity; however, only GLP or guideline studies were evaluated for this endpoint due to their higher reliability and adequacy in evaluating this endpoint)
    - *In vitro*: In a non-GLP-compliant sister chromatid exchange (SCE) assay conducted according to UKEMS 1983, 1984, *S. typhimurium* tester strain TA1535 and CHO cells were exposed to TEA (purity not specified; vehicle not specified) at 0.07-17.9 mM, with and without metabolic activation (rat liver S9). No information on precipitation was provided, and cytotoxicity was reported at the highest dose. No increase in the incidence of SCE was observed in either cell strain at any dose in the presence or absence of metabolic activation (Klimisch 2, reliable with restrictions).
    - *In vivo*: In a non-GLP-compliant chromosome aberration assay, male Wistar rats (number not specified) were exposed to air concentrations of TEA (purity not specified) at 0, 1, or 10 mg/m^3 (equivalent to 0, 0.001, and 0.010 mg/L, respectively) via continuous inhalation for 30 or 90 days. At the end of the exposure period, the animals were sacrificed and bone marrow cells were isolated for evaluation of chromosome aberrations. At the low concentration, an increase in the incidence of cells with aneuploidy was observed after 30 days, but not after 90 days. However, no increase in the incidence of aneuploidy was observed at the high concentration after either 30 days or 90 days. Based on the lack of a dose-response, the study authors concluded that treatment with TEA did not increase the incidence of chromosome aberrations (Klimisch 2, reliable with restrictions).
- NTP 2018
    - *In vivo*: In a 3-month inhalation study, male and female B6C3F1/N mice (10/sex/dose) were exposed via whole body inhalation to 0, 12.5, 25, 50, 100, and 200 ppm TEA (purity not specified) for 6.2 hours/day, 5 days/week, for 14 weeks. Peripheral blood samples were obtained and the frequency of micronucleated erythrocytes were examined. An equivocal increase in micronucleated erythrocytes was reported in male samples with a statistically significant dose-dependency between 12.5 and 200 ppm, but pairwise comparisons to the concurrent control group was not statistically significant. There was no increase reported for female samples. There were no bone marrow toxicity based on a lack of significant changes in the percent of polychromatic (i.e., immature) erythrocytes.
- OECD 2012
    - OECD evaluated the chemical group of tertiary amines, including TEA, and concluded they were not genotoxic. *ToxServices notes that OECD did not review the subchronic inhalation micronucleus study conducted by National Toxicology Program (NTP) (2018).*
- Based on the weight of evidence, a score of Low was assigned. TEA was negative for mutagenicity in bacterial mutagenicity assays, and for clastogenicity in an *in vivo* OECD Guideline 474 micronucleus assay. NTP (2018) reported equivocal results in males and negative results in females for clastogenicity in a peripheral blood *in vivo* micronucleus assay in mice exposed to TEA in a subchronic inhalation study. However, based on consistently negative data on the target in other

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reliable, guideline studies reported in the ECHA dossier, with support from conclusions by an authoritative body (i.e., OECD), TEA has a low genotoxicity concern.

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

TEA was assigned a score of Moderate for reproductive toxicity based on the limited evidence of effects on male reproductive organs (i.e., slightly reduced sperm mobility and sperm morphological changes without data on fertility) in rats exposed to the target chemical in a 3-month inhalation study. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of reproductive toxicity in animals is available (CPA 2018b). The confidence in the classification is reduced due to lack of reproducibility of the findings across studies and the unclear toxicological significance of the effects observed.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any screening lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Inhalation:* In a repeated-dose inhalation toxicity study conducted in a manner similar to OECD Guidelines 413 and 452 (only two concentrations tested), male and female Fischer 344 rats (50/sex/dose group) were exposed whole body to concentrations of TEA (greater than 99.9% purity) at 0, 25, and 247 ppm (equivalent to 0, 103, or 1,020 mg/m^3, respectively, as identified by the authors of the ECHA dossier and calculated to be equivalent to 0, 0.103, and 1.020 mg/L, respectively [mg/m^3 * 1m^3/ 1,000L = mg/L]) for 6 hours/day, 5 days/week, for 28 weeks to produce a maximum of 127 exposure days. ToxServices calculated the equivalent concentrations for a 7-day/week exposure frequency to be 0, 0.0736, and 0.7286 mg/L, respectively (5 day/week exposure mg/L *5/7 = adjusted 7-day/week exposure mg/L). The animals were evaluated for clinical signs of toxicity, hematology, clinical chemistry, and gross pathology and histopathology of reproductive organs (testes, seminal vesicles, urinary bladder, testes, uterus, and ovaries). Mortality was observed as 1 female at the low concentration at week 6, and 1 male at week 8 and 2 females at week 3 (both accidental) at the high concentration. At the high concentration, closed eyes and eyes buried in fur were observed during treatment. Slightly reduced body weight gains were measured in high concentration males. No treatment-related effects were found on hematology, clinical chemistry, and gross pathology and histopathology of reproductive organs. The study authors specified that a viral infection was observed in the treated animals. The study authors identified a systemic toxicity NOAEC of 1.020 mg/L (equivalent to 0.7286 mg/L for a 7-day/week exposure frequency), the highest dose tested (Klimisch 2, reliable with restrictions).
- NTP 2018
  - *Inhalation:* In a 3-month inhalation study, male and female F344 rats (10/sex/dose) were exposed via whole body inhalation to 0, 12.5, 25, 50, 100, and 200 ppm TEA (purity not specified) for 6.2 hours/day, 5 days/week, for 14 weeks. ToxServices calculated the corresponding daily exposure concentrations as 0, 0.037, 0.074, 0.148, 0.296, and 0.591 mg/L/day, respectively, based on the formula of MW * ppm concentration / 24,450 * 5 days / 7 days. No mortalities were reported, and body weights of the high dose group were reduced compared to controls. Reproductive parameters such as sperm motility and morphology was evaluated. Male rats in the top three dose groups exhibited statistically significantly decreased epididymal sperm motility (3, 4, and 6%, respectively) and for the top two dose groups, effects on sperm morphology was reported including a statistically significantly increased number of spermatid heads per mg testis (10% change in both

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groups). *ToxServices identified a NOAEC of 0.074 mg/L and LOAEC of 0.148 mg/L for this study based on decreased sperm motility.*

- ECHA 2023a
    - *Oral: Surrogate: TMA (CAS #75-50-3)*: In a combined repeated dose toxicity study with reproduction/developmental toxicity screen test conducted according to OECD Guideline 422/OPPTS 870-3650 (GLP status not specified), male and female Sprague-Dawley rats (13/sex/dose group) were administered oral doses of surrogate TMA (30.8% solution) in water at 0, 8, 40, or 200 mg/kg/day via gavage. Males and females were dosed 2 weeks prior to breeding, continuing through breeding (2 weeks), gestation (3 weeks), and lactation (4 days) for a total of 42 days. Parental animals were evaluated for clinical signs of toxicity, body weight, estrous cycle, sperm measures, reproductive performance, gross pathology, and histopathology. Two high dose males died prior to the scheduled sacrifice, one on day 25 and the other on day 42. One high dose female died on pregnancy day 22 (administration day 38). No treatment-related effects were observed on estrous cycle, sperm measures, reproductive performance, or histopathology of reproductive organs. The mating rate, conception rate, pregnancy period, the birth rate, nursing state, the number of corpora lutea, the number and rate of implantation, the viability of the delivered pups, sex ratio, and body weight and form were also unaffected by treatment with TMA. The study authors established a NOAEL of 200 mg/kg/day, the highest dose tested, for reproductive toxicity based on the lack of adverse effects on reproduction observed in this study (Klimisch 2, reliable with restrictions).
- ECHA 2023c
    - *Oral: Surrogate: TMA chloride (CAS #593-81-7)*: In a non-GLP, non-guideline subchronic toxicity study, male Sprague-Dawley rats (5-6/dose) were exposed to TMA hydrochloride in the feed at 0, 0.04, 0.08, 0.16, 0.31 or 0.62% for 90 days. Animals were evaluated for mortality, clinical signs, body weight, hematology urinalysis, gross pathology, and histopathology. Decreased body weight gain was measured at the two highest doses (by 16.6% and 52%, respectively). The weight of seminal vesicles was reduced to half to one third of the control values, (presumably at the two highest doses) with gross pathological findings of reduced size of seminal vesicles, reduced number of secretory granules, tubular collapse in the prostate, the reduced secretory substances in the prostate at the highest dose. Study authors identified a NOAEL of 0.16% in the diet, equivalent to 79 mg/kg/day TMA as calculated by ECHA dossier authors, based on decreased weight gain and organ weights. Therefore, the LOAEL is 0.31%, which is equivalent to 150 mg/kg/day TMA according to calculations by the ECHA dossier authors (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Moderate was assigned. No oral or dermal data were identified for TEA; however, oral data were available for conservative surrogate TMA and TMA chloride. Although male reproductive organ weight and pathology were affected in a subchronic study with surrogate TMA hydrochloride with a NOAEL of 79 mg TMA/kg/day and LOAEL of 150 mg TMA/kg/day in rats, reproductive performance did not appear to have been affected in a reproductive/developmental toxicity screen study at the higher dose of 200 mg/kg/day. Therefore, TEA is not a reproductive toxicant following oral exposures. For the inhalation route, however, decreased sperm motility at 50 ppm and above and effects on sperm morphology at 100 and 200 ppm were reported in male rats exposed to TEA for 3 months. The extent of effects was slight (i.e., ≤ 10%), which were not found in the longer-duration study in the same strain of rats at higher concentrations (i.e., 247 ppm). No mating was carried out to determine if these changes affect fertility of the animals. Therefore, ToxServices classified TEA to GHS Category 2 based on the limited evidence of effects on male reproductive organs via the inhalation route.

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Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
TEA was assigned a score of Low for developmental toxicity based on negative developmental toxicity results for the surrogate TMA and TBA. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the classification is low as it is based on a reliable study for a weak surrogate, and a screening study on a conservative surrogate.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK – Pregnancy Risk Group D.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral: Surrogate: TMA (CAS #75-50-3)*: In the previously described combined repeated dose toxicity study with reproduction/developmental toxicity screen test conducted according to OECD Guideline 422/OPPTS 870-3650 (GLP status not specified), male and female Sprague-Dawley rats (13/sex/dose group) were administered oral doses of surrogate TMA (30.8% solution) in water at 0, 8, 40, or 200 mg/kg/day via gavage. Males and females were dosed 2 weeks prior to breeding, continuing through breeding (2 weeks), gestation (3 weeks), and lactation (4 days) for a total of 42 days. Maternal examinations consisted of clinical signs of toxicity, body weight, delivery observations, and ovarian and uterine content. Offspring examinations included pup weights, number of delivered pups, number of dead pups, and the incidence of malformations. One high dose female died on administration day 38 prior to the scheduled sacrifice. Prior to death, the dam exhibited salivation and abnormal breathing noises sporadically from administration day 11. Salivation and abnormal breathing noises were also observed in the high dose animals that survived to the scheduled sacrifice, in addition to one case of emaciation. No treatment-related effects were reported on maternal body weights or body weight gains. No embryotoxicity or teratogenicity was found with treatment. The study authors identified a maternal toxicity NOAEL and LOAEL of 40 mg/kg/day and 200 mg/kg/day, respectively, based on increased mortality, and a NOAEL of 200 mg/kg/day for developmental toxicity based on the lack of embryotoxicity and teratogenicity reported with treatment (Klimisch 2, reliable with restrictions).
  - *Oral: Surrogate: TBA (CAS #102-82-9)*: In a GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414, pregnant female Sprague-Dawley rats (20/dose group) were administered oral doses of TBA (99.3% purity) in 1% aqueous hydroxypropyl-methylcellulose gel at 0, 15, 45, or 135 mg/kg/day via gavage on gestation day (GD) 6-15. The dams were sacrificed on GD 20. The dams were evaluated for clinical signs of toxicity, body weight, and ovarian and uterine content. The fetal examinations consisted of evaluating the incidence of external, visceral, and skeletal abnormalities. Transiently reduced food consumption and body weight gain were measured in the high dose dams following the start of dosing. Three of the high dose dams died prior to the scheduled sacrifice on days 7 and 8 of the study. Red discoloration of the lungs was reported in these animals at necropsy. A slight, dose-related increase in the mean fetal body weight was reported. No malformations were found with treatment. The study authors identified the maternal NOAEL and LOAEL as 45 mg/kg/day and 135 mg/kg/day, respectively, based on increased mortality and a NOAEL of 135 mg/kg/day for developmental toxicity based on the lack of treatment-related effects (Klimisch 1, reliable without restriction).

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- Based on the weight of evidence, a score of Low was assigned. No adverse treatment-related effects on development were identified up to 135 mg/kg/day, the highest dose tested, in a GLP-compliant OECD Guideline 414 prenatal developmental toxicity study in rats exposed to oral doses of surrogate TBA. Furthermore, no treatment-related effects up to 200 mg/kg/day, the highest dose tested, were reported on developmental toxicity in an oral combined repeated dose toxicity study with reproduction/developmental toxicity screen test in rats exposed to surrogate TMA.

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
  - TEA was active in 0/8 estrogen receptor (ER) assays, 0/9 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/10 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix J).
- DTU 2023
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models (Appendix K):
    - TEA is predicted to be negative for estrogen receptor α binding (full training set and balanced training set, human *in vitro*), estrogen receptor α activation (human *in* vitro), and androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by the CaseUltra and SciQSAR models;
    - TEA is predicted to be negative for estrogen receptor activation (CERAPP data *in vitro*) and for androgen receptor binding, inhibition and activation (CoMPARA data *in vitro*) and thyroperoxidase (TPO) inhibition (QSAR1 and QSAR2, rat *in vitro*) by the Leadscope models.

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>
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): H
TEA was assigned a score of High for acute toxicity based on European Risk Assessment Committee (RAC)-adopted EU harmonized classifications of GHS Category 3 for oral, dermal, and inhalation routes based on a default oral acute toxicity estimate (ATE) of 100 mg/kg, a default dermal ATE value of 300 mg/kg, and 4-hour vapor inhalation LC_{50} value of 7.25 mg/L from a GLP-compliant, OECD Guideline 403 acute inhalation study in rats. GreenScreen® criteria classify chemicals as a High hazard when they are classified as GHS Category 3 acute toxicants (CPA 2018b). Confidence in the score is high based on measured data on the target chemical with support from the RAC-adopted EU harmonized classification.

