Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

triethylamine

EC Number: 204-469-4
CAS Number: 121-44-8

CLH-O-0000007001-91-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

10 June 2021

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

triethylamine

EC Number: **204-469-4**

CAS Number: **121-44-8**

Index Number: **612-004-00-5**

Contact details for dossier submitter:

Environment Agency Austria, Spittelauer Lände 5, A-1090 Vienna

on behalf of the Austrian Competent Authority (Austrian Federal Ministry for Sustainability and Tourism, Stubenring 1, 1010 Vienna, Austria)

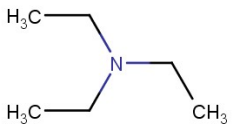
Version number: 02 **Date: December 2019**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	N,N-diethylethanamine
Other names (usual name, trade name, abbreviation)	Triethylamine Diethylaminoethane Diethylethanamine
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	204-469-4
EC name (if available and appropriate)	Triethylamine
CAS number (if available)	121-44-8
Other identity code (if available)	RTECS Number: YE0175000 FEMA Number: 4246 ICSC Number: 0203 UN Number: 1296 PubChem CID: 8471
Molecular formula	$C_6H_{15}N$
Structural formula	 **(source:** European Chemicals Agency, http://echa.europa.eu/**)**
SMILES notation (if available)	CCN(CC)CC
Molecular weight or molecular weight range	101.193 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 80 wt %

1.2 Composition of the substance

Triethylamine is a mono-constituent substance.

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Triethylamine (EC 204-469-4)	Not applicable	Flam. Liq. 2; H225 Acute Tox. 4*; H302 Acute Tox. 4*; H312 Acute Tox. 4*; H332 Skin Corr. 1A; H314 STOT SE 3; H335: C ≥ 1%	Flam. Liq. 2; H225 Acute Tox. 4; H302 Acute Tox. 3; H311 Acute Tox. 3; H331 Skin Corr. 1A; H314 STOT SE 3; H335

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No data available				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No data available					

Table 5: Test substances (non-confidential information)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
The test substance is triethylamine in all studies where the test substance was explicitly stated. If available, the purity is given in the study records below.				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Current and proposed classification and labelling

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	612-004-00-5	triethylamine	204-469-4	121-44-8	Flam. Liq. 2 Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * Skin Corr. 1A	H225 H332 H312 H302 H314	GHS02 GHS05 GHS07 Dgr	H225 H332 H312 H302 H314		STOT SE 3; H335: C ≥ 1%	
Dossier submitters proposal	612-004-00-5	triethylamine	204-469-4	121-44-8	**Modify** Acute Tox. 3 Acute Tox. 3 Acute Tox. 4 Eye Dam 1 **Retain** Flam. Liq. 2 Skin Corr. 1A	**Modify** H331 H311 H302 H318 **Retain** H225 H314	**Modify** GHS06 **Retain** GHS02 GHS05 Dgr	**Modify** H331 H311 **Retain** H225 H302 H314		**Add** Oral: ATE = 500 mg/kg Dermal: ATE = 420 mg/kg Inhal: ATE = 7.2 mg/L **Retain** STOT SE 3; H335: C ≥ 1%	
Resulting Annex VI entry if agreed by RAC and COM	612-004-00-5	triethylamine	204-469-4	121-44-8	Flam. Liq. 2 Acute Tox. 3 Acute Tox. 3 Acute Tox. 4 Skin Corr. 1A Eye Dam 1	H225 H331 H311 H302 H314 H318	GHS02 GHS05 GHS06 Dgr	H225 H331 H311 H302 H314		Oral: ATE = 500 mg/kg Dermal: ATE = 420 mg/kg Inhal: ATE = 7.2 mg/L STOT SE 3; H335: C ≥ 1%	

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*Hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*Hazard class not assessed in this dossier*	No
Oxidising gases	*Hazard class not assessed in this dossier*	No
Gases under pressure	*Hazard class not assessed in this dossier*	No
Flammable liquids	*Hazard class not assessed in this dossier*	No
Flammable solids	*Hazard class not assessed in this dossier*	No
Self-reactive substances	*Hazard class not assessed in this dossier*	No
Pyrophoric liquids	*Hazard class not assessed in this dossier*	No
Pyrophoric solids	*Hazard class not assessed in this dossier*	No
Self-heating substances	*Hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*Hazard class not assessed in this dossier*	No
Oxidising liquids	*Hazard class not assessed in this dossier*	No
Oxidising solids	*Hazard class not assessed in this dossier*	No
Organic peroxides	*Hazard class not assessed in this dossier*	No
Corrosive to metals	*Hazard class not assessed in this dossier*	No
Acute toxicity via oral route	Acute Tox 4; H302	Yes
Acute toxicity via dermal route	Acute Tox 3, H311	Yes
Acute toxicity via inhalation route	Acute Tox 3; H331	Yes
Skin corrosion/irritation	*Hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	Eye Dam 1, H318	Yes
Respiratory sensitisation	*Hazard class not assessed in this dossier*	No
Skin sensitisation	*Hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*Hazard class not assessed in this dossier*	No
Carcinogenicity	*Hazard class not assessed in this dossier*	No
Reproductive toxicity	*Hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	*Hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*Hazard class not assessed in this dossier*	No
Aspiration hazard	*Hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*Hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*Hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Triethylamine had a harmonized classification under the Dangerous Substances Directive (67/548/EEC). This was translated to a harmonized CLP classification in Annex VI to Regulation (EC) No 1272/2008 (CLP Regulation) and the minimum classification (according Annex VII) was applied to acute toxicity for all routes (marked as Acute Tox. 4 * for all routes).

The currents harmonized classification (Annex VI, table 3.1) for triethylamine is:

Flam. Liq. 2; H225

Acute Tox. 4*; H302

Acute Tox. 4*; H312

Acute Tox. 4*; H332

Skin Corr. 1A; H314

STOT SE 3; H335: C ≥ 1%

The frequency of hazard classifications among all C&L notifications (occurring in at least 10% of notifications) was retrieved from ECHA dissemination site [accessed 12/2020] and is given below. In total 5840 companies provided notifications with hazard classifications (62 aggregated notifications). Two companies reported triethylamine as not classified.

Hazard classifications occurring in at least 10% of notifications:

Hazard code	Hazard statement	% of notifications
H314	Causes severe skin burns and eye damage	100
H225	Highly Flammable liquid and vapour	100
H302	Harmful if swallowed	100
H311	Toxic in contact with skin	50.6
H312	Harmful in contact with skin	49.3
H318	Causes serious eye damage	47.3
H331	Toxic if inhaled	49.2
H332	Harmful if inhaled	49.7
H335	May cause respiratory irritation	50.4

RAC general comment

Triethylamine is manufactured and/or imported in the European Economic Area in quantities of 10 000 - 100 000 tonnes per year. It is used in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

- Change in existing entry due to changes in the criteria (translation from DSD to CLP)
- Disagreement by DS with current self-classification

Further detail on need of action at Community level

There is a harmonised classification entry in Annex VI to CLP containing a minimum classification (*) and it is concluded that a refinement of the classification based on available data is justified. Differences in self-classification between different notifiers in the C&L Inventory and registration dossiers are discovered.

Triethylamine is an important industrial chemical. A correct classification for acute toxicity is essential to minimize uncertainties in classification along the supply chain and to ensure a high level of protection of workers by setting the right risk management measures.

5 IDENTIFIED USES

Triethylamine is manufactured and/or imported in the European Economic Area in 10 000 - 100 000 tonnes per year. It is used in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing (see Table 8 for details) (ECHA Dissemination site, 2019).