- Authoritative and Screening Lists
  - *Authoritative:*
    - European Union (EU) – GHS (H-statements) Annex 6 Table 3-1 – H302 – Harmful if swallowed [Acute toxicity (oral) – Category 4]

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        - EU – GHS (H-statements) Annex 6 Table 3-1 – H312 – Harmful in contact with skin [Acute toxicity (dermal) – Category 4]
        - EU – GHS (H-statements) Annex 6 Table 3-1 – H332 – Harmful if inhaled [Acute toxicity (inhalation) – Category 4]
    - *Screening:*
        - GHS – New Zealand – Acute oral toxicity – Category 4
            - Based on an oral LD_{50} of 460 mg/kg in rats (CCID 2023).
        - GHS – New Zealand – Acute dermal toxicity – Category 3
            - Based on a dermal LD_{50} of 420 mg/kg in rabbits (CCID 2023).
        - GHS – New Zealand – Acute inhalation toxicity – Category 4
            - Based on its association with the R Phrase R20: harmful by inhalation (CCID 2023).
        - GHS – Japan – H302 – Harmful if swallowed [Acute toxicity (oral) – Category 4]
            - Based on oral LD_{50} values of 460-1,029 mg/kg in rats (NITE 2006, 2016).
        - GHS – Japan – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
            - Based on dermal LD_{50} values of 415-578 mg/kg in rabbits (NITE 2006, 2016).
        - GHS – Japan – H332 – Harmful if inhaled [Acute toxicity (inhalation) – Category 4]
            - Based inhalation LC_{50} values of 5.163-10.74 mg/L in rats (NITE 2006, 2016).
        - GHS – Australia – H302 – Harmful if swallowed [Acute toxicity (oral) – Category 4]
        - GHS – Australia – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - GHS – Australia – H331 – Toxic if inhalation [Acute toxicity (inhalation) – Category 3]
        - GHS – Korea – H302 – Harmful if swallowed [Acute toxicity (oral) – Category 4]
        - GHS – Korea – H311 – Toxic in contact with skin [Acute toxicity (dermal) – Category 3]
        - GHS – Korea – H331 – Toxic if inhalation [Acute toxicity (inhalation) – Category 3]
- ECHA 2021, 2023a
    - Only Key or Supporting studies reported with a Klimisch score of 1 (reliable without restriction) or 2 (reliable with restrictions) were included in this evaluation due to their higher reliability and the oral LD_{50} values in these studies were within the same range for GHS categorization. However, ECHA (2021) classified the studies below as Klimisch 3 (not reliable) (ECHA 2021). Therefore, the oral and dermal acute toxicity studies below were considered for the weight of evidence as a whole.)
        - *Oral*: LD_{50} (Male and female rats, strain not specified) = 730 mg/kg (non-GLP-compliant, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
        - *Oral*: LD_{50} (rabbits, sex and strain not specified) > 370 mg/kg and < 1,470 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
        - *Oral*: LD_{50} (female cats, strain not specified) > 370 mg/kg and < 730 mg/kg (non-GLP-compliant) (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-*

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evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).

- *Oral*: LD_{50} (Male and female rats, strain not specified) = 1,030 mg/kg (10% water solution) and of < 182 mg/kg (undiluted) (non-GLP-compliant, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions).
  - *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3). ECHA RAC noted that for the undiluted test substance, mortality of 3/5 at 0.25 mL/kg, 4/5 at 0.5 mL/kg, and 5/5 at 1 mL/kg, indicate an LD_{50} of < 0.25 mL/kg, which is equivalent to 182 mg/kg based on a density of 0.73 g/mL. RAC therefore proposed a default acute toxicity estimate (ATE) of 100 mg/kg for this study. As this value falls between 50 and 300 mg/kg for Category 3, RAC recommended a Category 3 classification for this endpoint (ECHA 2021). ToxServices notes that the new classification has not been reflected in the ECHA C&L Inventory (ECHA 2023b) or Pharos (2023).*
- *Oral*: LD_{50} (male Sherman rats) = 460 mg/kg (non-GLP-compliant, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Dermal*: LD_{50} (male New Zealand Black rabbits) = 580 mg/kg (non-GLP-compliant, similar to OECD Guideline 402) (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Dermal:* ECHA RAC proposed to change the current harmonized Category 4 classification to GHS Category 3 for acute dermal toxicity of TEA based on a default ATE value of 300 mg/kg. RAC noted that the available three studies reviewed did not demonstrate clear dose-response, with limited reporting of the number of animals used or mortalities in some of the studies. Nevertheless, the available data support a Category 3 classification. The RAC opinion was adopted in 2021 (ECHA 2021). *ToxServices notes that the new classification has not been reflected in the ECHA C&L Inventory or Pharos*.

- The authors of the ECHA dossier identified a large number of studies for inhalation acute toxicity; however, only the GLP-compliant, OECD Guideline 403 study reported with a Klimisch score of 1 (reliable without restriction) by both ECHA (2021) and the authors of the ECHA dossier was evaluated for this endpoint due to its higher reliability. In addition, it is also the critical study determined by ECHA to classify the compound under GHS.
  - *Inhalation*: 1-hour whole body vapor LC_{50} (Male and female Sprague Dawley derived Crl:CD BR VAF/Plus rats) = 3,496 ppm (equivalent to 14.5 mg/L) (GLP-compliant, OECD Guideline 403) (Klimisch 1, reliable without restriction).
    - Calculated to be a 4-hour vapor LC_{50} of 7.25 mg/L (1-hour LC_{50} / 2 = 4-hour LC_{50}) in rats as identified by ECHA (2021). *Based on the results of this study, ECHA (2021) classified TEA as GHS Category 3.*

- Based on the weight of evidence, a score of High was assigned. The oral LD_{50} value for undiluted TEA was in the range of < 182 to 1,030 mg/kg in rats, 370 to 1,470 mg/kg in rabbits, and 370 to 730 mg/kg in cats. In addition, ECHA (2021) concluded that none of the 11 oral acute toxicity studies across five species (rat, mouse, rabbit, guinea pig, and cat) exposed orally to TEA reported in the ECHA dossier are reliable or conclusive on their own; however, when considered together, the results of these studies support the newly proposed harmonized EU GHS Category 3 classification

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based on an acute toxicity estimate (ATE) of 100 mg/kg. Therefore, ToxServices classified TEA to GHS Category 3 for acute oral toxicity, which corresponds to LD_{50} values > 50 mg/kg and ≤ 300 mg/kg (UN 2021). Furthermore, ToxServices classified TEA to GHS Category 3 for acute dermal toxicity, which corresponds to LD_{50} values > 200 and ≤ 1,000 mg/kg (UN 2021), based on an LD_{50} of 580 mg/kg in rabbits. This is supported by the newly proposed EU harmonized classification of Category 3 (ECHA 2021). Lastly, based on the 4-hour vapor inhalation LC_{50} value of 7.25 mg/L calculated by ECHA (2021) from the 1-hour vapor LC_{50} value of 3,496 ppm (equivalent to 14.5 mg/L), reported in the OECD Guideline 403 acute inhalation study in rats exposed to the target chemical, ECHA (2021) classified TEA as a GHS Category 3 acute inhalation toxicant. Therefore, ToxServices classified TEA to GHS Category 3 for acute inhalation toxicity, which corresponds to 4-hour vapor LC_{50} values > 2.0 and ≤ 10.0 mg/L (UN 2021). These proposed classifications for oral, dermal, and inhalation acute toxicity have been adopted by the European RAC in 2021, and is currently awaiting adoption by the EC, at which time it will be included in Annex VI to CLP and appear in the C&L Inventory.

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

TEA was assigned a score of Moderate for systemic toxicity (single dose) based on ToxServices classifying it to GHS Category 3 for respiratory irritation. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation (CPA 2018b). Confidence in the score is high based on high quality measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – Australia – H335 – May cause respiratory irritation (unverified) [Specific target organ toxicity – single exposure; Respiratory tract irritation – Category 3].
- ECHA 2021, 2023a
  - *Oral:* In the previously described non-GLP-compliant acute oral toxicity study conducted in a manner similar to OECD Guideline 401 that identified an oral LD_{50} of 730 mg/kg in rats (strain not specified), animals were evaluated for mortality, clinical signs, and gross pathology. Male and female rats (strain not specified) were administered 15, 58, 230, 366, 580, 920, and 3,660 mg/kg TEA as a 1, 10 and 20% solution in olive oil via gavage (n=1, 1, 5, 5, 5, 5, and 5, respectively). Two animals (1/dose) were also administered undiluted TEA at 920 and 3,660 mg/kg. Animals were observed for 7 days. Mortality was observed at 920 mg/kg (4/6) and 3,660 mg/kg (1/1) in animals that received diluted solutions, and all animals that received undiluted test substance died before scheduled sacrifice. Unkempt fur was observed 24 hours after dosing at 580 mg/kg, strong convulsions and trembling were observed at 920 mg/kg following dosing followed by unkempt fur and blood crusted nose and snouts at 24 hours post-dosing, and gasping at 2 minutes after dosing followed by death was observed at 3,660 mg/kg. Animals that received undiluted TEA exhibited convulsions and strong tremor at 920 mg/kg and heavy tremor and abdominal position at 3,660 mg/kg. Animals that received undiluted TEA (920 and 3,660 mg/kg) exhibited stomachs filled with dark red contents. No further details were available (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights, and at non-lethal doses up to 580 mg/kg, only transient unkempt fur was observed. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*

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- *Oral:* In the previously described non-GLP-compliant acute oral toxicity study that identified an oral LD_{50} value of greater than 370 mg/kg and less than 1,470 mg/kg in rabbits (sex and strain not specified), animals (2/dose) were administered TEA at doses of 370, 730, and 1,460 mg/kg as a 10% solution in olive oil via gavage and were evaluated for mortality, clinical signs, and gross pathology. Mortality occurred at 730 mg/kg (1/2) and 1,460 mg/kg (2/2). Reduced food intake was observed at 370 mg/kg, convulsions, abdominal position, lateral position, dyspnea, and weak tonus were observed at 730 mg/kg, and imbalance, lateral position, convulsions, and dyspnea were observed at 1,460 mg/kg. At necropsy, blood rich lungs and slackened heart were observed at 730 and 1,460 mg/kg, dilated and blood-filled blood vessels were observed at 730 mg/kg, and reddened and macerated fundus and reddened duodenum were observed at 1,460 mg/kg (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights, and at the non-lethal dose of 370 mg/kg, only reduced food intake was found. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Oral:* In the previously described non-GLP-compliant acute oral toxicity study that identified an oral LD_{50} value of greater than 370 mg/kg and less than 730 mg/kg in female cats (strain not specified), animals (2/dose) were administered TEA at doses of 370 and 730 mg/kg as a 5 and 10% solution in olive oil via gavage and were evaluated for mortality, clinical signs, and gross pathology. Both animals at 730 mg/kg died, while neither died at 370 mg/kg. Salivation and vomiting were observed shortly after dosing with 730 mg/kg followed by screaming, tremor, staggering, and convulsions after 4 minutes. At 370 mg/kg, vomiting was observed 15 minutes after dosing and apathy was observed the following morning. Diffuse reddening of the stomach with small hemorrhagic areas and macerating of the mucous membrane was observed at 730 mg/kg (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights, and at the non-lethal dose of 370 mg/kg, transient vomiting and apathy were observed. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Oral:* In the previously described non-GLP-compliant acute oral toxicity study conducted in a manner similar to OECD Guideline 401 that identified an oral LD_{50} value of 1,030 mg/kg in male Wistar rats for the substance as a 10% water solution and of < 182 mg/kg for the undiluted substance, animals (5/dose) were administered TEA at doses of 0.5, 1 and 2 mL/kg (diluted) and 0.25, 0.5 and 1 mL/kg (undiluted) via gavage and were evaluated for mortality, clinical signs, and gross pathology. Mortality occurred in all animals at 2 mL/kg (diluted), 3/5 animals at 0.25 mL/kg (undiluted), 4/5 at 0.5 mL/kg (undiluted), and in all animals at 1 mL/kg (undiluted). The animals exhibited sluggishness, tremors, gasping, and convulsions. Lungs with petechiae, distended and gas-filled stomachs with red pylori, mottled livers and kidneys, yellow and reddened intestines filled with liquid, and darkened kidney medullae and adrenals were observed at necropsy. No doses were specified for the observations (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Oral:* In the previously described non-GLP acute oral toxicity study conducted in a manner similar to OECD Guideline 401 that identified an oral LD_{50} value of 460 mg/kg in male Sherman rats, animals (5/dose) were administered TEA at doses of 252, 500 and 1,000 mg/kg as a 20% dispersion in 1% Tergitol 7 via gavage and evaluated for mortality, clinical signs, and gross pathology. Mortality occurred in 1/5 animal at 252 mg/kg, 3/5 at 500 mg/kg, and 4/5 at 1,000 mg/kg. Hemorrhage of the stomach and kidney congestion were observed at necropsy. No doses were specified for the effects observed (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights and all doses*

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tested were lethal. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).

- *Dermal*: In the non-GLP-compliant acute dermal toxicity study conducted in a manner similar to OECD Guideline 402 that identified an LD_{50} of 580 mg/kg in male New Zealand Black rabbits, animals (4/dose) were administered 0.5, 1, and 2 mL/kg undiluted TEA (purity not specified) under occlusive conditions for 24 hours. Animals were evaluated for mortality, clinical signs, and gross pathology. Mortalities were reported for the top two dose groups, 1.0 mL/kg and 2.0 mL/kg in which 3/4 and 2/4 animals died, respectively. Necrosis of the skin and scab formation were observed. Darkening of the lungs and kidneys, pale and mottled livers, and pale spleens were observed at necropsy. The doses at which these effects occurred were not specified (Klimisch 2, reliable with restrictions). *ToxServices notes this study lacks data on body weights. ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3)(ECHA 2021).*
- *Inhalation:* In the previously described GLP-compliant acute inhalation study conducted according to OECD Guideline 403 in which a 1-hour vapor LC_{50} of 3,496 ppm, equivalent to 14.5 mg/L was calculated to be a 4-hour vapor LC_{50} of 7.25 mg/L (1 hour LC_{50} / 2 = 4 hour LC_{50}) in rats as identified by ECHA (2021). Male and female Sprague Dawley derived Crl:CD BR VAF/Plus rats (5/sex/dose) were exposed whole-body to 2,450, 3,200 4,000 and 5,050 ppm TEA (99.8% purity) for 1 hour. Mortalities were reported for the top three doses, 3,200 4,000 and 5,050 ppm, in which 2/10, 9/10, and all animals died, respectively. Labored breathing, tremors, and increased salivation were observed upon removal from the exposure chamber. During the 14-day post treatment observation period, labored breathing was also observed. The effects were observed at concentrations as low as 2,450 ppm (equivalent to 10.14 mg/L for 1 hour or 5.07 mg/L for 4 hours), and were all reversible by day 6. There were no treatment related effects on body weight gain for both males and females in 2,450 ppm dose group and females in the 3,200 ppm dose group; however, body weight gain was reduced for males in the 3,200 ppm dose group. No macroscopic abnormalities were reported for the lowest dose groups or in deceased animals in the top dose group, 5,050 ppm; however, discolored lungs were reported for surviving animals in the 4,000 ppm dose group (Klimisch 1, reliable without restriction).
- *Inhalation:* In a non-GLP-compliant nasal irritation and pulmonary toxicity study, male Swiss mice (6/dose) were exposed to a single exposure of 4 to 6 concentrations in the range of 77 – 305 ppm TEA vapor (purity unspecified) for 15 minutes via nasal or tracheal cannulation. Animals were evaluated for breathing frequency in order to establish an RD_{50} value, the limit where decrease of 50% in respiratory rate is found. The study authors concluded TEA is irritative to the mucous membranes and the respiratory tract based on an RD_{50} value of 156 ppm (Klimisch 2, reliable with restrictions).

- Based on the weight of evidence, a score of Moderate was assigned. A lack of systemic toxicity (excluding neurotoxicity) was reported in surviving animals following single oral doses up to 580 mg/kg in rats, rabbits, and cats exposed to the target chemical, which indicates that the LOAELs would exceed the guidance value of 300 mg/kg for Category 1. Although ECHA (2021) concluded that none of the 11 oral acute toxicity studies across five species (rat, mouse, rabbit, guinea pig, and cat) exposed to TEA reported in the ECHA dossier were reliable or conclusive on their own (ECHA 2021), these studies were considered together as a whole in ECHA's evaluation for acute toxicity; therefore, ToxServices considered these studies together as a whole as the weight of evidence in the evaluation of this endpoint as well. Furthermore, reported clinical signs are related to neurotoxicity and/or local irritation (see neurotoxicity and irritation endpoints) that are likely related to the corrosivity of TEA; therefore, TEA is not a concern for systemic toxicity with single oral exposure

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at non-corrosive concentrations (AICIS 2016). For the dermal route, systemic toxicity effects on the liver, kidneys, and spleen in rabbits were reported in the only acute dermal toxicity study identified for TEA; however, this study was unreliable (Klimisch 3) in the ECHA evaluation (ECHA 2021), and the doses at which these effects were observed were unspecified, to determine if any of the effects occurred at non-lethal doses. For the inhalation route, there were no systemic toxicity effects reported in surviving animals following single inhalation exposures up to 2,450 ppm (equivalent to 10.14 mg/L for 1 hour or 5.07 mg/L for 4 hours) in rats in an OECD Guideline 403 study. However, reduced body weight and lung pathology were found in surviving animals at higher concentrations, but may be related to the corrosiveness of the compound. Transient respiratory effects (i.e., labored breathing and discolored lungs) were observed in this study. Irritation to the nasal mucosa and respiratory tract were found in mice exposed to single nasal or tracheal exposures of TEA in a nasal irritation and pulmonary toxicity study with a reported RD_{50} value of 156 ppm. Therefore, ToxServices classified TEA as GHS Category 3. While these effects were observed at concentrations as low as 5.07 mg/L that is below the guidance value for GHS Category 1 (i.e., 10 mg/L for vapor), they were transient and the severity does not warrant worse GHS classifications than Category 3.