Table 8: Registered uses of triethylamine (according to ECHA dissemination site, 2019)

Formulation	Use as processing aid (catalyst) in polymerisation
	Formulaton of preparations
	Distribution
Uses at industrial sites	Use in Coatings (paint, ink, toners, adhesives)
	Use as processing aid (catalyst)
	Use in Foundry
	Mining chemicals
	Use in paper, textile and leather production
	Use as intermediate
	Use in gas treatment
	Industrial use resulting in manufacture of another substance
	Industrial spraying
Uses by professional workers	Use in Coatings (paint, ink, toners, adhesives), professional
	Formulation of preparations

	Production and use of coatings
	Use in gas treatment
	Use in foundry
	Laboratory use
	Use as a reactant
	Mining chemicals
Article service life	Leather articles

6 DATA SOURCES

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov[1]
- TOXNET[2], ChemID*plus*[3], IPCS[4], eChemPortal[5], EPA Comptox Dashboard[6], EPA Chemview[7]
- Chemical Abstracts, Medline, Biosis, Embase, SciSearch, PQScitech (at host STN International Europe[8])

in addition to unspecific databases (e.g., *google scholar*).

The REACH registration dossier for triethylamine, available from ECHA's disseminated database (2019) has been analysed for study references, which then have been considered as data sources for this CLH report.

Relevant reviews and monographs with toxicological risk assessments on triethylamine were analysed for study references. Used reviews are Greim (1996), ACGIH (2001), NTP (1998), NTP (2018).

Whenever secondary sources were encountered, it was attempted to retrieve the respective primary sources.

[1] https://www.ncbi.nlm.nih.gov/pubmed assessed at 7.2.2019
[2] https://toxnet.nlm.nih.gov/ assessed at 7.2.2019
[3] https://chem.nlm.nih.gov/chemidplus/ assessed at 7.2.2019
[4] http://www.inchem.org/ assessed at 7.2.2019
[5] http://www.echemportal.org/echemportal/page.action?pageID=9 assessed at 7.2.2019
[6] https://comptox.epa.gov/dashboard/
[7] https://chemview.epa.gov/chemview
[8] http://www.stn-international.de/index.php?id=123 assessed at 13.2.2019

7 PHYSICOCHEMICAL PROPERTIES

Table 9: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	Liquid	(ECHA Dissemination, 2019)	WoE approach, measured at 20 °C and 1013.25 hPa
Melting/freezing point	-115 °C	(ECHA Dissemination, 2019)	Measured, at 1013.25 hPa
Boiling point	90 °C	(ECHA Dissemination, 2019)	Measured, at 1013.25 hPa
Density	0.73 g/cm³	(ECHA Dissemination, 2019)	WoE approach, measured, no temperature given
Vapour pressure	72 hPa	(ECHA Dissemination, 2019)	Measured, at 20 °C
Surface tension	20.05 mN/m	(ECHA Dissemination, 2019)	WoE approach, measured at 25 °C
Water solubility	112400 mg/L	(ECHA Dissemination, 2019)	Measured, at 20 °C
Partition coefficient n-octanol/water	1.45	(ECHA Dissemination, 2019)	Measured, at pH 13
Flash point	-11 °C	(ECHA Dissemination, 2019)	WoE approach, measured at 1013.25 hPa
Flammability	Flammable	(ECHA Dissemination, 2019)	WoE approach
Explosive properties	Non explosive	(ECHA Dissemination, 2019)	WoE approach
Self-ignition temperature	215 °C	(ECHA Dissemination, 2019)	WoE approach, measured, lowest of 3 different experimental values
Oxidising properties	No oxidising properties	(ECHA Dissemination, 2019)	Estimated, based on chemical structure
Granulometry	Not applicable		
Stability in organic solvents and identity of relevant degradation products	No data	(ECHA Dissemination, 2019)	
Dissociation constant	10.75 (pKa)	(ECHA Dissemination, 2019)	WoE approach, measured, medium of 3 different experimental values, at 25 °C
Viscosity	0.363 mPa*s	(ECHA Dissemination, 2019)	WoE approach, average of 3 different experimental values, at 25 °C

8 EVALUATION OF PHYSICAL HAZARDS

Not performed for this substance.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not performed for this substance.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

For the evaluation of this endpoint 11 studies are available. Each study is reliable with restrictions as the reporting is limited.

Table 10: Summary table of animal studies on acute oral toxicity

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (REACH registration): 2, key study Reliability (this assessment): 3	Rat, strain not specified 5 animals (male + female) per dose group, male/female ratio not specified	Triethylamine Impurities: up to 1% diethylamine, No further information on purity No information on source	As 10% in vehicle: 230, 366, 580, 929 mg/kg bw Further test series: As 1%: 15, 58 mg/kg bw As 20%: 3660 mg/kg bw As 100%: 929, 3660 mg/kg bw Single application via gavage Unknown if vehicle was water or olive oil (inconsistent statements in dossier regarding used vehicle) No information on fasting before treatment 7 days post-exposure	730 mg/kg bw no confidence interval or information on statistical method provided Mortalities, 10% in vehicle: 929 mg/kg: 3/5 580 mg/kg: 0/5 366 mg/kg: 0/5 230 mg/kg: 0/5 Mortalities, 100%: 3660 mg/kg: 1/1 929 mg/kg: 1/1 Mortalities, 1% in vehicle: 58 mg/kg: 0/1 15 mg/kg: 0/1	BASF AG (1960) [Study 001, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
			observation		
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (REACH registration): 2 Reliability (this assessment): 3	Rat, Wistar 5 males per dose	Triethylamine Source: Production quality samples from Union Carbide Corporation No information on purity	As 100%: 0.25, 0.5, 1.0 mL/kg bw As 10%: 0.5, 1.0, 2.0 mL/kg bw Vehicle: water Animals were not fasted prior to exposure 14 days post-exposure observation	1030 mg/kg bw reported as 1.41 mL/kg bw (95% CI: 1.03-1.95) mortalities (100%): 0.25 mL/kg: 3/5 0.5 mL/kg: 4/5 1.0 mL/kg: 5/5 mortalities (10% in vehicle): 0.5 mL/kg: 0/5 1.0 mL/kg: 0/5 2.0 mL/kg: 5/5	Primary source: Myers and Ballantyne (1997) [Study 004, REACH registration]
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (this assessment): 3	Rat, strain not specified 10 male and 10 female per dose group	Triethylamine, Technical purity, without further information on purity Source: Former VEB Synthesewerk Schwarzheide (today BASF Schwarzheide GmbH)	Several dose levels tested (males: 5, females: 6), doses not specified Single application via gavage 18 h fasting period prior to treatment Variable concentration in vehicle (peanut oil): constant volume 5 mL/kg 14 days post-exposure observation	male: 590 mg/kg bw (95% CI: 539 – 645 mg/kg bw) female: 560 mg/kg bw (95% CI: 530 – 592 mg/kg bw) No results on individual dose groups given	Schmidt et al. (1974)
Acute oral toxicity Not similar to guideline GLP: no Reliability (REACH registration): 2 &	Rabbit, strain not specified 2 animals per dose group, sex not specified	Triethylamine No information on purity No information on source	370, 730, 1460 mg/kg bw Single application via gavage Concentration in vehicle (olive oil): 10%	> 370 mg/kg bw & < 1460 mg/kg bw	Primary source: unnamed study report (1960) [Study 002, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
3 Reliability (this assessment): 3					*study record 002 and 011 in the registration dossier is the same study (same confidential study report)*
Acute oral toxicity Not similar to guideline GLP: no Reliability (REACH registration): 2 Reliability (this assessment): 3	Cat, strain not specified 2 females per dose group	Triethylamine Impurities: up to 1% diethylamine No further information on purity No information on source	370, 730 mg/kg bw Single application via gavage Concentration in vehicle (olive oil): 5% and 10%	> 370 mg/kg bw & < 730 mg/kg bw	Primary source: unnamed study report (1960) [Study 003, REACH registration]
Acute oral toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 3	Cat, strain not specified 2 animals per group, sex not specified	No information given (name, source, purity)	At least 365, 730 mg/kg bw No further information	> 365 mg/kg bw & < 730 mg/kg bw	Primary source: unnamed study report (1960) [Study 010, REACH registration]
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (REACH registration): 2 & 4 (lower reliability is from secondary sources of the same study) Reliability (this assessment): 3	Rat, Sherman 5 males per dose	Triethylamine No information on purity No information on source	0.252, 0.50 and 1.0 g/kg bw Single application via gavage Concentration in vehicle (1% Tergitol): 20%	460 mg/kg bw	Primary sources: Smyth et al. (1951) and TSCA Submission OTS 0515571 (US EPA, 1987) Several secondary sources are given as references. [Study 005, 006, 008 and 013 REACH registration]
Acute oral toxicity Similar to OECD 401	Mouse, strain not specified No information on animal numbers	Triethylamine No information on purity No information on	No explicit information Graphical representation of dose-response	546 mg/kg bw	Kagan (1965) [Study 009, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	or sex	source	suggests 5 dose groups covering a range of approx. 250 – 700 mg/kg bw		
Acute oral toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 3	Rat, strain not specified male + female tested, but no information on numbers	Triethylamine No information on purity No information on source	Application via gavage Doses not specified, but inclusive of 60 and 300 mg/animal No further information	> 60 mg/animal < 300 mg/animal	Unnamed US EPA TSCA submission (1965) [Study 012, REACH registration]
Acute oral toxicity Similarity to guideline unknown GLP: unknown Reliability (REACH registration): 4 Reliability (this assessment): 4	Mouse, strain not specified No information on animal numbers or sex	Triethylamine No information on purity No information on source	No information	500 mg/kg bw	Liot and Filov (1964) Secondary source: Safety Data Sheet of Atochem North America,Inc. The secondary source could not be located. Primary source could not be evaluated as no English translation was available. [Study 007, REACH registration]
Acute oral toxicity Similarity to guideline unknown GLP: unknown Reliability (this assessment): 4	Mouse, rabbit, guinea pig, strains not specified No information on animal numbers or sex	No information given (name, source, purity)	No information given	Mouse: 114 mg/kg bw Rabbit: 615 mg/kg bw Guinea pig: 350 mg/kg bw	Secondary source: Sax and Lewis (1989) Primary source not obtainable