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

TEA was assigned a score of High for systemic toxicity (repeated dose) based on the lowest vapor (duration adjusted) LOEC of 0.076 mg/L for histopathological changes to nasal and respiratory epithelium in subchronic inhalation exposure studies in mice and rats, resulting in ToxServices classifying TEA as a GHS Category 1 systemic toxicant (repeated exposure). GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when vapor subchronic inhalation LOAECs are less than 0.2 mg/L, and they are classified as GHS Category 1 for systemic toxicity - repeated exposure (CPA 2018b). Confidence is high as it is based on a reliable experimental study on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan – H373 – May cause damage to organs through prolonged or repeated exposure – Specific target organs/systemic toxicity following repeated exposure - Category 2
      - Based on respiratory tract effects observed in rats at 4.14 mg/L in a 10-day study in rats (NITE 2016).
- AICIS 2016
  - *Oral:* AICIS concluded that short chain (C2-C3) alkyl amines, including TEA, are not a concern for significant systemic toxicity with repeated oral exposure at non-corrosive concentrations.
- ECHA 2023a (The authors of the ECHA dossier identified a few more studies for this endpoint; however, only those reported with a Klimisch score of 1 (reliable without restriction) or 2 (reliable with restrictions) are included in this evaluation due to their higher reliability).
  - *Inhalation*: In the previously described repeated-dose inhalation toxicity study conducted in a manner similar to OECD Guidelines 413 and 452 (only two concentrations tested), male and female Fischer 344 rats (50/sex/dose group) were exposed whole body to vapor concentrations of TEA (greater than 99.9% purity) at 0, 25, and 247 ppm (equivalent to 0, 103, or 1,020 mg/m^3, respectively, as identified by the authors of the ECHA dossier and calculated to be equivalent to 0, 0.103, and 1.020 mg/L, respectively [mg/m^3 * $1m^3$/ 1,000L

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= mg/L]) for 6 hours/day, 5 days/week, for 28 weeks to produce a maximum of 127 exposure days. ToxServices calculated the equivalent concentrations for a 7-day/week exposure frequency to be 0, 0.0736, and 0.7286 mg/L, respectively (5 day/week exposure mg/L *5/7 = adjusted 7-day/week exposure mg/L). The animals were evaluated for clinical signs of toxicity, hematology, clinical chemistry, gross pathology, and histopathology. Mortality was observed as 1 female at the low concentration at week 6, and 1 male at week 8 and 2 females at week 3 (both accidental) at the high concentration. At the high concentration, closed eyes and eyes buried in fur were observed during treatment. Slightly reduced body weight gains were measured in high concentration males. No treatment-related effects were found on hematology or clinical chemistry. Chronic inflammation of the lungs was observed in all treated and control animals after 30 and 125 exposures. Male lung weights increased in a concentration-related manner, but were not statistically significant and were not associated with histopathological changes. Liver necrosis (focal) was observed in all treated and control animals after 125 exposures. Minimal focal necrosis of myofibers in the heart was observed in males at the low concentration following 125 exposures. The study authors specified that a viral infection was observed in the treated animals. The systemic toxicity NOAEC was identified as 1.020 mg/L and the local irritation NOAEC value was identified as 0.103 mg/L (equivalent to 0.0736 mg/L for 7-day/week exposure frequency) and the LOAEC as 1.020 mg/L (equivalent to 0.7286 mg/L for a 7-day/week exposure frequency), respectively, based on nasal and ocular irritation (Klimisch 2, reliable with restrictions). *As the study duration is longer than 90 days (equivalent to 13 weeks), the vapor GHS guidance value of 0.2 mg/L/day for Category 1 is divided by a factor of 2.15 (i.e., 28 weeks/13 weeks) to an adjusted value of 0.1 mg/L for a 28-week study (UN 2021). As the 7-day exposure adjusted systemic toxicity NOAEC of 0.0736 mg/L/day, which is the highest concentration tested, is less than the vapor duration adjusted GHS guidance value of 0.1 mg/L; GHS classification is not possible. ToxServices also notes that the findings are confounded by the viral infection in the tested animals.*

- *Inhalation*: A subacute inhalation toxicity study was performed with male and female Fischer 344 rats (5/sex/dose) exposed to concentrations of TEA (99% purity) at 1,000 ppm (equivalent to 4.319 mg/L) 6 hours/day, 5 days/week for 10 days. A minimum of 8 tissues were examined from each animal including the nasal cavity, trachea, lung, heart, esophagus, kidney and spleen. Two males and one female died after the seventh day of exposure. All treated animals had moderate necrotizing inflammation of the nasal cavity. Squamous metaplasia in the trachea and moderate thymic atrophy was noted in 7 of 10 animals. Keratitis was noted in three animals. Perivascular edema of the lung was noted in the animals which died (Klimisch 2, reliable with restrictions). *Based on the study duration of less than 28 days, this study was not considered sufficient for classification.*
- *Inhalation*: In a 3-month inhalation study, male and female F344 rats (10/sex/dose) were exposed via whole body inhalation to 0, 12.5, 25, 50, 100, and 200 ppm TEA (purity not specified) for 6.2 hours/day, 5 days/week, for 14 weeks. No mortalities were reported. An increased number of non-neoplastic lesions were reported with exposure to 25, 50, 100, and 200 ppm for both males and females. Histopathology found increased incidences of atrophy of the olfactory epithelium in the nose of males exposed to 50 ppm and above and females exposed to concentrations of 25 ppm and above, hyperplasia in the respiratory epithelium of the nose males and females exposed to concentrations of 25 ppm and above, cellular infiltration of the alveolus of the lungs in females exposed to 100 and 200 ppm, and corneal lesions in males and females exposed to the top dose. NTP (2018) established a NOEC of 12.5 ppm for systemic effects based on non-neoplastic respiratory epithelium hyperplasia of the nasal cavity (NTP 2018). *Adjusting for the less than daily exposure frequency, the*

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*longer daily exposure duration, and converting the dose units from ppm to mg/L, 12.5 ppm is equivalent to 12.5 * 101.19 / 24,450 * 5 days / 7 days * 6.2 hours / 6 hours = 0.038 mg/L. The LOEC of 25 ppm is therefore calculated to be 0.076 mg/L.*

- *Inhalation*: In another 3-month inhalation study, male and female B6C3F1/N mice (10/sex/dose) were exposed to whole body inhalation doses of 0, 12.5, 25, 50, 100, and 200 ppm TEA (purity not specified) for 6.2 hours/day, 5 days/week, for 14 weeks. No mortalities were reported. An increased number of non-neoplastic lesions were reported with exposure to 50 ppm and above for both males and females including an increased incidence of atrophy and cytoplasmic vacuolization of the olfactory epithelium in the nose of males and females exposed to 50 ppm and above, squamous metaplasia in the respiratory epithelium of the nose males and females exposed to 200 ppm, turbinate hyperostosis in all animals at every dose, and turbinate necrosis in top dose males and females. NTP (2018) established a NOEC of 12.5 ppm for systemic effects based on non-neoplastic turbinate hyperostosis of the nasal cavity (NTP 2018). *Adjusting for the less than daily exposure frequency, the longer daily exposure duration, and converting the dose units from ppm to mg/L, 12.5 ppm is equivalent to 12.5 * 101.19 / 24,450 * 5 days / 7 days * 6.2 hours / 6 hours = 0.038 mg/L. The LOEC of 25 ppm is therefore calculated to be 0.076 mg/L.*
- *Oral*: *Surrogate: TMA (CAS #75-50-3)*: In the previously described combined repeated dose toxicity study with reproduction/developmental toxicity screen test conducted in a manner similar to OECD Guideline 422 (GLP status not specified), Sprague-Dawley rats (13/sex/dose group) were administered oral doses of surrogate TMA (30.8% solution) in water at 0, 8, 40, or 200 mg/kg/day via gavage. Males and females were dosed 2 weeks prior to breeding, continuing through breeding (2 weeks), gestation (3 weeks), and lactation (4 days) for a total of 42 days. Parental animals were evaluated for clinical signs of toxicity, body weight, estrous cycle, sperm measures, reproductive performance, gross pathology, and histopathology. Two high dose males died prior to the scheduled sacrifice, one on day 25 and the other on day 42. One high dose female died on pregnancy day 22 (administration day 38). Prior to death, one or more of these animals exhibited salivation, abnormal breathing noise, dyspnea, emaciation, soiled fur, decreased body temperature, and tottering. High dose animals that survived to the scheduled sacrifice exhibited salivation, abnormal breathing noises, emaciation (1 female), and decreased contact response (1 male). At the high dose, body weight gains of males were decreased relative to controls. Ulcers and inflammation of the stomach and intestinal tracts, including, squamous hyperplasia and edema in submucosa, were observed in high dose males and females. Study authors established the systemic toxicity NOAEL and LOAEL as 40 and 200 mg/kg/day, respectively, based on increased mortality and histopathological changes to the gastrointestinal tract (Klimisch 2, reliable with restrictions).

- ECHA 2023c
  - *Oral: Surrogate: TMA chloride (CAS #593-81-7)*: In a non-GLP, non-guideline subchronic toxicity study, male Sprague-Dawley rats (5-6/dose) were exposed to TMA hydrochloride in the feed at 0, 0.04, 0.08, 0.16, 0.31 or 0.62% for 90 days. Animals were evaluated for mortality, clinical signs, body weight, hematology urinalysis, gross pathology, and histopathology. Decreased body weight gain was measured at the two highest doses (by 16.6% and 52%, respectively). The weight of seminal vesicles was reduced to half to one third of the control values, (presumably at the two highest doses) with gross pathological findings of reduced size of seminal vesicles, reduced number of secretory granules, tubular collapse in the prostate, the reduced secretory substances in the prostate at the highest dose. Study authors identified a NOAEL of 0.16% in the diet, equivalent to 79 mg/kg/day TMA as

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calculated by ECHA dossier authors, based on decreased weight gain and organ weights. Therefore, the LOAEL is 0.31%, which is equivalent to 150 mg/kg/day TMA according to calculations by the ECHA dossier authors (Klimisch 2, reliable with restrictions).

- Based on the weight of evidence, a score of High was assigned. Repeated dose oral toxicity studies on TEA were non-guideline, performed decades ago, and/or were non-GLP compliant. They were judged not appropriate to identify effect levels for risk assessments by OECD (2012) and AICIS (2016), assigned Klimisch scores of 3 (not reliable) or 4 (not assignable) by REACH dossier authors, or missing critical information to determine the NOAEL/LOAEL. Therefore, data on surrogate TMA are presented to support the safety of TEA. Surrogate TMA produced a NOAEL of 40 mg/kg/day based on increased mortality and histopathological changes to the gastrointestinal tract at the LOAEL of 200 mg/kg/day in an OECD Guideline 422 combined reproduction and developmental toxicity screening test in rats. However, these critical effects are likely due to the corrosivity of TMA (ECHA 2023a). The 90-day rat study on TMA hydrochloride salt, which did not cause any local effects, reported a systemic toxicity NOAEL of 79 mg TMA /kg/day and LOAEL of 150 mg TMA/kg/day based on reduced body weight gain and organ weight effects. This LOAEL is higher than the GHS cutoff of 100 mg/kg/day for subchronic oral studies (UN 2021). However, subchronic inhalation exposure studies in mice and rats produced the lowest vapor (duration adjusted) LOEC of 0.076 mg/L based on histopathological changes to nasal and respiratory epithelium. This LOEC is below the GHS 90-day guidance value of 0.2 mg/L for Category 1 (UN 2021). While the effects reported are likely related to the corrosivity of TEA (ECHA 2023a), the severity of the effects and the LOEC value warrant GHS classification. Therefore, ToxServices classified TEA as a Category 1 specific target organ toxicant following repeated inhalation exposure under GHS criteria (UN 2021).

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

TEA was assigned a score of Very High for neurotoxicity (single dose) based on ToxServices conservatively classified TEA to GHS Category 1 for single exposure neurotoxicity based on a LOAEC of 5.07 mg/L/4h (i.e., < 10 mg/L/4h) for tremors and GHS Category 1 classification by Japan based on findings in humans. GreenScreen® criteria classify chemicals as a Very High hazard for neurotoxicity (single dose) when a GHS Category 1 classification is warranted (CPA 2018b). Confidence in the score is low as it is not clear if reversible tremors are due to direct neurotoxicity, and limited human data are identified.

- Authoritative and Screening Lists
  - *Authoritative:*
    - Boyes – Neurotoxicants – Neurotoxic
  - *Screening:*
    - GHS Japan – H370 – Causes damage to organs – Specific target organs/systemic toxicity following single exposure – Category 1
      - Based on descriptions of central nervous system effects in humans. Inhalation exposure in humans led to electroencephalogram changes. No additional details were provided (NITE 2006, 2016).
- AICIS 2016
  - Short-term exposure of unknown concentrations of TEA was reported to cause disruption to the central nervous system in humans.
- ECHA 2021, 2023a
  - *Oral*: In the previously described non-GLP-compliant acute oral toxicity study conducted in a manner similar to OECD Guideline 401 that identified an oral LD_{50} of 730 mg/kg in rats, Male and female rats (strain not specified) were administered 15, 58, 230, 366, 580, 920, and

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3,660 mg/kg TEA as a 1, 10 and 20% solution in olive oil via gavage (n=1, 1, 5, 5, 5, 5, and 5, respectively). Two animals (1/dose) were also administered undiluted TEA at 920 and 3,660 mg/kg. Animals were observed for 7 days. Mortality was observed at 920 mg/kg (4/6) and 3,660 mg/kg (1/1) in animals that received diluted solutions, and all animals that received undiluted test substance died before scheduled sacrifice. Strong convulsions and trembling were observed at 920 mg/kg following dosing. Animals that received undiluted TEA exhibited convulsions and strong tremor at 920 mg/kg and heavy tremor and abdominal position at 3,660 mg/kg (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3) (ECHA 2021).*

- *Oral*: In the previously described non-GLP-compliant acute oral toxicity study that identified an oral LD_{50} value of greater than 370 mg/kg and less than 1,470 mg/kg in rabbits (sex and strain not specified), animals (2/dose) were administered TEA at doses of 370, 730, and 1,460 mg/kg as a 10% solution in olive oil via gavage and were evaluated for mortality, clinical signs, and gross pathology. Mortality occurred at 730 mg/kg (1/2) and 1,460 mg/kg (2/2). Convulsions, abdominal position, lateral position, and weak tonus were observed at 730 mg/kg, and imbalance, lateral position, and convulsions were observed at 1,460 mg/kg (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3) (ECHA 2021).*
- *Oral*: In the previously described non-GLP-compliant acute oral toxicity study that identified an oral LD_{50} value of greater than 370 mg/kg and less than 730 mg/kg in female cats (strain not specified), animals (2/dose) were administered TEA at doses of 370 and 730 mg/kg as a 5 and 10% solution in olive oil via gavage and were evaluated for mortality, clinical signs, and gross pathology. Both animals at 730 mg/kg died, while neither died at 370 mg/kg. Screaming, tremor, staggering, and convulsions were reported 4 minutes after dosing with 730 mg/kg. At 370 mg/kg, vomiting was observed 15 minutes after dosing and apathy was observed the following morning (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3) (ECHA 2021).*
- *Oral*: In the previously described non-GLP-compliant acute oral toxicity study conducted in a manner similar to OECD Guideline 401 that identified an oral LD_{50} value of 1,030 mg/kg in male Wistar rats for the substance as a 10% water solution and of < 182 mg/kg for the undiluted substance, animals (5/dose) were administered TEA at doses of 0.5, 1 and 2 mL/kg (diluted) and 0.25, 0.5 and 1 mL/kg (undiluted) via gavage and were evaluated for mortality, clinical signs, and gross pathology. Mortality occurred in all animals at 2 mL/kg (diluted), 3/5 animals at 0.25 mL/kg (undiluted), 4/5 at 0.5 mL/kg (undiluted), and in all animals at 1 mL/kg (undiluted). The animals exhibited sluggishness, tremors, gasping, and convulsions. No doses were specified for the observations (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable (Klimisch 3) (ECHA 2021).*
- *Dermal*: In the non-GLP-compliant acute dermal toxicity study conducted in a manner similar to OECD Guideline 402 that identified an LD_{50} of 580 mg/kg in male New Zealand Black rabbits, animals (4/dose) were administered 0.5, 1, and 2 mL/kg undiluted TEA (purity not specified) under occlusive conditions for 24 hours. Animals were evaluated for mortality, clinical signs, and gross pathology. Mortalities were reported for the top two dose groups, 1.0 mL/kg and 2.0 mL/kg in which 3/4 and 2/4 animals died, respectively. Necrosis of the skin and scab formation were observed. Darkening of the lungs and kidneys, pale and mottled livers, and pale spleens were observed at necropsy. The doses at which these effects occurred were not specified (Klimisch 2, reliable with restrictions). *ECHA (2021) in its re-evaluation of TEA concluded that this study was not reliable due to a lack of dose response in mortality (Klimisch 3)(ECHA 2021).*

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  - *Inhalation*: In the previously described GLP-compliant acute inhalation study conducted according to OECD Guideline 403 in which a 1-hour vapor LC_{50} of 3,496 ppm, equivalent to 14.5 mg/L was calculated to be a 4-hour vapor LC_{50} of 7.25 mg/L (1 hour LC_{50} / 2 = 4 hour LC_{50}) in rats as identified by ECHA (2021). Male and female Sprague Dawley derived Crl:CD BR VAF/Plus rats (5/sex/dose) were exposed whole-body to 2,450, 3,200 4,000 and 5,050 ppm TEA (99.8% purity) for 1 hour. Mortalities were reported for the top three doses, 3,200 4,000 and 5,050 ppm, in which 2/10, 9/10, and all animals died, respectively. Labored breathing, tremors, and increased salivation were observed upon removal from the exposure chamber. During the 14-day post treatment observation period, labored breathing was also observed. The effects were observed at concentrations as low as 2,450 ppm (equivalent to 10.14 mg/L for 1 hour or 5.07 mg/L for 4 hours), and were all reversible by day 6. There were no treatment related effects on body weight gain for both males and females in 2,450 ppm dose group and females in the 3,200 ppm dose group; however, body weight gain was reduced for males in the 3,200 ppm dose group. No macroscopic abnormalities were reported for the lowest dose groups; however, discolored lungs were reported for surviving animals in the 4,000 ppm dose group (Klimisch 1, reliable without restriction).

- Based on the weight of evidence, a score of Very High was assigned. Neurological symptoms such as convulsion, tremor, weak tonus, imbalance, lateral position, staggering, and/or sluggishness were observed at oral doses that also caused mortality in animal studies, with unknown reversibility. Only transient vomiting and apathy were observed at a non-lethal oral dose of 370 mg/kg, which are not typical of transient narcosis that warrant GHS Category 3 classification. Although ECHA (2021) concluded that none of the 11 oral acute toxicity studies across five species (rat, mouse, rabbit, guinea pig, and cat) exposed to TEA reported in the ECHA dossier were reliable or conclusive on their own (ECHA 2021), these studies were considered together as a whole in ECHA's evaluation of acute oral toxicity; therefore, ToxServices considered these studies together as a whole as the weight of evidence in the evaluation of oral single exposure neurotoxicity as well. However, none of the studies specifically evaluated neurobehavior or pathology of neuronal tissues. For the dermal route, no clinical signs or gross pathological findings indicative of neurotoxicity were reported in an acute dermal toxicity study in rabbits. Although ECHA dossier authors considered this study reliable (Klimisch 2), ECHA RAC concluded it to be unreliable (Klimisch 3). For the inhalation route, tremors were reported following single inhalation exposures in an OECD Guideline 403 study in rats exposed to the target chemical at concentrations as low as 5.07 mg/L/4h. The effect was reversible by Day 6 post exposure. Although TEA does not have a harmonized EU GHS classification, it is listed by Boyes as a neurotoxicant and as a GHS Category 1 specific target organs/systemic toxicity single exposure toxicant according to Japan based on neurotoxic effects observed in humans. Therefore, ToxServices conservatively classified TEA to GHS Category 1 for single exposure neurotoxicity based on a LOAEC of 5.07 mg/L/4h (i.e., < 10 mg/L/4h) for tremors and GHS Category 1 classification by Japan based on findings in humans.

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

TEA was assigned a score of Low for neurotoxicity (repeated dose) based on a NOAEL of 150 mg/kg/day in a subchronic oral toxicity study with neurobehavioral examination in rats exposed to surrogate TBA. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data are available, and they are not GHS-classified (i.e., subchronic oral LOAEL values greater than 100 mg/kg/day) (CPA 2018b). Confidence is low as it is based on data for a weak surrogate, TBA.

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

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  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral*: *Surrogate: TMA (CAS #75-50-3)*: In the previously described combined repeated dose toxicity study with reproduction/developmental toxicity screen test conducted in a manner similar to OECD Guideline 422 (GLP status not specified), Sprague-Dawley rats (13/sex/dose group) were administered oral doses of surrogate TMA (30.8% solution) in water at 0, 8, 40, or 200 mg/kg/day via gavage. Males and females were dosed 2 weeks prior to breeding, continuing through breeding (2 weeks), gestation (3 weeks), and lactation (4 days) for a total of 42 days. Parental animals were evaluated for clinical signs of toxicity, body weight, estrous cycle, sperm measures, reproductive performance, gross pathology, and histopathology. Two high dose males died prior to the scheduled sacrifice, one on day 25 and the other on day 42. One high dose female died on pregnancy day 22 (administration day 38). Prior to death, animals exhibited salivation, abnormal breathing noise, dyspnea, emaciation, soiled fur, decreased body temperature, and tottering. High dose animals that survived to the scheduled sacrifice exhibited salivation, abnormal breathing noises, emaciation (1 female), and decreased contact response (1 male). Neurobehavioral exam was not performed. The systemic toxicity NOAEL and LOAEL were identified as 40 and 200 mg/kg/day, respectively, by the study authors based on increased mortality and histopathological changes to the gastrointestinal tract (Klimisch 2, reliable with restrictions). *The authors of the ECHA dossier report this study lacks data on detailed clinical observation, sensory reactivity to stimuli, assessment of grip strength, and motor activity.*
  - *Oral: Surrogate: TBA (CAS #102-82-9)*: In a GLP-compliant subchronic toxicity study conducted according to OECD Guideline 408, Wistar rats (10/sec/dose) were exposed to TBA via daily gavage in coin oil vehicle at 0, 25, 75, and 225 mg/kg/day for 13 weeks. The dose for the highest dose group was reduced to 150 mg/kg/day from day 50 of treatment in females, due to excess toxicity leading to premature deaths. Additional 5/sex/dose animals from the control and the highest dose groups were kept for another 28 days without treatment before sacrifice to investigate recovery. A functional observation battery (FOB) was administered during week 12 and week 17 (recovery group) in 5/sex/dose, including hearing ability, pupillary reflex, statis righting reflex, fore- and hind-limb grip strength, locomotor activity, and total movements and ambulation. Histopathology was performed on the brain, optic nerve, sciatic nerve, and tibial nerve. No effects were found on these parameters (Klimisch 1, reliable without restriction). *ToxServices identified a NOAEL of 225/150 mg/kg/day for neurotoxicity based on the lack of effects observed on these parameters.*
- Based on the weight of evidence, a Low was assigned. No dermal or inhalation repeated dose toxicity studies were available that specifically examined neurotoxicity in the form of a functional observation batter (FOB). For the oral route, no neurobehavioral examination was performed in the OECD Guideline 422 study in rats exposed to surrogate TMA in which clinical signs of neurotoxicity (emancipation and decreased contact response) were reported. However, these emancipation and decreased contact response was only observed in one animal each, at the highest dose of 200 mg/kg/day that also caused mortality in another animal before the scheduled sacrifice. Therefore, these clinical signs are not likely signs of direct neurotoxicity but rather secondary to severe systemic toxicity. The subchronic oral toxicity study with the surrogate TBA in rats with a NOAEL of 150 mg/kg/day was more reliable in evaluating this endpoint because it includes a formal evaluation of neurotoxicity in the form of an FOB and neuropathology that are not evaluated in the OECD Guideline 422 study on TMA. Therefore, ToxServices relied on the results from the subchronic study on TBA to score this endpoint. The NOAEL of 150 mg/kg/day is higher than the

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GHS Category 2 cutoff of 100 mg/kg/day. Therefore, TEA is not classified as a repeated exposure systemic toxicant based on neurotoxicity.

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

TEA was assigned a score of Low for skin sensitization based on negative results in a mouse ear swelling test in mice for the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high based on reliable, measured data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- AICIS 2016, ECHA 2023a (The authors of the ECHA dossier identified another study for this endpoint; however, they assigned that study a Klimisch 3 (not reliable) score. Therefore, that study was not included in this evaluation.)
  - A non-GLP-compliant mouse ear swelling test was performed with female CF1 (CR) mice (10/dose group) administered topical applications of TEA (purity not specified). The induction phase consisted of four topical applications of 100 µL of 1% TEA in FCA to the abdomen on days 0, 1, 2, and 3. On day 10, the challenge dose was applied as 10 µL pure TEA to the dorsal and ventral surfaces of the ear. No positive reactions were observed at 24 or 48 hours after the application of the challenge dose. The animals were re-challenged on day 17 using the same parameters as the first challenge application. No positive reactions were observed at re-challenge. The vehicle and positive controls were valid. The authors of the ECHA dossier concluded TEA was not sensitizing (Klimisch 2, reliable with restrictions).

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

TEA was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential and according to ECHA's guidance on respiratory sensitization evaluation. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). Confidence in the score was low as this evaluation did not include non-immunologic mechanisms of respiratory sensitization, and no specific data were available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - TEA does not contain any structural alerts for respiratory sensitization (Appendix D).
- DTU 2023
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models: TEA is predicted to be negative for respiratory sensitization in humans by the CASE Ultra model. The predictions from the remaining models were outside their applicability domains (Appendix L).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which

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human experience is the main evidence of activity (ECHA 2017). As TEA was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by TEA, and as TEA does not contain any structural alerts for respiratory sensitization (OECD 2023), TEA is not expected to be a respiratory sensitizer.

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

TEA was assigned a score of Very High for skin irritation/ corrosivity based on association with the EU-GHS authoritative list of H314 supported by screening lists and experimental data (corrosive when applied undiluted to the skin of rabbits under occlusive and nonocclusive conditions in three dermal irritation assays; two of which were non-guideline, and one was equivalent to OECD Guideline 404). GreenScreen® criteria classify chemicals as a Very High hazard for skin irritation when associated with EU-GHS hazard statement of H314 and when they are classified to GHS Category 1 (CPA 2018b). Confidence is high based on reliable data supported by the EU harmonized classification and screening lists.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU – GHS (H-statements) Annex 6 Table 3-1 – H314 – Causes severe skin burns and eye damage [Skin corrosion/irritation – Category 1A or 1B or 1C].
  - *Screening:*
    - GHS – Japan – H314 – Causes severe skin burns and eye damage [Skin corrosion/irritation – Category 1].
      - Based on corrosive effects observed in rabbits exposed for 3 minutes, 1 hour or 4 hours under occlusion (NITE 2016).
    - GHS – New Zealand – Skin corrosion category 1B.
      - Based on its association with the R Phrase R35: causes severe skin burns (CCID 2023).
    - GHS – Australia – H314 – Causes severe skin burns and eye damage [Skin corrosion/irritation – Category 1A or 1B or 1C].
    - GHS – Korea – H314 – Causes severe skin burns and eye damage [Skin corrosion/irritation – Category 1].
- ECHA 2023a (The authors of the ECHA dossier identified additional studies for this endpoint; however, they assigned those studies Klimisch scores of 3 (not reliable) or 4 (not assignable). Due to the presence of more reliable studies described above, ToxServices did not include the remaining studies in this report.)
  - A non-GLP-compliant dermal irritation test conducted in a manner similar to OECD Guideline 404 (only two animals tested) was performed with rabbits (2 total, strain and sex not specified) administered a topical application of an unspecified amount of undiluted TEA (purity not specified) for 1, 5, or 15 minutes under occlusive dressing. An observation period of 26 days followed the exposure period. An exposure of 1 minute caused marked edema and hemorrhagic areas on the day of application that remained unchanged for one week. Scar formation was observed at the end of the exposure period. Following exposure for 5 or 15 minutes, red-brown necrosis of leather-like consistency was observed on the day of application. On day 8, the necrosis developed into hard crusts. After three weeks, scar formation was observed. The study authors concluded that TEA was corrosive to skin (Klimisch 2, reliable with restrictions).
  - A GLP-complaint dermal irritation test was performed with rabbits (6 total, strain and sex not specified) administered dermal applications of an unspecified amount of TEA (purity not

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specified) for 3 minutes or 1 hour under semi-occlusive dressing. Study authors concluded that TEA was corrosive to the skin in this study (Klimisch 2, reliable with restrictions).
    - A dermal irritation study conducted in a manner similar to OECD Guideline 404 was performed with rabbits (5/dose group, strain and sex not specified) administered dermal applications of an unspecified amount of TEA (purity not specified) to shaved skin at 0.01 mL without dressing (open) for 30 minutes or 0.05 mL under occlusive dressing for 4 hours. The reactions were scored at 18-24 hours for the open condition and at 4, 24, and 48 hours for the occlusive dressing). The open condition produced minor to moderate irritation, while the occlusive condition produced necrosis. The study authors considered TEA to be corrosive to skin (Klimisch 2, reliable with restrictions).
    - A non-GLP-compliant dermal irritation test conducted according to 49 CFR, Sect. 173.240, was performed with rabbits administered a dermal application of an unspecified amount of triethylamine (purity not specified) to intact and abraded skin for 4 hours under occlusive dressing. An observation period of 72 hours followed the exposure period. At 72 hours, the erythema score was 2/4 and the edema score was 1-2 in all animals. No differences were observed in the intact and abraded skin (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Very High was assigned. TEA was corrosive in three dermal irritation studies when applied undiluted to the skin of rabbits under occlusive and nonocclusive conditions. Furthermore, TEA has a harmonized EU GHS Category 1 classification for skin irritation. Therefore, TEA is assigned GHS Category 1.