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

No animal study is available that is of sufficient reliability to be conclusive on its own. Several old studies, similar to OECD Guideline 401, are available (For the evaluation of this endpoint 11 studies are available. Each study is reliable with restrictions as the reporting is limited.

Table 10), however lacking information on purity of the test material is limiting the reliability of these studies.

In total, data on five species (rat, mouse, rabbit, guinea pig, cat) is available. The reported LD_{50} values are in the range of 114 (mice) – <1460 mg/kg bw (rabbit) (114 – 1030 mg/kg bw if studies that just provide lower and upper bounds of the LD_{50} are excluded). Studies, for which a detailed report is available (RL3 studies), report LD_{50} in a range from >365 (cat) to < 1460 mg/kg bw (rabbit) (460 – 1030 mg/kg bw if studies that just provide lower and upper bounds of the LD_{50} are excluded).

No human studies with relevance for comparison with the CLP criteria are available.

10.1.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (oral) if the LD_{50}/ATE values are > 300 and ≤ 2000 mg/kg bw.
- Acute Tox 3 (oral) if the LD_{50}/ATE values are > 50 and ≤ 300 mg/kg bw.

Each individual study is of insufficient reliability. Using a WoE approach, the available studies still allow a conclusive comparison with the CLP criteria because of the narrow spectrum of reported results. With the exception of a single RL4 study, all studies homogenously report results that clearly correspond to a classification, according to the CLP criteria, as acute oral toxicity category 4 (300 - 2000 mg/kg bw).

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the criteria triethylamine has to be classified as Acute Tox 4, H302 for acute oral toxicity.
An ATE value of 500 mg/kg bw has to be assigned based on the conversion values from Table 3.1.2.

10.2 Acute toxicity - dermal route

Table 11: Summary table of animal studies on acute dermal toxicity

Method, guideline, reliability	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal toxicity Similar to OECD 402 GLP: no	Rabbit, New Zealand Black 4 males per dose group	Triethylamine Source: Production quality samples from Union Carbide	0.5, 1.0, 2.0 mL/kg bw 24 h exposure, no vehicle 14 day post	580 mg/kg bw (reported as 0.794 mL/kg bw (95% CI: 0.486 – 1.30 mL/kg bw), converted using a	Myers and Ballantyne (1997) [Study 001, REACH registration]

Method, guideline, reliability	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Reliability (REACH registration): 2, key study Reliability (this assessment): 3		Corporation No further information on purity substance	exposure observation period	density of 0.73 g/mL) mortalities: 0.5 mL/kg: not reported 1.0 mL/kg: 3/4 2.0 mL/kg: 2/4	
Acute dermal toxicity Similar to OECD 402 GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	Rabbit, strain not specified 4 animals per dose	Triethylamine Purity: 100% No information on source	200, 2000, 5000 mg/kg bw Details of exposure not specified 7 day post exposure observation period	> 200 mg/kg bw & < 2000 mg/kg bw mortalities: 200 mg/kg: 0/4 2000 mg/kg: 3/4 5000 mg/kg: 4/4	TSCA submission OTS 0515253 (Bio Dynamics Inc., 1987) [Study 003, REACH registration]
Acute dermal toxicity Similar to OECD 402 GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	Rabbit, albino 3 – 5 males per dose	Triethylamine No information on purity No information on source	0.252, 0.50, 1.0, 2.0 mL/kg bw 24 h exposure	420 mg/kg bw (mistakenly also reported as 570 mg/kg bw, which is a conversion/unit mistake from originally 570 mL/kg bw)	unnamed study report (1989) and Smyth et al. (1951) [Study 002 and 004, REACH registration]

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

There is limited data available on dermal toxicity. No animal study is available that is of sufficient reliability to be conclusive on its own. Three studies on rabbits are available, which followed test protocols similar to OECD guideline 402 (Table 11), but they either lack information on the purity of the test substance (Myers and Ballantyne, 1997; Smyth, 1951) or have insufficient detail on exposure and a large dose spacing (Bio Dynamics Inc., 1987). These studies report LD_{50} values of 420 mg/kg bw, 580 mg/kg bw and a range from 200 - 2000 mg/kg bw.

No human studies with relevance for comparison with the CLP criteria are available.

10.2.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- **Acute Tox 4 (dermal) if the LC_{50}/ATE values are > 1000 and ≤ 2000 mg/kg bw**
- **Acute Tox 3 (dermal) if the LC_{50}/ATE values are > 200 ≤ 1000 mg/kg bw**

Each individual study is of insufficient reliability. Because of the high congruency of the reported results, the available data still allow a conclusive comparison with the CLP criteria by using a WoE approach.

The two studies that calculated an LD_{50}, are both well within the concentration range corresponding to acute dermal toxicity, category 3 (200 - 1000 mg/kg bw). The concentration range for possible LD_{50} values provided by the third study (LD_{50} between 200 and 2000 mg/kg bw) also includes the concentration range corresponding to category 4 (1000 – 2000 mg/kg bw). Because of the large dose spacing in this study, it is not possible to use the data as an argument in favour of any of the two categories, but the study neither has weight in contradicting the category indicated by the other studies.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Based on the available data triethylamine has to be classified as Acute Tox 3, H 311 for acute dermal toxicity.