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

TEA was assigned a score of Very High for eye irritation/ corrosivity based on ToxServices classifying it as a GHS Category 1 eye irritant (corrosive to the eyes of rabbits in three ocular irritation assays, including an OECD Guideline 405 study) with support from a harmonized classification from an authoritative body. GreenScreen® criteria classify chemicals as a Very High hazard for skin irritation when associated with EU-GHS hazard statement of H314 and when they are classified to GHS Category 1 for skin or eye irritation (CPA 2018b). Confidence is high based on reliable data supported by EU harmonized classification and screening lists.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - GHS – Japan – H318 – Causes serious eye damage [Serious eye damage / eye irritation – Category 1].
            - Based on corrosive reactions observed in rabbits after exposure to 0.1 mL of the substance (NITE 2006, 2016).
        - GHS – New Zealand – Serious eye damage category 1; EU Manufacturer REACH hazard submissions – H318 – Causes serious eye damage (unverified) [Serious eye damage / eye irritation – Category 1]
            - Based on its alkalinity and severe injury observed following application of a drop to rabbit eyes (CCID 2023).
- SCOEL 2017, NITE 2016
    - Blurred vision has been reported in humans after exposure to TEA (SCOEL 2017), which is attributed to its irritation potential (NITE 2016).
- ECHA 2023a (The authors of the ECHA dossier identified a few more studies for this endpoint; however, only Key or Supporting studies reported with a Klimisch score of 1 (reliable without restriction) or 2 (reliable with restrictions) were included in this evaluation due to their higher reliability.)

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  - A non-GLP-compliant ocular irritation test conducted in a manner similar to OECD Guideline 405 (50 µl used) was performed with rabbits (2 total, strain and sex not specified) administered ocular instillations of 50 µl undiluted TEA (purity not specified) without rinsing. The animals were observed for 19 days. Severe corneal opacity, bleeding of the nictitating membrane, chemosis, conjunctival edema, and redness of the eyes were observed after 10 minutes. These symptoms persisted for the subsequent 2 weeks, with the corneal opacity regarded as irreversible. The study authors concluded that TEA was highly irritating or corrosive in this study (Klimisch 2, reliable with restrictions). *ECHA (2021) notes that while this study does not report scoring, the observation period of 19 days is the most similar to OECD Guideline 405 criteria which require 21 days, and the results of this study support its classification of TEA as a GHS Category 1 eye irritant (ECHA 2021).*
  - A non-GLP-compliant ocular irritation test was performed with New Zealand White rabbits (3 total, sex not specified) administered ocular instillations of 0.1 mL TEA (purity not specified). The animals were observed for 7 days. TEA was corrosive to the eyes but these effects were overcome by washing (no further details provided) (Klimisch 2, reliable with restrictions).
  - An ocular irritation test conducted according to OECD Guideline 405 was performed with rabbits (5 total, strain and sex not specified) administered ocular instillations of 5 µL TEA (purity not specified). The animals were observed for 18-24 hours following treatment. The treated animals exhibited severe iritis, corneal opacity, necrosis and/or hemorrhage of the eyelids, and chemosis. The study authors concluded that TEA was corrosive to the eyes (Klimisch 2, reliable with restrictions). *ECHA (2021) notes in the original study there is no mention of necrosis and hemorrhage of the eyelids, and chemosis (ECHA 2021).*
- Based on the weight of evidence, a score of Very High was assigned. TEA was highly irritating or corrosive in three ocular irritation studies in rabbits. In addition, ECHA (2021) concluded that 9 ocular irritation studies identified in the ECHA dossier when considered together provided enough evidence to classify TEA to Category 1 (H318) according to GHS criteria (UN 2021). ToxServices notes that while this proposed harmonized classification is adopted by RAC in 2021, the RAC opinion is awaiting adoption by the EC, at which time the ECHA C&L inventory website will be updated to include the new classification. Therefore, TEA is assigned GHS Category 1.

Ecotoxicity (Ecotox)

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

TEA was assigned a score of High for acute aquatic toxicity based on the measured 72-hour EC_{50} values of 6.8 – 8 mg/L (i.e., 1 – 10 mg/L) in an OECD Guideline 201 study for acute aquatic toxicity to algae. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 1 mg/L to 10 mg/L (CPA 2018b). The confidence in the score is high based on reliable, guideline studies for the target chemical for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – Japan – H401 – Toxic to aquatic life [Hazardous to the aquatic environment (acute) – Category 2].
      - Based on measured 72-hour EC_{50} values of 6.8 – 8 mg/L in an OECD Guideline 201 study for acute aquatic toxicity to algae (NITE 2016).
- ECHA 2023a

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- 96-hour LC_{50} (*Oryzias latipes*, Japanese rice fish) = 24 mg/L (GLP-compliant, OECD Guideline 203) (Klimisch 2, reliable with restrictions).
- 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 36 mg/L (GLP-compliant, EPA OTS 797.1400) (Klimisch 2, reliable with restrictions).
- 48-hour LC_{50} (*Leuciscus idus*, ide) = greater than 500 mg/L (non-GLP-compliant) (Klimisch 2, reliable with restrictions).
- 48-hour LC_{50} (*Ceriodaphnia dubia*, water flea) = 17 mg/L (GLP-compliant, EPA/600/4-90/027) (Klimisch 2, reliable with restrictions).
    - *The authors of the ECHA dossier note that this study was performed at a pH greater than 8.5 which may have affected results; therefore, ToxServices did not use this study for classification of this endpoint.*
- 48-hour mobility EC_{50} (*Daphnia magna*) = 200 mg/L (non-GLP-compliant, similar to OECD Guideline 202) (Klimisch 2, reliable with restrictions).
- 48-hour mobility EC_{50} (*D. magna*) = 34 mg/L (non-GLP-compliant, OECD Guideline 202) (Klimisch 2, reliable with restrictions).
- 72-hour growth rate EC_{50} (*Raphidocelis subcapitata*, green algae) = 8 mg/L (OECD Guideline 201, GLP status not specified) (Klimisch 2, reliable with restrictions).
    - *The study authors identified an area under the (growth) curve (AUC) 72-hour EC_{50} value of 6.8 mg/L. Additionally, TEA is classified by Japan as GHS Category 2 based on the results of this study (NITE 2016).*

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

TEA was assigned a score of Moderate for chronic aquatic toxicity based on chronic aquatic toxicity NOECs as low as 1.1 mg/L (measured LOEC values of 3.2 – 320 mg/L and an estimated chronic value (ChV) of 3.16 mg/L for fish, measured NOEC values of 7.1 – 11 mg/L for crustacea, and measured 72-hour NOEC value of 1.1 mg/L in an OECD Guideline 201 study for algae). GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score was reduced due to reliance on a modeled ChV for the fish trophic level.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2023a
    - A 60-day aquatic toxicity test was performed with rainbow trout (*O. mykiss*). The mortality LOEC was greater than 100 mg/L, the weight LOEC was 3.2 mg/L, and the length LOEC was 100 mg/L (nominal). NOECs were not reported (Klimisch 2, reliable with restrictions).
    - In an early life stage toxicity test conducted in a manner similar to OECD Guideline 210 with zebrafish (*Danio rerio*) over 7 days, the 7-day embryotoxicity LOEC was 100 mg/L at 25°C and the 7-day mortality LOEC was 320 mg/L. NOECs were not reported (Klimisch 2, reliable with restrictions).
    - In a reproduction test conducted according to OECD Guideline 211 with *D. magna* over 21 days, the reproduction NOEC was identified as 11 mg/L (Klimisch 2, reliable with restrictions).
    - In a GLP-compliant reproduction test conducted according to EPA Method 1002.0 (1989) with *C. dubia* over 7 days, the reproduction NOEC was identified as 7.1 mg/L (measured) (Klimisch 1, reliable without restriction).

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  - 72-hour growth rate NOEC (*R. subcapitata*, green algae) = 1.1 mg/L (OECD Guideline 201, GLP status not specified). Furthermore, the study authors identified an AUC 72-hour NOEC value of 1.8 mg/L for growth (Klimisch 2, reliable with restrictions).
- U.S. EPA 2017a
  - TEA belongs to the aliphatic amines ECOSAR chemical class. The most conservative predicted ChV is 3.16 mg/L in fish, 0.39 mg/L in daphnia, and 1.48 mg/L in algae (U.S. EPA 2017a, Appendix M).
- Based on the weight of evidence, a score of Moderate was assigned. The GreenScreen® criteria for this endpoint are based on NOECs. The lowest NOECs for aquatic invertebrates and algae is 1.1 mg/L. For fish, the lowest LOEC is 3.2 mg/L, and no NOEC was reported for this study. The NOEC could be lower than 1 mg/L, which would warrant High or Very High scores. Therefore, ToxServices performed ECOSAR modeling to determine the ChV for the fish trophic level, and the modeled data also support a Moderate score.

Environmental Fate (Fate)

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

TEA was assigned a score of Very Low for persistence based on ready biodegradability guideline studies for TEA and surrogate TBA (meeting the 10-day window), and two authoritative bodies concluding TEA and surrogate TBA are readily biodegradable within the 10-day window. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil, sediment, or water is the dominant environmental compartment and the 10-day window is met (CPA 2018b). Confidence is high based on the measured biodegradation data for the target chemical and a surrogate with a larger molecule size that is expected to be degraded more slowly than the target chemical and supporting conclusions from an authoritative body.

- 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 2023a
  - A non-GLP-compliant ready biodegradability test conducted according to ISO 7827 (evaluation in an aqueous medium of the ultimate aerobic biodegradability of organic compounds), which is similar to OECD Guideline 301 A (DOC Die Away test) was performed with an unspecified inoculum system exposed to TEA (purity not specified) at an unspecified concentration for 21 days. The level of degradation was 1% after 7 days, 92% after 14 days, and 96% after 21 days based on the biological oxygen demand (BOD)/chemical oxygen demand (COD) ratio. The study authors concluded that TEA was readily biodegradable in this test (Klimisch 2, reliable with restrictions).
  - A biodegradability test was performed with sludge (no further details specified) exposed to TEA (purity not specified) at 100 mg/L for 28 days. At the end of the exposure period, the level of degradation was 28% based on BOD, 44% based on TOC removal, and 93% based on gas chromatography detection of the degradation product diethylamine (Klimisch 2, reliable with restrictions).
  - An inherent biodegradability test conducted according to OECD Guideline 302 C (Modified MITI test) was performed with non-adapted, activated sludge exposed to TEA (purity not specified) at 30 mg/L for 28 days. At the end of the exposure period, the level of degradation was 25-34% (Klimisch 2, reliable with restrictions).
  - A non-GLP-compliant ready biodegradability test was performed with adapted, industrial activated sludge exposed to TEA (purity not specified) at an unspecified concentration for

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10 days. At the end of the exposure period the level of degradation was 2.9-3.4% (Klimisch 2, reliable with restrictions).
    - *Surrogate: TBA (CAS #102-82-9)*: TBA was readily biodegradable in a GLP-compliant CO_2 evolution test performed according to OECD Guideline 301B, ISO DIS 9439, EPA OPPTS 835.3110, and EU Method C.4-C with non-adapted, domestic activated sludge exposed to TBA (99.54% purity) at 20 mg/L (organic carbon) for 28 days. The level of degradation was -2.5% after 7 days, 24.9% at 9 days, 34.9% at 11 days, 57% at 18 days, and 80.3% at 29 days. At the end of the 10-day window (days 8-18) the degradation was 43% and 71% in the two replicates. The study authors postulate that the low level of degradation in one replicate might have been due to the presence of dissolved carbon dioxide in the flasks. After the addition of HCl to drive off dissolved carbon dioxide, an improved correlation between the replicates was observed. Therefore, they conclude that TBA is readily biodegradable. (Klimisch 1, reliable without restriction).
- OECD 2012
    - OECD concluded that chemicals in the tertiary amines category, including TEA, are readily biodegradable in standard ready biodegradation tests.
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that TEA is not expected to be readily biodegradable. Fugacity modeling predicts 69.9% will partition to soil with a half-life of 75 days, 29.5% will partition to water with a half-life of 37.5 days, 0.487% will partition to air with a half-life of 2.77 hours, and 0.128% will partition to sediment with a half-life of 337.5 days (Appendix N).
- Based on the weight of evidence, a score of Very Low was assigned. TEA was biodegradable in four biodegradability tests including an OECD Guideline 301A study; however, due to insufficient information and variable results, these studies alone were not sufficient to determine readily biodegradable status. Therefore, data on surrogate TBA are presented to support the readily biodegradability of TEA. In an OECD Guideline 301B biodegradability test, surrogate TBA is readily biodegradable based on 88% degradation in 28 days within the 10-day window; however, variability was found between the replicates within the study. The variability in results for TEA and surrogate TBA may be due to the volatility of these chemicals requiring a closed system within study design to reliability examine biodegradability, and neither the DOC die-away test (OECD Guideline 301A) nor the CO_2 Evolution test (OECD Guideline 301B) is a suitable test for volatile compounds (OECD 1992), unless the tests demonstrate the removal of the test substance was not the result of volatilization (OECD 2001). Although neither test provided evidence that the removal was not a result of volatilization, the authors of the ECHA dossier report that the EU (1995) concluded that TEA was readily biodegradable based on these studies. This agrees with OECD's conclusion (OECD 2012). No data were found regarding environmental partitioning. Modeling using the U.S. EPA's EPI Suite™ v 4.11 program (U.S. EPA 2017b) found that TEA will mainly partition to soil at 69.9% with a half-life of 75 days.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

TEA was assigned a score of Very Low for bioaccumulation based on a low measured log K_{ow} of 1.45 and low measured BCF of 0.5. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4 and BCF values are no greater than 100 (CPA 2018b). Confidence in the score is high as it is based on experimental data.

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

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- ECHA 2023a
    - A bioaccumulation study conducted according to OECD Guideline 305C was performed with carp (*Cyprinus carpio*) exposed to TEA (purity not specified) at 0.5 mg/L for 42 days. The measured BCF at the end of the exposure period was less than 0.5 (Klimisch 2, reliable with restrictions).
    - TEA has a log K_{ow} value of 1.45 at an unspecified temperature and pH of 13 as identified in literature (Klimisch 2, reliable with restrictions).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
TEA was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was low as it was not based on an authoritative list or measured data on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
    - The authors of the ECHA dossier reported that TEA was non-explosive and non-oxidizing due to a lack of chemical groups associated with explosive and oxidizing properties, and non-oxidizing on the basis of its chemical structure. Additionally, no evidence of pyrophoric properties was identified by the authors of the ECHA dossier.
    - TEA has an auto-ignition temperature in the range of 215 – 249°C reported by numerous peer-reviewed sources and/or databases (Klimisch 2, reliable with restrictions).
- PubChem 2023a, OSHA 2021
    - Occupational Safety and Health Administration (OSHA) has reported that TEA has a lower and upper explosion limit of 1.2% and 8%, respectively, and an instability rating of 0 from the National Fire Protection Association (NFPA) ("Normally stable, even under fire exposure conditions, and is not reactive with water").
- Millipore Sigma 2023
    - A material safety data sheet for TEA (as tradename: triethylamine, ≤ 100% purity) did not provide data related to explosive properties; however, it does state that TEA vapor/air-mixtures are explosive when mixed with air. Additionally, an upper explosion limit of 9.3% and lower explosion limit of 1.2% were reported for TEA. Furthermore, TEA is stable under recommended storage conditions and storage and handling of TEA should avoid exposure to heat, flames, and sparks.
- NITE 2006, 2016
    - National Institute of Technology (NITE) reports Class 3 Dangerous Goods (DG) packaging group as the rationale for a GHS Not Classified classification for self-heating substances, and corrosivity to metals.
- Based on the weight of evidence, ToxServices identified TEA as not reactive. TEA is not self-heating up to 215°C under standard pressure. It is not expected to be explosive or self-reactive based on chemical structure and an NFPA instability rating of 0. TEA has no reactive functional groups that would make it oxidizing or explosive, and it is not a peroxide. As it is not explosive, it does not require desensitization. It is stable under recommended storage conditions. TEA is a volatile chemical and vapor/air-mixtures when heated increase the risk of explosion of TEA.