An ATE value of 420 mg/kg bw has to be assigned.

10.3 Acute toxicity - inhalation route

Table 12: Summary table of animal studies on acute inhalation toxicity

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance, , form**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
Acute inhalation toxicity According to OECD 403 GLP: yes Reliability (REACH registration): 1 (entry as key study), 2 & 4 (other entries of this study in the dossier) Reliability (this assessment): 1	Rat, Sprague-Dawley 5 males and 5 females per dose group	Triethylamine, as vapour Purity 99.8% No information on source	2450, 3200, 4000, 5050 ppm 1 h exposure 14 days post exposure observation period	14.5 mg/L (reported as 3496 ppm) mortalities: 2450 ppm: 0/10 3200 ppm: 2/10 4000 ppm: 9/10 5050 ppm: 10/10	TSCA submission OTS 0557602 (IRDC, 1995) Several primary and secondary sources are given as references.: [Study 001, 004, 013 , REACH registration]
Acute inhalation toxicity Similar to OECD 403 GLP: no Reliability	Rat, Wistar 6 males per dose group	Triethylamine, as vapour No information on purity No information on source	2000, 4000 ppm 4 hour exposure	10.9 mg/L (reported as 2600 ppm)	Myers and Ballantyne (1997) [Study 003, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance, , form**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
(REACH registration): 2 Reliability (this assessment): 3					
Acute inhalation toxicity Similar to OECD 403 GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	Rat, strain not specified 6 rats per dose, sex not specified	Triethylamine as vapour, No information on purity No information on source	500, 1000, 2000 ppm 4 h exposure	> 4.1 mg/L & < 8.2 mg/L (reported as > 1000 ppm & < 2000 ppm)	Smyth et al. (1951) [Study 008 and 0015, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	Guinea pig, strain not specified 6 animals per dose group, mixed sex, no information on ratio	Triethylamine as vapour, No information on purity No information on source	2000 ppm 2 h exposure	< 8.2 mg/L (equivalent to < 2000 ppm) (reported in registration the dossier as LC50 = 2000 ppm)	Carpenter et al. (1948) [Study 010, REACH registration]
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 3	Guinea pig, strain not specified 6 animals per dose group, mixed sex, no information on ratio	Triethylamine as vapour, No information on purity No information on source	250, 500, 1000 ppm 4 h exposure	> 4.1 mg/L (equivalent to > 1000 ppm) (reported in registration dossier as LC50 = 1000 ppm)	Carpenter et al. (1948) [Study 011, REACH registration]
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (REACH registration): 3 Reliability (this	No information given	No information given (name, source, purity)	No information on concentrations 1 h exposure	> 2.1 mg/L	unnamed study report 1976 [Study 005, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance, , form**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
assessment): 3					
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 3	Mouse, Swiss OF1 6 males per dose group	Triethylamine as vapour, No information on purity No information on source	4 to 6 concentrations in the range 77 – 305 ppm 15 min exposure	> 1.26 mg/L reported as > 305 ppm (no mortalities at 305 ppm, the highest tested concentration)	Gagnaire et al. (1989) [Study 016, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 3	Rat, strain not specified 4 males per dose group	Triethylamine as vapour, No information on purity No information on source	80, 100, 120, 140 ppm Unreliable method of producing the test atmosphere 1 h exposure	> 0.33 & < 0.58 mg/L Reported as > 80 & < 140 ppm mortalities: 80 ppm: 1/4 100 ppm: 2/4 120 ppm: 2/4 140 ppm: 4/4	TSCA submission OTS 0515467 (Ashland Chemical Company, 1970) [Study 012, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 2 Reliability (this assessment): 3	Rat, strain not specified 3 male & 3 female animals per dose group.	Triethylamine, as vapour No information on purity No information on source	333 mg/L, saturated atmosphere 2 and 8 min exposure	Not determinable	Primary source: unnamed study (1960) [Study 002, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 3	Rat, strain not specified 6 animals per dose group. No information on sex	Triethylamine, as vapour No information on purity No information on source	Saturated atmosphere 2 and 8 min exposure	Not determinable	unnamed study report (1960) Although the study design & results suggest this is the same study as Study 002, the references are not matching [Study 017, REACH registration]

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance, , form**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 4	Mouse, strain not specified No further information given	No information given (name, source, purity)	No information on concentrations 2 h exposure	6 mg/L (reported as 1450 ppm)	Kochetkova and Kulagina (1964) The primary source is not obtainable [Study 006 and 014, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 4 Reliability (this assessment): 4	Mouse, strain not specified No further information given	Triethylamine No information on purity No information on source	No information on concentrations 2 h exposure	10 mg/L (reported as 2420 ppm)	Liot and Filov (1964) The primary source could not be evaluated (not available in English) [Study 007, REACH registration]
Acute inhalation toxicity Not similar to guideline GLP: no Reliability (REACH registration): 3 Reliability (this assessment): 4	Rabbit, strain not specified No further information	Triethylamine No information on purity No information on source	Saturated atmosphere 5 min exposure	No information on results given	Primary source: unnamed study report (1960) [Study 018, REACH registration]
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (this assessment): 4	No information given	Triethylamine No information on purity No information on source	No information on concentrations 2 h exposure	1.9 mg/L (reported as 460 ppm)	Secondary source: ACGIH (2001) Primary source not obtainable

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

One inhalation toxicity study of high relevance and reliability (GLP conform and without specified deviations from guideline) is available (IRDC, 1995). Using 1 h of exposure, a LC_{50} of 14.5 mg/L for rats

was determined. Several additional studies with limited reliability and varying exposure durations are available. These studies provide data on several species (rats, mice and guinea pigs) and the determined LC_{50} values range from 1.9 mg/L to 10.9 mg/L. One additional study (Ashland Chemical Company, 1970) used an unreliable method of producing the test atmosphere and obtained a LC_{50} range for rats (0.33 mg/L – 0.58 mg/L) and slope of the dose-response relationship that is contradicted by all other studies.

No human studies with relevance for comparison with the CLP criteria are available.

10.3.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (inhal) if the LC_{50} values are > 10.0 mg/L and ≤ 20.0 mg/L (4h exposure)
- Acute Tox 3 (inhal) if the LC_{50} values are > 2.0 mg/L and ≤ 10.0 mg/L (4h exposure)
- Acute Tox 2 (inhal) if the LC_{50} values are > 0.5 and ≤ 2 mg/L (4h exposure)

The key study was performed with 1 h exposure time. According to the CLP criteria, LC_{50} derived from 1 h exposures against vapours needs to be scaled down by a factor of 2 to be used as ATE for classification purposes. This results in an ATE of 7.2 mg/L corresponding to a classification as category 3 for acute inhalation toxicity.

Among the studies with insufficient reliability are some which are of little relevance for comparison with the CLP criteria due to either very short exposure times to saturated or highly concentrated atmospheres or overall low exposure concentrations that did not lead to effects relevant for the endpoint acute toxicity.

The remaining studies are predominantly indicating LC_{50} values or ranges that correspond to category 3 as well (Carpenter et al., 1948; Kocketkova and Kulagina, 1964; Loit and Filov, 1964; Smyth et al., 1951), with the exceptions of the study by Myers and Ballantyne (1997), which is just slightly outside the upper bound of category 3 with 10.9 mg/L at 4 h of exposure and a study result reported in the ACGIH documentation (ACGIH, 2001), which is just below the lower bound of category 3.

Taken together, the ATE of 7.2 mg/L derived from the key study should be used to classify triethylamine according to the CLP criteria for acute inhalation toxicity.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Triethylamine has to be be classified as Acute Tox 3, H331 for acute inhalation toxicity. An ATE value of 7.2 mg/L has to be assigned.

RAC evaluation of acute toxicity

ACUTE TOXICITY – ORAL ROUTE

Summary of the Dossier Submitter's proposal

Eleven studies are included in the CLH dossier for acute toxicity via the oral route. According to the DS, none of the studies is sufficiently reliable to be conclusive on its own; nevertheless, they allow a conclusive comparison with the CLP criteria because of the narrow spectrum of reported results. The studies for which a detailed report is available give LD_{50}'s in a range from >365 (cat) to < 1460 mg/kg bw (rabbit), corresponding to acute oral toxicity category 4 (300 - 2000 mg/kg bw). The dossier submitter proposed to classify triethylamine as Acute Tox 4**;** H302, with the default ATE of 500 mg/kg bw.

***Table**: Oral studies*

Method, reliability	**LD_{50}**	**Test substance**	**Dose levels**	**Mortalities**	**Study**
Rat, Wistar 5 males/dose Animals were not fasted 14 days observation Reliability (DS): 3	As 100%: <182 mg/kg bw (< 0.25 ml/kg) 1030 mg/kg bw reported as 1.41 mL/kg bw (95% CI: 1.03-1.95)	Triethylamine Source: Production quality samples from Union Carbide Corporation No information on purity Vehicle: water	As 100%: 0.25, 0.5, 1.0 mL/kg bw As 10%: 0.5, 1.0, 2.0 mL/kg bw	0.25 mL/kg: 3/5 0.5 mL/kg: 4/5 1.0 mL/kg: 5/5 0.5 mL/kg: 0/5 1.0 mL/kg: 0/5 2.0 mL/kg: 5/5	Myers and Ballantyne, 1997 Similar to OECD 401 GLP: no
Rat, strain not specified 10%: 5 animals (male + female) /dose 1%, 20% and 100%: 1 animal/dose 7 days observation Reliability (DS): 3	730 mg/kg bw no confidence interval or information on statistical method	Triethylamine Impurities: up to 1% diethylamine No further information on purity No information on source vehicle: olive oil or water (inconsistent statements)	As 10% in vehicle: 230, 366, 580, 929 mg/kg bw As 1%: 15, 58 mg/kg bw As 20%: 3660 mg/kg bw As 100%: 929, 3660 mg/kg bw	230 mg/kg: 0/5 366 mg/kg: 0/5 580 mg/kg: 0/5 929 mg/kg: 3/5 15 mg/kg: 0/1 58 mg/kg: 0/1 3660 mg/kg: 1/1 929 mg/kg: 1/1 3660 mg/kg: 1/1	BASF AG, 1960 Similar to OECD 401 GLP: no
Rat, Sherman 5 males/ dose Reliability (DS): 3	460 mg/kg bw (95% CI: 0.25 - 0.85)	Triethylamine No information on purity No information on source Vehicle not specified 20 %	As 20% in vehicle: 0.252, 0.50 and 1.0 g/kg bw	252 mg/kg 1/5 500 mg/kg 3/5 1000 mg/kg 4/5	Smyth *et al.* (1951) and TSCA Submission OTS 0515571 (US EPA, 1987)

		dispersion of triethylamine in 1 % "Tergitol"			Similar to OECD 401 GLP: no
Rat, strain not specified 10 male and 10 female/dose 18 h fasting 14 days observation Reliability (DS) 3	male: 590 mg/kg bw female: 560 mg/kg bw	Triethylamine, Technical purity, without further information Source: Former VEB Synthesewerk Schwarzheide (today BASF Schwarzheide GmbH)	Several dose levels tested doses not specified Variable concentration in vehicle (peanut oil): constant volume 5 mL/kg	No results on individual dose groups given	Schmidt *et al.* (1974) Similar to OECD 401 GLP: no
Rabbit, strain not specified 2 animals/ dose sex not specified Reliability (DS): 3	> 370 mg/kg bw & < 1460 mg/kg bw	Triethylamine No information on purity No information on source	370, 730, 1460 mg/kg bw Concentration in vehicle (olive oil): 10%	370 mg/kg bw: 0/2 730 mg/kg bw: 1/2 1460 mg/kg bw: 2/2	Unnamed study report, 1960 Not similar to guideline GLP: no
Cat, strain not specified 2 females/ dose Reliability (DS): 3	> 370 mg/kg bw & < 730 mg/kg bw	Triethylamine Impurities: up to 1% diethylamine No further information on purity No information on source	370, 730 mg/kg bw Concentration in vehicle (olive oil): 5% and 10%	370 mg/kg bw: 0/2 730 mg/kg bw: 2/2	Unnamed study report, 1960 Not similar to guideline GLP: no
Mouse, strain not specified No information on animal numbers or sex Reliability (DS): 3	546 mg/kg bw	Triethylamine No information on purity No information on source	Graphical representation of dose-response suggests 5 dose groups of approx. 250 – 700 mg/kg bw		Kagan (1965) Similar to OECD 401 GLP: no
Cat, strain not specified 2 animals/dose sex not specified Reliability (DS): 3	> 365 mg/kg bw & < 730 mg/kg bw	No information given (name, source, purity)	At least 365, 730 mg/kg bw No further information		Unnamed study report, 1960 Not similar to guideline GLP: no
Rat, strain not specified male + female tested, but no information on numbers Reliability (DS): 3	> 60 mg/animal < 300 mg/animal	Triethylamine No information on purity No information on source	Doses not specified, but inclusive of 60 and 300 mg/animal		Unnamed US EPA TSCA submission, 1965 Not similar to guideline GLP: no
Mouse, strain not specified	500 mg/kg bw	Triethylamine No information	No information		Liot and Filov (1964)

No information on animal numbers or sex Reliability (DS): 4		on purity No information on source			Similarity to guideline unknown GLP: unknown
Mouse, rabbit, guinea pig, strains not specified No information on animal numbers or sex Reliability (DS): 4	Mouse: 114 mg/kg bw Rabbit: 615 mg/kg bw Guinea pig: 350 mg/kg bw	No information given (name, source, purity)	No information given		Primary source not obtainable Secondary source: Sax and Lewis, 1989 Similarity to guideline unknown GLP: unknown

Comments received during consultation

Two MSCAs commented and agreed with the Acute Tox 4, H302 classification and the generic ATE of 500 mg/kg bw.

Assessment and comparison with the classification criteria

There are 11 studies available for this endpoint, with data on five species (rat, mouse, rabbit, guinea pig and cat). However, none of them are or guideline studies or conform to GLP. Of these, five studies lack details to the extent that they cannot be assessed by RAC: the source and purity of the substance, used doses, mortality/dose and in 4 of them the number of animals/dose are unknown. These 5 are listed at the end of the table on oral studies (Table 1.).

Of the remaining 6 studies 2 are not similar to the current guideline. They were conducted in cat or rabbit, 2 animals/dose and state only that the LD_{50} is >370 and <1460 mg /kg bw (rabbit, 10% dilution in olive oil, Unnamed study report (1960)) and >370 and <730 mg/kg bw (cat, 5 and 10% dilution in olive oil, Unnamed study report (1960)).

The remaining 4 studies were conducted in rats, similar to the OECD 401 Guideline (Myers and Ballantyne (1997), BASF AG (1960), Smyth *et al.* (1951), and Schmidt *et al.* (1974)).