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However, this is not typically evaluated under the explosiveness endpoint of GHS. Overall, TEA is GHS Not Classified for reactivity (UN 2021). No data were found regarding corrosivity to metal.

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

TEA was assigned a score of High for flammability based on ToxServices classifying it to GHS Category 2 flammable liquid, and authoritative lists – EU harmonized H225, and U.S. DOT Class 3, Group 2. GreenScreen® criteria classify chemicals as a High hazard for flammability when they are classified as GHS Category 2 flammable liquids (H225) or DOT Class 3, Group 2 (CPA 2018b). The confidence in the score was high as it was based on authoritative lists with support from measured data.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU – GHS (H-Statements) – Flammable liquid and vapor [H225] (Flammable liquids – Category 2).
    - U.S. DOT Hazard Class 3, Group 2.
  - *Screening:*
    - GHS – New Zealand – Flammable liquids – Category 2.
      - Based on a flashpoint of -6.67ºC, and a boiling point of 89ºC (CCID 2023).
    - GHS – Japan – Flammable liquid and vapor [H225] (Flammable liquids – Category 2).
      - Based on a flashpoint of -6.67ºC, a boiling point of 89ºC, and classification to hazard class or division 3 (flammable liquid), packaging group II, and label code 3 (NITE 2016).
    - GHS – Australia – Flammable liquid and vapor [H225] (Flammable liquids – Category 2).
    - GHS – Korea – Flammable liquid and vapor [H225] (Flammable liquids – Category 2).
- ECHA 2023a
  - TEA has a flash point of -11°C as determined in an Abel-Pensky closed cup test conducted in a manner similar to ISO 13736 (1997): Determination of flashpoint for petroleum products and other liquids. This study was reported by numerous peer-reviewed sources. TEA was determined to be a flammable liquid (Klimisch 2, reliable with restrictions).
  - TEA has a boiling point of 90ºC, reported by numerous peer-reviewed sources (Klimisch 2, reliable with restrictions).
  - As previously described, TEA has an auto-ignition temperature in the range of 215-249°C reported by numerous peer-reviewed sources and/or databases (Klimisch 2, reliable with restrictions).
- HSDB 2016, OSHA 2021
  - OSHA has reported that TEA has a flashpoint of 20ºF (equivalent to -6.7ºC) and an NFPA fire rating of 3 ("Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials produce hazardous atmospheres with air under almost all ambient temperatures or, though unaffected by ambient temperatures, are readily ignited under almost all conditions.").
- Millipore Sigma 2023
  - TEA is classified as hazard class or division 3 (flammable liquid), packaging group II, and label code 3.
- Based on the above data, ToxServices classified TEA as a Category 2 flammable liquid under GHS criteria (UN 2021). GHS criteria define Category 2 flammable liquids as chemicals with flash points less than 23°C and an initial boiling point greater than 35°C.

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Use of New Approach Methodologies (NAMs)[9] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 2, Type I (input data) uncertainties in TEA's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. TEA's Type II (extrapolation output) uncertainties include lack of defined applicability domains of Toxtree and OECD QSAR Toolbox in examination of structural alerts, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions and *in vitro* receptor binding activity assays, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of TEA's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: Only limited experimental data are available. **Endocrine activity:** No *in vivo* data for hormone signaling pathways are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). **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[10]. The *in vitro* sister chromatid exchange (SCE) assay (as defined in OECD 479, a

[9] 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).

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

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	guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[11]. **Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays and of *silico* modeling of receptor binding is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OncoLogic/Danish QSAR
Mutagenicity	Y	*In vitro* data: bacterial reverse mutation assay/SCE assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: Danish QSAR; *In vitro* high throughput data: EDSP Tox 21 screening assays
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/Danish QSAR
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD Guidelines 301 A, 301 B, and 302 C Biodegradation tests
Bioaccumulation	N	

[11] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

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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

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APPENDIX B: Results of Automated GreenScreen® Score Calculation for TEA (121-44-8)

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
									S	R *	S	R *	*	*								
Table 2: Chemical Details																						
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	**TEA**	**121-44-8**	*L*	*L*	*M*	*L*	DG	**H**	**M**	**H**	*vH*	*L*	**L**	*L*	**vH**	**vH**	**H**	*M*	**vL**	**vL**	*L*	**H**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
TEA	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
TEA	2

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

Table 5: Data Gap Assessment Table

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

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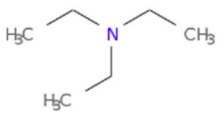
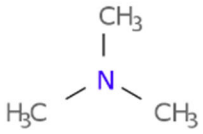
APPENDIX C: MCS Tanimoto Coefficient Output for TEA (CAS #121-44-8)

Compound Similarity

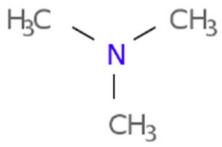
7 compound(s) in workbench

Select two compounds to compare from the grid below.

Selected Compounds

Target: TEA (CAS #121-44-8)	TMA (CAS #75-50-3)
	
remove	remove

AP Tanimoto: 0
MCS Tanimoto: 0.5714
MCS Size: 4
MCS Min: 1.0000
MCS Max: 0.5714
SMILES: N(C)(C)C Target: TEA (CAS #121-44-8)

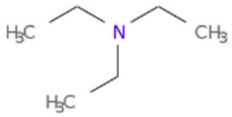
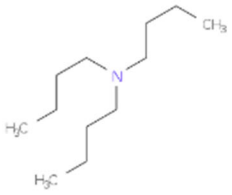


Compound Similarity

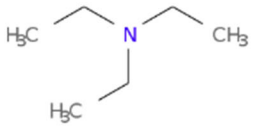
7 compound(s) in workbench

Select two compounds to compare from the grid below.

Selected Compounds

Target: TEA (CAS #121-44-8)	TBA (CAS #102-82-9)
	
remove	remove

AP Tanimoto: 0.137931
MCS Tanimoto: 0.5385
MCS Size: 7
MCS Min: 1.0000
MCS Max: 0.5385
SMILES: N(CC)(CC)CC Target: TEA (CAS #121-44-8)



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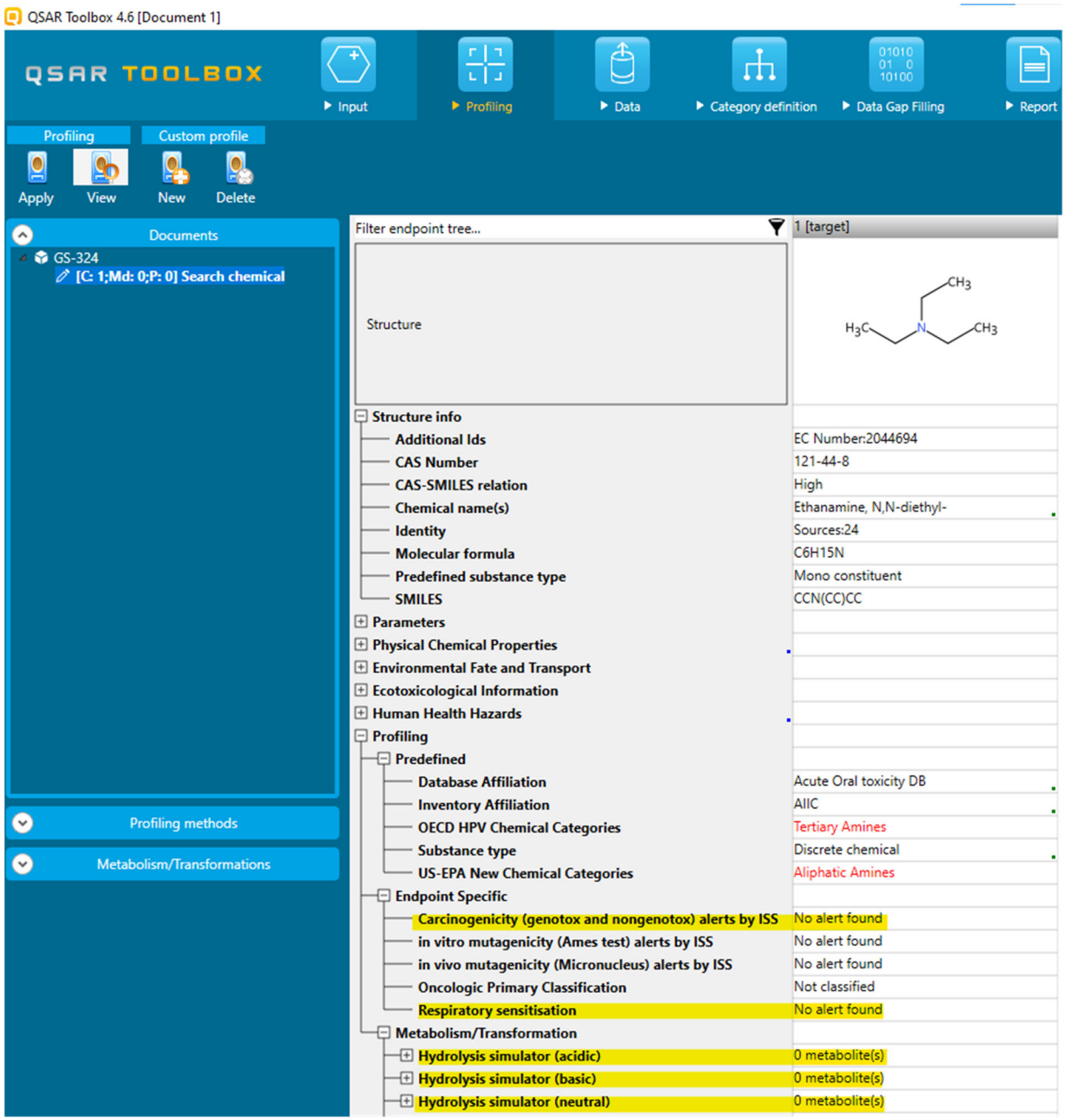
APPENDIX D: OECD Toolbox Profiling Results for TEA (CAS #121-44-8)



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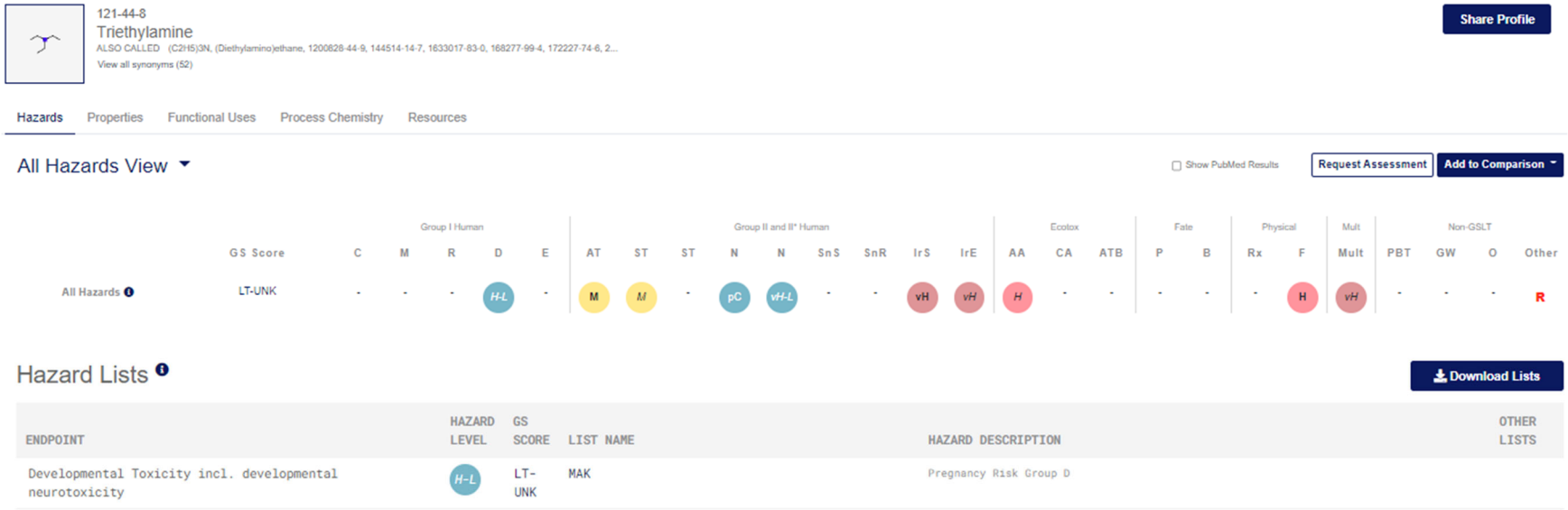
APPENDIX E: Pharos Output for TEA (CAS #121-44-8)



121-44-8
Triethylamine
ALSO CALLED (C2H5)3N, (Diethylamino)ethane, 1200828-44-9, 144514-14-7, 1633017-83-0, 168277-99-4, 172227-74-6, 2...
View all synonyms (52)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

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

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Developmental Toxicity incl. developmental neurotoxicity	H-L	LT-UNK	MAK	Pregnancy Risk Group D	

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Acute Mammalian Toxicity	M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H302 - Harmful if swallowed [Acute toxicity (oral) - Category 4]	+19
	M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H312 - Harmful in contact with skin [Acute toxicity (dermal) - Category 4]	
	M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H332 - Harmful if inhaled [Acute toxicity (inhalation) - Category 4]	
	vH-H	LT-UNK	GHS - Australia	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	H	LT-UNK	GHS - Australia	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	
	H	LT-UNK	GHS - Korea	H311 - Toxic in contact with skin [Acute toxicity (dermal) - Category 3]	
	H	LT-UNK	GHS - Korea	H331 - Toxic if inhaled [Acute toxicity (inhalation) - Category 3]	
	H	LT-UNK	GHS - New Zealand	Acute dermal toxicity category 3	
	H	LT-UNK	GHS - Japan	H311 - Toxic in contact with skin [Acute Toxicity (dermal) - Category 3]	
	M	LT-UNK	GHS - Australia	H302 - Harmful if swallowed [Acute toxicity (oral) - Category 4]	
	M	LT-UNK	GHS - Japan	H302 - Harmful if swallowed [Acute Toxicity (oral) - Category 4]	
	M	LT-UNK	GHS - Japan	H332 - Harmful if inhaled [Acute toxicity (inhalation: vapor) - Category 4]	
	M	LT-UNK	GHS - Korea	H302 - Harmful if swallowed [Acute toxicity (oral) - Category 4]	
	M	LT-UNK	GHS - New Zealand	Acute inhalation toxicity category 4	
	M	LT-UNK	GHS - New Zealand	Acute oral toxicity category 4	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H302 - Harmful if swallowed (unverified) [Acute toxicity (oral) - Category 4]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H311 - Toxic in contact with skin (unverified) [Acute toxicity (dermal) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H312 - Harmful in contact with skin (unverified) [Acute toxicity (dermal) - Category 4]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H331 - Toxic if inhaled (unverified) [Acute toxicity (inhalation) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H332 - Harmful if inhaled (unverified) [Acute toxicity (inhalation) - Category 4]	