Myers and Ballantyne (1997) reported an LD_{50} of 1030 mg/kg bw (reported as 1.41 mL/kg bw, with 95% CI: 1.03-1.95) with the substance as a 10% w/w dilution in water. The applied doses were 0.5, 1.0 and 2.0 mL/kg, with mortalities of 0/5, 0/5 and 5/5 respectively. The study also used the undiluted (100%) substance: the applied doses were 0.25, 0.5 and 1.0 mL/kg bw, with mortalities of 3/5, 4/5 and 5/5 respectively. Thus, a dose of 0.25 mL/kg bw resulted in 3/5 mortality, which, converted using a density of 0.73 g/mL, results in a dose of 182 mg/kg bw. Therefore, for the undiluted substance, the LD_{50} is below 182 mg/kg bw. According to the study the animals could not be dosed lower with acceptable accuracy.

In the BASF AG (1960) study the reported LD_{50} was 730 mg/kg bw, derived from the 10% diluted samples (probably in olive oil), as only this dilution had 5 animals/dose. (The 1%, 20% and 100% doses had 1-1 animal/dose). The applied doses were 230, 366, 580 and 929 mg/kg bw, with mortalities of 0/5, 0/5, 0/5 and 3/5 respectively.

In the Smyth *et al.* (1951) study the reported LD_{50} was 460 mg/kg bw (95% CI: 0.25 - 0.85), with the substance as a 20 % dispersion of triethylamine in 1% Tergitol, the vehicle was not specified. The applied doses were 252, 500 and 1000 mg/kg bw, with mortalities of 1/5, 3/5 and 4/5 respectively.

In the Schmidt *et al.* (1974) study the reported LD_{50}'s were 590 mg/kg bw (male) and 560 mg/kg bw (female). The LD_{50}'s were derived from samples of variable concentrations in vehicle (peanut oil) with a constant volume of 5 mL/kg. Several dose levels were tested with doses not specified; 10 animals/sex/ dose were used. There are no results of mortalities in individual dose groups given.

The LD_{50} values given by the DS in the studies are between 460 – 1030 mg/kg bw. However, it has to be mentioned that all the given LD_{50} values are derived from the diluted substance. There are two studies which use the undiluted substance: the Myers and Ballantyne (1997) and the BASF AG (1960) studies.

The Myers and Ballantyne (1997) study, at doses of 182, 365, and 730 mg/kg bw (0.25, 0.5 and 1.0 mL/kg bw) for the 100% substance, reported mortalities of 3/5, 4/5 and 5/5 respectively. As a dose of 182 mg/kg bw resulted in 3/5 mortality, the LD_{50} is below 182 mg/kg bw for undiluted triethylamine.

The BASF AG (1960) study, besides 1%, 10% and 20% dilutions also used undiluted substance, but unfortunately used only 1 animal per dose group and high doses for the undiluted substance. At doses of 929 and 3660 mg/kg the mortality was 1/1 in both cases, so no further conclusion can be drawn from this study regarding the toxicity of undiluted triethylamine.

According to the Guidance on the Application of the CLP Criteria: „If there are different LD_{50} values from tests using different vehicles (e.g. water vs. corn oil or neat substance vs. corn oil), generally the lowest valid value would be the basis for classification."

The Myers and Ballantyne (1997) study has enough detail that it can be considered as a valid study. It was conducted in a similar manner to the OECD 401 Guideline; the source of the substance was production quality samples from Union Carbide Corporation. It used Wistar rats, 5 males/dose, with an observation period of 14 days. Clinical observations were made (sluggishness, tremors, gasping, and convulsions). Gross necropsy evaluation was made (lungs with petechiae, distended and gas-filled stomachs with red pylori, mottled livers and kidneys, darkened kidney medullae and adrenals, intestines appearing reddened, yellow and liquid-filled). The data show dose-response both in the undiluted and the 10% water-diluted form of the substance.

Triethylamine has a wide range of LD_{50}'s: 1030 mg/ kg bw (diluted in water), 460 mg/ kg bw (20% dispersion in 1% Tergitol, unknown vehicle), 560-730 mg/ kg bw (diluted in oil) and an LD_{50} below 182 mg/ kg bw for the undiluted substance. There is an indication that the vehicle affects the toxicity of the substance, but also that the undiluted substance is more toxic than the diluted, which may be due to corrosiveness (classified as Skin Corr. 1A) but nevertheless it should be taken into account.

Since the LD_{50} obtained with the undiluted substance (< 182 mg/ kg bw) is within the range ($50 < LD50 \leq 300$ mg/kg bw) the classification Acute Tox 3 H301 (Toxic if

swallowed) is appropriate.

However, as the study on which the classification is based does not have lower doses than 182 mg/kg bw, at which 3/5 animals died - showing that the LD_{50} is clearly below this dose - RAC proposes that the default ATE value of 100 mg/kg bw is warranted.

RAC proposes that triethylamine should be classified as **Acute Tox. 3; H301 (Toxic if swallowed) with a default ATE of 100 mg/kg bw**.

ACUTE TOXICITY – DERMAL ROUTE

Summary of the Dossier Submitter's proposal

There are 3 studies on rabbits in the CLH dossier which followed test protocols similar to OECD guideline 402, none of which is sufficiently reliable to be conclusive on its own. They lack information on the purity of the test substance or have insufficient detail on exposure and a large dose spacing. The studies report LD_{50} values of 420 mg/kg bw, 580 mg/kg bw and a range from 200 - 2000 mg/kg bw. The two studies used to calculate an LD_{50}, are both within the concentration range corresponding to acute dermal toxicity, category 3 ($200 < LD_{50} \leq 1000$ mg/kg bw). The dossier submitter proposed to classify triethylamine as Acute Tox 3**;** H 311, with an ATE value of 420 mg/kg bw.

Table*: Dermal studies (contains data from the CLH dossier and the REACH registration)*

Method, reliability	**LD_{50}**	**Test substance**	**Dose levels**	**Mortalities**	**Study**
Rabbit, New Zealand Black 4 males/dose 24 h exposure 14 days observation Reliability (DS): 3	580 mg/kg bw reported as 0.794 mL/kg bw (95% CI: 0.486-1.30) Converted using a density of 0.73 g/mL	Triethylamine Source: Production quality samples from Union Carbide Corporation No information on purity No vehicle used	0.5, 1.0 and 2.0 mL/kg bw	0.5 mL/kg: 0/4 1.0 mL/kg: 3/4 2.0 mL/kg: 2/4	Myers and Ballantyne, 1997 Similar to OECD 402 GLP: no
Rabbit, strain not specified 4 animals/dose Details of exposure not specified 7 days observation Reliability (DS): 3	> 200 mg/kg bw & < 2000 mg/kg bw	Purity: 100% No information on source	200, 2000 and 5000 mg/kg bw	200 mg/kg bw: 0/4 2000 mg/kg bw: 3/4 5000 mg/kg bw: 4/4	TSCA submission OTS 0515253 (Bio Dynamics Inc. 1987) Similar to OECD 402 GLP: no
Rabbit, albino 3-5 males/ dose 24 h exposure Reliability (DS): 3	420 mg/kg bw	Triethylamine No information on purity No information on source	0.252, 0.50 and 1.0 and 2.0 mL/kg bw	0.252 mL/kg bw: 2/3 or 2/5 0.50 mL/kg bw: no mortality reported 1.0 mL/kg bw: all animals	Unnamed study report (1989) and Smyth *et al.* (1951) Similar to

				2.0 mL/kg bw: all animals	OECD 402 GLP: no

Comments received during consultation

One MSCA agreed with the Acute Tox. 3 (H311) classification as well as a dermal ATE of 420 mg/kg bw. Another MSCA agreed with the classification but suggested that the generic ATE of 300 mg/kg seems more appropriate, as all studies are rated with a Klimisch score of 3.