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Systemic Toxicity/Organ Effects-Single Exposure	M	LT-UNK	GHS - Australia	H335 - May cause respiratory irritation [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	
Neurotoxicity-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H336 - May cause drowsiness or dizziness (unverified) [Specific target organ toxicity - single exposure; Narcotic effects - Category 3]	
Neurotoxicity-Repeated Exposure	vH-L	LT-UNK	Boyes - Neurotoxicants	Neurotoxic	
Skin Irritation/Corrosivity	vH	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H314 - Causes severe skin burns and eye damage [Skin corrosion/irritation - Category 1A or 1B or 1C]	+5
	vH	LT-UNK	GHS - Australia	H314 - Causes severe skin burns and eye damage [Skin corrosion/irritation - Category 1A or 1B or 1C]	
	vH	LT-UNK	GHS - Japan	H314 - Causes severe skin burns and eye damage [Skin corrosion / irritation - Category 1]	
	vH	LT-UNK	GHS - Korea	H314 - Causes severe skin burns and eye damage [Skin corrosion/irritation - Category 1]	
	vH	LT-UNK	GHS - New Zealand	Skin corrosion category 1B	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H314 - Causes severe skin burns and eye damage (unverified) [Skin corrosion/irritation - Category 1A or 1B or 1C]	
Eye Irritation/Corrosivity	vH	LT-UNK	GHS - Japan	H318 - Causes serious eye damage [Serious eye damage / eye irritation - Category 1]	+2
	vH	LT-UNK	GHS - New Zealand	Serious eye damage category 1	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified) [Serious eye damage/eye irritation - Category 1]	
Acute Aquatic Toxicity	H	LT-UNK	GHS - Japan	H401 - Toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 2]	
Flammability	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	+5
	H	LT-UNK	GHS - Australia	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Japan	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Korea	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H225 - Highly flammable liquid and vapour (unverified) [Flammable liquids - Category 2]	

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Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - Japan	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3]
Systemic Toxicity/Organ Effects [Repeated Exposure] and/or Neurotoxicity [Repeated Exposure]	M	LT-UNK	GHS - Japan	H373 - May cause damage to organs through prolonged or repeated exposure [Specific target organs/systemic toxicity following repeated exposure - Category 2]
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	vH	LT-UNK	GHS - Japan	H370 - Causes damage to organs [Specific target organs/systemic toxicity following single exposure - Category 1]

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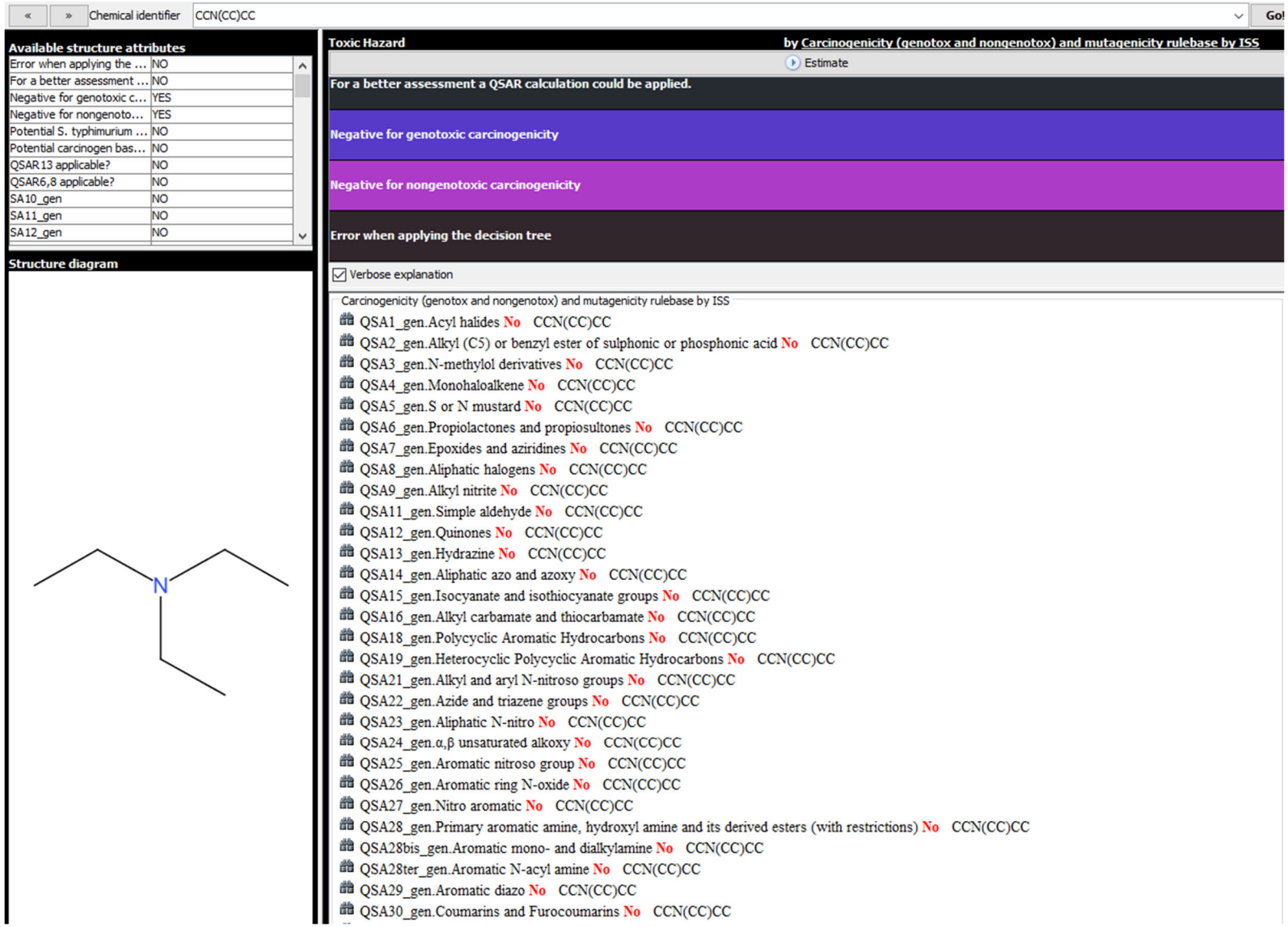
APPENDIX F: Toxtree Carcinogenicity Results for TEA (CAS #121-44-8)



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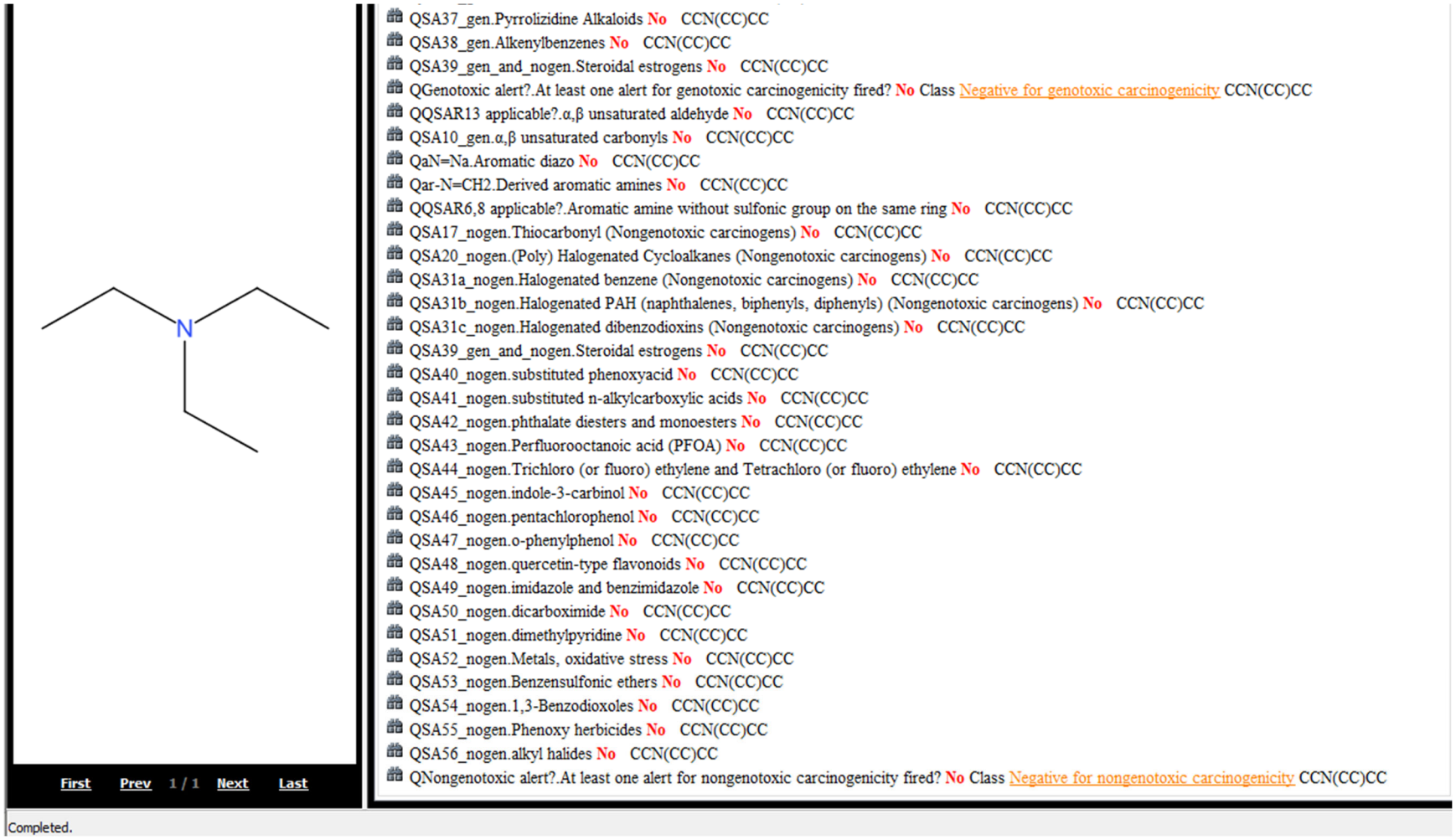

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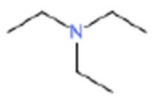
APPENDIX G: VEGA Results for TEA (CAS #121-44-8)

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:
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- predicted substance falls into a neuron that is populated by no compounds of the training set

Compound: Molecule 0
Compound SMILES: N(CC)(CC)CC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.608
P(NON-Carcinogen): 0.392
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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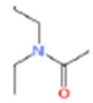
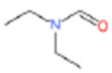
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



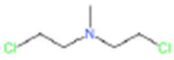
Compound #1

CAS: 685-91-6
Dataset id:238 (Test Set)
SMILES: O=C(N(CC)CC)C
Similarity: 0.846
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #2

CAS: 617-84-5
Dataset id:241 (Training Set)
SMILES: O=CN(CC)CC
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

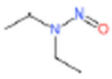


Compound #3

CAS: 51-75-2
Dataset id:530 (Test Set)
SMILES: N(C)(CCCl)CCCl
Similarity: 0.783
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #4

CAS: 127-19-5
Dataset id:269 (Training Set)
SMILES: O=C(N(C)C)C
Similarity: 0.756
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 55-18-5
Dataset id:580 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #6

CAS: 111-68-2
Dataset id:357 (Test Set)
SMILES: NCCCCCCC
Similarity: 0.743
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.385 Explanation: The predicted compound is outside the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.832 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✔	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
⚠	Concordance for similar molecules Concordance index = 0.51 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✔	Model class assignment reliability Pos/Non-Pos difference = 0.217 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.

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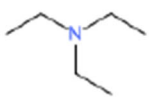
1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: N(CC)(CC)CC
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

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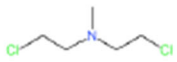
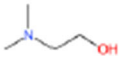
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

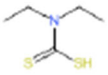
CAS: 51-75-2
Dataset id:292 (Training Set)
SMILES: N(C)(CCCl)CCCl
Similarity: 0.783
Experimental value : Carcinogen
Predicted value : Carcinogen

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



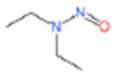
Compound #2

CAS: 108-01-0
Dataset id:875 (Training Set)
SMILES: OCCN(C)C
Similarity: 0.78
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #3

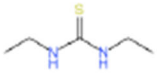
CAS: 148-18-5
Dataset id:741 (Training Set)
SMILES: CCN(C(=S)S)CC
Similarity: 0.757
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #4

CAS: 55-18-5
Dataset id:516 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen

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



Compound #5

CAS: 105-55-5
Dataset id:182 (Training Set)
SMILES: N(C(NCC)=S)CC
Similarity: 0.734
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA17 Thiocarbonyl (Nongenotoxic carcinogens)

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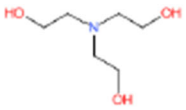
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #6

CAS: 102-71-6
Dataset id:652 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.728
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.743
Explanation: The predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.781
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 = 0.499
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.

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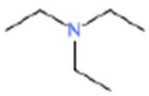
1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: N(CC)(CC)CC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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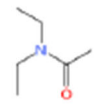
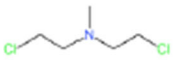
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

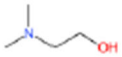
CAS: 685-91-6
Dataset id:820 (Training Set)
SMILES: O=C(N(CC)CC)C
Similarity: 0.846
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

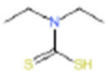
CAS: 51-75-2
Dataset id:235 (Training Set)
SMILES: N(C)(CCCl)CCCl
Similarity: 0.783
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 11



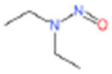
Compound #3

CAS: 108-01-0
Dataset id:776 (Training Set)
SMILES: OCCN(C)C
Similarity: 0.78
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

CAS: 148-18-5
Dataset id:576 (Training Set)
SMILES: C(N(CC)CC)(=S)S
Similarity: 0.757
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 55-18-5
Dataset id:428 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen

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

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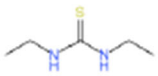
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #6

CAS: 105-55-5
Dataset id:147 (Training Set)
SMILES: N(C(NCC)=S)CC
Similarity: 0.734
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.603 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.8 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.644 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0.321 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.

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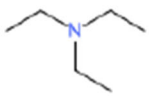
1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: N(CC)(CC)CC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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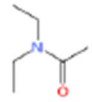
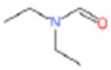
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



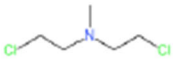
Compound #1

CAS: 685-91-6
Dataset id:238 (Test Set)
SMILES: O=C(N(CC)CC)C
Similarity: 0.846
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

CAS: 617-84-5
Dataset id:241 (Training Set)
SMILES: O=CN(CC)CC
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



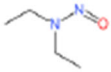
Compound #3

CAS: 51-75-2
Dataset id:530 (Test Set)
SMILES: N(C)(CCCl)CCCl
Similarity: 0.783
Experimental value : Carcinogen
Predicted value : Carcinogen

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

Compound #4

CAS: 127-19-5
Dataset id:269 (Training Set)
SMILES: O=C(N(C)C)C
Similarity: 0.756
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 55-18-5
Dataset id:580 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 8; Carcinogenity alert no. 50; Carcinogenity alert no. 55; Carcinogenity alert no. 63

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

Compound #6

CAS: 111-68-2
Dataset id:357 (Test Set)
SMILES: NCCCCCCC
Similarity: 0.743
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.616
Explanation: The predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.813
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 0.651
Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..

Concordance for similar molecules
Concordance index = 0.335
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.

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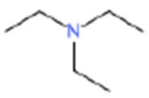
1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).

Compound: Molecule 0
Compound SMILES: N(CC)(CC)CC
Experimental value: NON-Carcinogen
Predicted Oral Carcinogenic class: Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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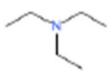
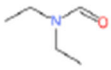
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



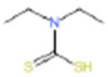
Compound #1

CAS: 121-44-8
Dataset id:726 (Training Set)
SMILES: N(CC)(CC)CC
Similarity: 1
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



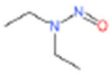
Compound #2

CAS: 617-84-5
Dataset id:455 (Test Set)
SMILES: O=CN(CC)CC
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



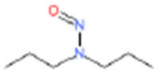
Compound #3

CAS: 148-18-5
Dataset id:275 (Training Set)
SMILES: C(N(CC)CC)(=S)S
Similarity: 0.757
Experimental value : Carcinogen
Predicted value : Carcinogen



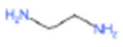
Compound #4

CAS: 55-18-5
Dataset id:222 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 621-64-7
Dataset id:225 (Training Set)
SMILES: O=NN(CCC)CCC
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 107-15-3
Dataset id:507 (Training Set)
SMILES: NCCN
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

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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 = 1 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✖	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..
✔	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.