In response to the second comment, the DS stated that the ATE was chosen based on the lowest LD_{50} value derived from a study, however, due to the limited reliability of the studies, also a generic ATE of 300 mg/kg can be applied.

Assessment and comparison with the classification criteria

There are 3 rabbit studies available for this endpoint, similar to OECD guideline 402.

In the Myers and Ballantyne (1997) study the LD_{50} was 580 mg/kg bw (reported as 0.794 mL/kg bw with 95% confidence limits of 0.486 to 1.30 mL/kg, converted using the density of the test material (0.73 g/mL). The mortalities are 0/4, 3/4 and 2/4 at increasing doses (0.5, 1.0 and 2.0 mL/kg bw), therefore no clear dose-response can be shown.

The CLH dossier does not include mortality data of the Unnamed (1989)/Smyth *et al.* (1951) study, but the REACH registration (Study 004) does: "Mortality was observed within 14 days of dosing in 2 animals at 0.252 ml/kg and in all animals at 1.0 and 2.0 ml/kg", which helps to assess the dose-response and the usefulness of the study in determining an ATE.

In the Unnamed (1989)/Smythe *et al.* (1951) study the LD_{50} was 420 mg/kg bw, the applied doses were 0.252, 0.5, 1.0 and 2.0 ml/kg. The CLH dossier does not contain information on the mortalities, but the REACH registration states, "Mortality was observed within 14 days of dosing in 2 animals at 0.252 ml/kg and in all animals at 1.0 and 2.0 ml/kg". Unfortunately, it is not clear how many animals/doses were used: the CLH dossier mentions 3-5 males/dose, and the REACH registration states "3 groups of 5 and 1 group of 3 male rabbits" were used. Altogether we can deduce that at 0.252 mL/kg bw the mortality was 2/3 or 2/5, at 0.5 mL/kg bw there was no reported mortality and at 1 and 2 mL/kg bw all animals died, therefore there was no clear dose-response in this study either.

In the third study (Bio Dynamics Inc. (1987)) the doses used were 200, 2000 and 5000 mg/kg bw, the mortalities were 0/4, 3/4 and 4/4 respectively, with a conclusion that the LD_{50} is higher than 200, and lower than 2000 mg/kg bw.

The reported LD_{50} values of 580 mg/kg bw and 420 mg/kg bw indicate category 3 ($200 < LD_{50} \leqslant 1000$ mg/kg bw), which is not contraindicated by the third study. The studies have limitations but are considered to be adequate for classification. Therefore, concurring with the dossier submitter RAC proposes Acute Tox. 3 (H311) classification.

No study can be selected as key study for setting the ATE. Also, in none of the studies was a clear dose-response demonstrated and there is the added uncertainty regarding

the number of animals used/mortalities in the second study. Given all these considerations, RAC proposes that the default ATE value of 300 mg/kg bw is warranted.

RAC proposes that triethylamine should be classified as **Acute Tox. 3; H311 (Toxic in contact with skin) with an ATE value of 300 mg/kg bw**.

ACUTE TOXICITY – INHALATION ROUTE

Summary of the Dossier Submitter's proposal

There are 14 studies included in the CLH dossier for this endpoint.

However, one study has a reliability score of 1, was performed according to GLP and without specified deviations from OECD guideline 403 (IRDC, 1995). This study was assigned as a key study. Using a 1 h exposure, an LC_{50} of 14.5 mg/L for rats was determined. The DS, following the CLP criteria, calculated that an LC_{50} derived from a 1 h exposure with vapours needs to be reduced by a factor of 2 to be used as ATE for classification purposes. This results in an ATE of 7.2 mg/L, corresponding to a classification as category 3 for acute inhalation toxicity.

Studies with insufficient reliability (very short exposure times/saturated or highly concentrated atmospheres/low exposure concentrations) are of little relevance. One study (Ashland Chemical Company, 1970) used an unreliable method of producing the test atmosphere and obtained a LC_{50} range for rats (0.33 mg/L – 0.58 mg/L) and slope of the dose-response relationship that is contradicted by all other studies.

The remaining studies predominantly indicate LC_{50} values or ranges that correspond to category 3 in line with the key study (Carpenter *et al.*, 1948; Kocketkova and Kulagina, 1964; Loit and Filov, 1964; Smyth *et al.*, 1951), with the exceptions of the study by Myers and Ballantyne (1997), which is slightly above the upper boundary of category 3 with 10.9 mg/L at 4 h of exposure and a study result reported in the ACGIH documentation (ACGIH, 2001), which is just below the lower boundary of category 3.

On the basis of the key study the DS proposed to classify triethylamine as Acute Tox 3, H331 for acute inhalation toxicity, with an ATE value of 7.2 mg/L.

***Table**: Inhalation studies*

Method, reliability	LC_{50}	Test substance	Dose levels, duration of exposure	Mortalities	Study
Rat, Sprague-Dawley 5 males and 5 females/ dose 14 days post-exposure observation Reliability (DS): 1	14.5 mg/L (reported as 3496 ppm)	Triethylamine as vapour Purity 99.8% No information on source	2450, 3200, 4000, 5050 ppm 1 h exposure	2450 ppm: 0/10 3200 ppm: 2/10 4000 ppm: 9/10 5050 ppm: 10/10	TSCA submission OTS 0557602 (IRDC, 1995) According to OECD 403 GLP: yes
Rat, Wistar	10.9 mg/L	Triethylamine	2000, 4000	2000 ppm: 1/6	Myers and

6 males/dose 14 days post-exposure observation Reliability (DS): 3	(reported as 2600 ppm)	as vapour No information on purity No information on source	ppm 4 h exposure	4000 ppm: 6/6	Ballantyne, 1997 Similar to OECD 403 GLP: no
Rat, strain not specified 6 animals/ dose sex not specified Reliability (DS): 3	> 4.1 mg/L & < 8.2 mg/L (reported as > 1000 ppm & < 2000 ppm)	Triethylamine as vapour No information on purity No information on source	500, 1000, 2000 ppm 4 h exposure	1000 ppm: 1/6 2000 ppm: 6/6	Smyth *et al.* 1951 Similar to OECD 403 GLP: no
Guinea pig, strain not specified 6 animals / dose, mixed sex, no information on ratio Reliability (DS): 3	< 8.2 mg/L (equivalent to < 2000 ppm) (reported in registration the dossier as LC_{50} = 2000 ppm)	Triethylamine as vapour No information on purity No information on source	2000 ppm 2 h exposure	No data	Carpenter *et al.* 1948 Not similar to guideline GLP: no
Guinea pig, strain not specified 6 animals / dose, mixed sex, no information on ratio Reliability (DS): 3	> 4.1 mg/L (equivalent to > 1000 ppm) (reported in registration dossier as LC_{50} = 1000 ppm)	Triethylamine as vapour No information on purity No information on source	250, 500, 1000 ppm 4 h exposure	No data	Carpenter *et al.* 1948 Similarity to guideline unknown GLP: no
Acute inhalation toxicity No information on species Reliability (DS): 3	> 2.1 mg/L	No information given (name, source, purity)	No information on concentrations 1 h exposure		unnamed study report 1976 Similarity to guideline unknown GLP: no
Mouse, Swiss OF1 6 males/ dose Reliability (DS): 3	> 1.26 mg/L reported as > 305 ppm	Triethylamine as vapour No information on purity No information on source	4 to 6 concentrations in the range 77 – 305 ppm 15 min exposure	No mortalities at top dose	Gagnaire *et al.* 1989 Not similar to guideline GLP: no
Rat, strain not specified 4 males/ dose Reliability (DS): 3	> 0.33 & < 0.58 mg/L Reported as > 80 & < 140 ppm	Triethylamine as vapour No information on purity No information on source	80, 100, 120, 140 ppm Unreliable method of producing the test atmosphere	80 ppm: 1/4 100 ppm: 2/4 120 ppm: 2/4 140 ppm: 4/4	TSCA submission OTS 0515467 (Ashland Chemical Co. 1970) Not similar to