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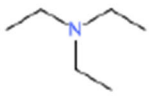
1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is NON-Carcinogen (GOOD reliability).

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

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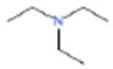
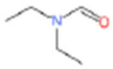
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



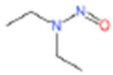
Compound #1

CAS: 121-44-8
Dataset id:726 (Training Set)
SMILES: N(CC)(CC)CC
Similarity: 1
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



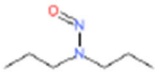
Compound #2

CAS: 617-84-5
Dataset id:422 (Training Set)
SMILES: O=CN(CC)CC
Similarity: 0.819
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #3

CAS: 55-18-5
Dataset id:195 (Training Set)
SMILES: O=NN(CC)CC
Similarity: 0.754
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #4

CAS: 621-64-7
Dataset id:193 (Test Set)
SMILES: O=NN(CCC)CCC
Similarity: 0.722
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #5

CAS: 107-15-3
Dataset id:480 (Test Set)
SMILES: NCCN
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #6

CAS: 1634-04-4
Dataset id:161 (Training Set)
SMILES: O(C)C(C)(C)C
Similarity: 0.713
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Symbols explanation:

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

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

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

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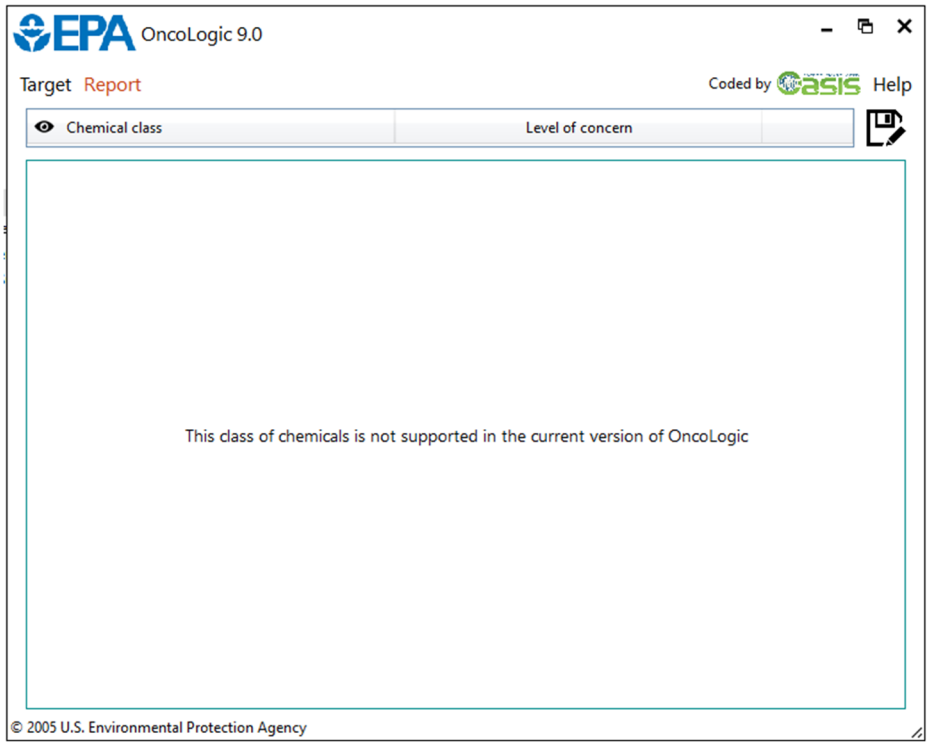
APPENDIX H: Oncologic Results for TEA (CAS #121-44-8)



OncoLogic Justification Report

CODE NUMBER: CF142

SUBSTANCE ID:

Final level of concern for this compound is LOW(*).

(*) Caution: Functional arm should be used if short term prediction test data are available

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APPENDIX I: Danish QSAR Carcinogenicity Results for TEA (CAS #121-44-8)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_IN	INC_OUT
FDA RCA Cancer Female Rat	NEG_IN	INC_OUT
FDA RCA Cancer Rat	NEG_IN	INC_OUT
FDA RCA Cancer Male Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Female Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Rodent	NEG_IN	INC_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	Not classified

OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

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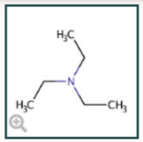
APPENDIX J: CompTox EDSP21 Results for TEA (CAS #121-44-8)



Triethylamine

121-44-8 | DTXSID3024366

Searched by DTXSID3024366.

Concentration Response Data

Analytical Data on Tox21 Browser

EXPORT

Name	Description	Endpoint Name	Active	Details	Rep. Plot	All Plots	Gene	Intended Target	Cell Line	Cell Format
(4) EDSP AR,EDSP ER,EDSP ster										
EDSP AR	Androgen receptor assays use...	ATG_AR_TRANS_up	Inactive				AR	steroidal	liver	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Agonist_ratio	Inactive				AR	steroidal	kidney	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Antagonist_ratio	Inactive				AR	steroidal	kidney	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Antagonist_viability	Inactive				-	cytotoxicity	kidney	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Agonist	Inactive				AR	steroidal	breast	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_...	Inactive				AR	steroidal	breast	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_...	Inactive				-	cytotoxicity	breast	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_10nM_R...	Inactive				AR	steroidal	breast	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_10nM_R...	Inactive				-	cytotoxicity	breast	cell line
EDSP ER	Estrogen receptor assays used...	ATG_ERa_TRANS_up	Inactive				ESR1	steroidal	liver	cell line
EDSP ER	Estrogen receptor assays used...	ATG_ERE_CIS_up	Inactive				ESR1	steroidal	liver	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_BLA_Agonist_ratio	Inactive				ESR1	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_BLA_Antagonist_ratio	Inactive				ESR1	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_BLA_Antagonist_viability	Inactive				-	cytotoxicity	kidney	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_LUC_VM7_Agonist	Inactive				ESR1	steroidal	ovary	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_LUC_VM7_Antagonist_0.5nM_E2	Inactive				ESR1	steroidal	ovary	cell line
EDSP ER	Estrogen receptor assays used...	TOX21_ERa_LUC_VM7_Antagonist_0.5nM_E2_...	Inactive				-	cytotoxicity	ovary	cell line
EDSP steroidogenesis	Steroidogenesis pathway assa...	TOX21_Aromatase_Inhibition	Inactive				CYP19A1	steroidogenesis-rela	breast	cell line
EDSP steroidogenesis	Steroidogenesis pathway assa...	TOX21_Aromatase_Inhibition_viability	Inactive				-	cytotoxicity	breast	cell line

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☐	EDSP thyroid	Thyroid pathway assays used i...	ATG_THRa1_TRANS_dn	Inactive				THRA	non-steroidal	liver	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	ATG_THRa1_TRANS_up	Inactive				THRA	non-steroidal	liver	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TRHR_HEK293_Agonist	Inactive				TRHR	thyrotropin-releasing	kidney	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TRHR_HEK293_Antagonist	Inactive				TRHR	thyrotropin-releasing	kidney	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Agonist	Inactive				THRA	non-steroidal	pituitary gland	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Antagonist	Inactive				THRA	non-steroidal	pituitary gland	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Antagonist_viability	Inactive				-	cytotoxicity	pituitary gland	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_Agonist_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_Antagonist_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line
☐	EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_wt_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line

Rows: **29 of 434** Total Rows: **434** Filtered: **29**

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APPENDIX K: Danish QSAR Endocrine Results for TEA (CAS #121-44-8)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	INC_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L		8110.203	16185.93	1027.537	34.47764
- µM		80148.26	159955.8	10154.53	340.7218
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		IN	IN	OUT	IN
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L		1710.794	3274.446	12.53596	147.1423
- µM		16906.75	32359.38	123.8854	1454.119
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		IN	IN	OUT	IN

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Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_OUT	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
(CAR) Activation at max. 50 µM (*in vitro*)					
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)	NEG	N/A	N/A	NEG_IN	N/A

DTU-developed models

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

OECD QSAR Toolbox v.4.2 profilers

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

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APPENDIX L: Danish QSAR Sensitization Results for TEA (CAS #121-44-8)

Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit	POS	POS_IN	POS_IN	POS_IN	POS_IN
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data only)				POS_IN	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data and REACH-registrations)	N/A			INC_OUT	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based, only negative predictions (open data only)				N/A	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based, only positive predictions (open data and REACH-registrations)	N/A			N/A	
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	INC_OUT	POS_OUT	POS_IN	NEG_IN
Respiratory Sensitisation in Humans		NEG_OUT	POS_OUT	POS_OUT	NEG_IN

DTU-developed models

**Based on commercial training set*

Protein binding by OASIS, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	Aldehydes
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	No alert found

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- metabolites from skin metabolism simulator only	Mono-carbonyls
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert
- metabolites from skin metabolism simulator only	DPRA above 21% (DPRA 13%) >> Non-Conjugated monoaldehydes (reactive); DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Non-alpha,beta-conjugated monoaldehydes (non reactive); DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive); Grey zone 9-21% (DPRA 13%) >> Non-alpha,beta-conjugated monoaldehydes (Grey zone)
- metabolites from auto-oxidation simulator only	
Keratinocyte gene expression, alerts in:	
- parent only	Not possible to classify according to these rules
- metabolites from skin metabolism simulator only	High gene expression >> Non-conjugated aldehydes and dialdehydes; Moderate gene expression >> Fragrance aldehydes
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	Not possible to classify according to these rules (GSH)

OECD QSAR Toolbox v.4.1 profilers

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

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APPENDIX M: ECOSAR Modeling Results for TEA (CAS #121-44-8)

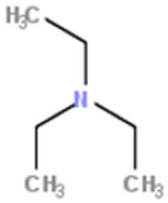
Created on May 26, 2023 11:02:21 AM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
121448	Ethanamine, N,N-diethyl-	N(CC)(CC)CC

Structure



Details	
Mol Wt	101.19
Selected LogKow	1.45
Selected Water Solubility (mg/L)	68600
Selected Melting Point (°C)	-114.7
Estimated LogKow	1.51
Estimated Water Solubility (mg/L)	67050.92
Measured LogKow	1.45
Measured Water Solubility (mg/L)	68600
Measured Melting Point (°C)	-114.7

Class Results:	

Aliphatic Amines

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	44.67	5	
Daphnid	48h	LC50	4.99	5	
Green Algae	96h	EC50	4.68	6.4	
Fish		ChV	3.16	8	
Daphnid		ChV	0.39	8	
Green Algae		ChV	1.48	8	

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APPENDIX N: EPI Suite™ Modeling Results for TEA (CAS #121-44-8)

(Estimations Used for Hazard Classification Are Highlighted and Bolded)

CAS Number: 000121-44-8
SMILES : N(CC)(CC)CC
CHEM : TRIETHYLAMINE
MOL FOR: C6 H15 N1
MOL WT : 101.19
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 1.45
Boiling Point (deg C) : 89.30
Melting Point (deg C) : -114.70
Vapor Pressure (mm Hg) : 57.1
Water Solubility (mg/L): 68600
Henry LC (atm-m3/mole) : 0.000149

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.51
Log Kow (Exper. database match) = 1.45
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 95.48 (Adapted Stein & Brown method)
Melting Pt (deg C): -70.61 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 59.1 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 7.88E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): -114.7 deg C
BP (exp database): 89.3 deg C
VP (exp database): 5.71E+01 mm Hg (7.61E+003 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 6.705e+004
log Kow used: 1.45 (user entered)
melt pt used: -114.70 deg C
Water Sol (Exper. database match) = 6.86e+004 mg/L (25 deg C)
Exper. Ref: YALKOWSKY,SH & HE,Y (2003)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 44037 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 8.54E-005 atm-m3/mole (8.66E+000 Pa-m3/mole)
Group Method: 2.23E-004 atm-m3/mole (2.26E+001 Pa-m3/mole)

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Exper Database: 1.49E-04 atm-m3/mole (1.51E+001 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: 1.490E-004 atm-m3/mole (1.510E+001 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.108E-004 atm-m3/mole (1.123E+001 Pa-m3/mole)
VP: 57.1 mm Hg (source: User-Entered)
WS: 6.86E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.45 (user entered)
Log Kaw used: -2.215 (user entered)
Log Koa (KOAWIN v1.10 estimate): 3.665
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.4941
Biowin2 (Non-Linear Model) : 0.3427
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.7207 (weeks-months)
Biowin4 (Primary Survey Model) : 3.4137 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4201
Biowin6 (MITI Non-Linear Model): 0.4154
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.3995
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): 7.61E+003 Pa (57.1 mm Hg)
Log Koa (Koawin est): 3.665
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 3.94E-010
Octanol/air (Koa) model: 1.14E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.42E-008
Mackay model : 3.15E-008
Octanol/air (Koa) model: 9.08E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 92.5604 E-12 cm3/molecule-sec
Half-Life = 0.116 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 1.387 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

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2.29E-008 (Junge-Pankow, Mackay avg)
9.08E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 50.81 L/kg (MCI method)
Log Koc: 1.706 (MCI method)
Koc : 45.9 L/kg (Kow method)
Log Koc: 1.662 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.624 (BCF = 4.204 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.3260 days (HL = 0.04721 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.430 (BCF = 2.689)
Log BAF Arnot-Gobas method (upper trophic) = 0.430 (BAF = 2.689)
log Kow used: 1.45 (user entered)

Volatilization from Water:
Henry LC: 0.000149 atm-m3/mole (entered by user)
Half-Life from Model River: 4.979 hours
Half-Life from Model Lake : 138.7 hours (5.778 days)

Removal In Wastewater Treatment:
Total removal: 8.74 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 percent
Total to Air: 6.89 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.487**	**2.77**	**1000**
Water	**29.5**	**900**	**1000**
Soil	**69.9**	**1.8e+003**	**1000**
Sediment	**0.128**	**8.1e+003**	**0**

Persistence Time: 486 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.487	2.77	1000
Water	29.5	900	1000
water	(29.5)		
biota	(4.16e-005)		
suspended sediment	(0.00225)		

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Soil	69.9	1.8e+003	1000
Sediment	0.128	8.1e+003	0

Persistence Time: 486 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.795	2.77	1000
Water	46.4	900	1000
water	(46.4)		
biota	(6.53e-005)		
suspended sediment	(0.000804)		
Soil	52.7	1.8e+003	1000
Sediment	0.114	8.1e+003	0

Persistence Time: 324 hr

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APPENDIX O: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for TEA. The GreenScreen® Benchmark Score for TEA has not changed over time. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria, and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017 and a version 1.4 update in the current report. However, the scores for several endpoints were changed due to the use of additional surrogates and re-evaluation of the weight of evidence: the reproductive toxicity score from *Low* (low confidence) to *Moderate* (low confidence), the single exposure systemic toxicity endpoint from **Very High** (high confidence) to **Moderate** (high confidence), the repeated exposure neurotoxicity endpoint from Data Gap to *Low* (low confidence), and the persistence endpoint from *High* (low confidence) to **Very Low** (high confidence). Additionally, confidence levels for a few endpoints were changed.

Table 5: Change in GreenScreen® Benchmark™ for TEA

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
August 18, 2014	BM-2	v. 1.2	Non-verified, original report.
August 15, 2017	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template.
June 15, 2023	BM-2	v. 1.4	BM-2 score was maintained; however, there was a reclassification of the mutagenicity endpoint from **Low** (high confidence) to *Low* (low confidence), the reproductive toxicity endpoint from *Low* (low confidence) to *Moderate* (low confidence), the developmental toxicity endpoint from **Low** (high confidence) to *Low* (low confidence), the single exposure systemic toxicity endpoint from **Very High** (high confidence) to **Moderate** (high confidence), the repeated exposure neurotoxicity endpoint from Data Gap to *Low* (low confidence), chronic aquatic toxicity endpoint from **Moderate** (high confidence) to *Moderate* (low confidence), and the persistence endpoint from *High* (low confidence) to **Very Low** (high confidence).

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