			1 h exposure		guideline GLP: no
Rat, strain not specified 3males and 3 females/ dose Reliability (DS): 3	Not determinable	Triethylamine as vapour No information on purity No information on source	333 mg/L, saturated atmosphere 2 and 8 min exposure		unnamed study, 1960 Not similar to guideline GLP: no
Rat, strain not specified 6 animals/ dose sex not specified Reliability (DS): 3	Not determinable	Triethylamine as vapour No information on purity No information on source	saturated atmosphere 2 and 8 min exposure		unnamed study, 1960 Not similar to guideline GLP: no
Mouse, strain not specified No further information given Reliability (DS): 4	6 mg/L (reported as 1450 ppm)	No information given (name, source, purity)	No information on concentrations 2 h exposure		Kochetkova and Kulagina 1964 Similarity to guideline unknown GLP: no
Mouse, strain not specified No further information given Reliability (DS): 4	10 mg/L (reported as 2420 ppm)	Triethylamine No information on purity No information on source	No information on concentrations 2 h exposure		Liot and Filov 1964 Not similar to guideline GLP: no
Rabbit, strain not specified No further information Reliability (DS): 4		Triethylamine No information on purity No information on source	Saturated atmosphere 5 min exposure		unnamed study report, 1960 Not similar to guideline GLP: no
Acute inhalation toxicity No information on species Reliability (DS): 4	1.9 mg/L (reported as 460 ppm)	Triethylamine No information on purity No information on source	No information on concentrations 2 h exposure		Secondary source: ACGIH (2001) Similarity to guideline unknown GLP: no

Comments received during consultation

Two MSCAs commented and agreed with the Acute Tox 3, H331 classification with an ATE value of 7.2 mg/L.

Assessment and comparison with the classification criteria

There are 14 studies (rat, mouse, guinea pig, rabbit) included in the CLH dossier for this endpoint. One of them is judged to be reliable without restrictions (key study), performed according to GLP and without specified deviations from OECD guideline 403 (IRDC, 1995).

The key study used a 1 hour exposure time and resulted in an LC_{50} (1h) of 14.5 mg/L. According to the Guidance on the Application of the CLP Criteria, conversion of the existing inhalation toxicity data which have been generated using a 1-hour exposure can be carried out by dividing by a factor of 2 for vapours. Therefore, an LC_{50} (4h) of 7.2 mg/L can be calculated from the key study, which indicates Category 3 (2.0 mg/L < LC_{50} ≤ 10.0 mg/L).

Five of the remaining studies do not give enough details for RAC to be able to assess them: the source and purity of the substance, used concentrations, mortality/dose and the number of animals/dose are unknown. 3 other studies used too short exposure durations (2-15 minutes) and/or too low exposure concentrations (no lethality occurred). One study arrived at an LC_{50} for one hour exposure of > 0.33 & < 0.58 mg/L but used an unreliable method of producing the test atmosphere.

Of the studies which are relevant for classification, three (Smyth *et al.* 1951, Carpenter *et al.* 1948 and Carpenter *et al.* 1948) result in a range supporting category 3 (4.1 ⩽LC_{50} ⩽ 8.2 mg/L). One study (Myers and Ballantyne, 1997) results in an LC_{50} of 10.9 mg/L indicating Category 4.

Overall, based on the key study which is considered fully reliable and adequate to serve as the basis for classification, an LC_{50} (4h) of 7.2 mg/L can be calculated, which corresponds to Category 3 according to the criteria for acute inhalation toxicity (2.0 mg/L < LC_{50} ≤ 10.0 mg/L.)

RAC proposes that triethylamine should be classified as **Acute Tox. 3; H331 (Toxic if inhaled), with an ATE value of 7.2 mg/L.**

10.4 Skin corrosion/irritation

Not performed for this substance.

10.5 Serious eye damage/eye irritation

Due to a classification of triethylamine for Skin Corrosion Category 1 serious damage to eyes is implicit as reflected in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage) (ECHA, 2017). However, a studies and information on eye irritation/corrosion is available and presented in the table below.

Table 13: Summary table of animal studies on eye corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **-Observations and time point of onset** **-Mean scores/animal** **-Reversibility**	**Reference**
Similar to OECD 405 Non GLP Reliability (REACH registration): 2, key study	Rabbit N=1	triethylamine	1 drop (~50µl) (not rinsed off) Observation 19 days	Scoring not reported severe corneal opacity (irreversible) bleeding of the nictating membrane conjunctival edema chemosis and redness	Anonymous (1960) [Study 01, REACH registration]
Similar to OECD 405 Reliability (REACH registration): 2	Rabbit N=5	triethylamine	0.0005 ml (washng done 18-24h after exposure) Observation 18-24h	Scoring not reported severe corneal opacity, iritis, necrosis and/or hemorrhage of the eyelids, and chemosis	Anonymous, (1997) [Study 02, REACH registration]
US EPA TSCA submission Reliability (REACH registration): 2	Rabbit, albino N=3	triethylamine	0.1 ml	Corrosive with washing Irritant with washing	Anonymous, (1976a) OTS0001118 [Study 03, REACH registration]
- Reliability (REACH registration): 4	New Zealand white rabbit N=3	triethylamine	0.1 ml Observation 7days	corrosive	Anonymous (1976b) [Study 04, REACH registration]
US EPA TSCA submission Reliability (REACH registration): 4	Albino rabbit	triethylamine	0.1 ml	Cornea score (unwashed) Mean 24/48/72h = 4 Conjunctivae redness (unwashed) Mean 24/48/72h = 3 Conjunctivae chemosis (unwashed) Mean 24/48/72h = 1 Cornea score (washed) Mean 24/48/72h = ~1 Conjunctivae redness (washed) Mean 24/48/72h = 3 Conjunctivae chemosis (washed) Mean 24/48/72h = 1	Anonymous (1986a) OTS 0513613 [Study 05, REACH registration]
- Reliability (REACH	rabbit	triethylamine	5% solutionin propylene glycol	5% strongly irritating, in contrast to a 1% solution. Grade 9 according to Carpenter	Myers R.C., Ballantyne B. (1997)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
registration): 4					OTS 0515571 [Study 06, REACH registration]
- Reliability (REACH registration): 4	rabbit	-	-	rabbit	Anonymous (1960) [Study 07, REACH registration]
- Reliability (REACH registration): 4	rabbit	triethylamine	50 ppm	Grade 9 score according to Carpenter "severe"	Smyth H.F. et al.(1951) [Study 08, REACH registration]
- Reliability (REACH registration): 4	rabbit	triethylamine	250 ug for 24h	Severe irritant	Anonymous (1986b) [Study 09, REACH registration]

10.5.1 Short summary and overall relevance of the provided information on eye corrosion/irritation

In the study by Anonymous (1960) triethylamine was applied to the conjunctival sac of one rabbit eye. The application of the test substance caused after 10 minutes severe corneal opacity, bleeding of the nictating membrane, conjunctival edema, chemosis and redness (no scores reported). The symptoms were persisting for the next 2 weeks. The corneal opacity is not regarded to be reversible.

In a second study (Anonymous, 1997) triethylamine (0.005ml) was applied into eyes of five rabbits. After 18 -24 h the treated eye was rinsed with water and stained with fluorescein. Eyes were examined for ocular and periocular injury and/or inflammation. The test material produced severe corneal opacity, iritis, necrosis and hemorrhage of the eyelids, and chemosis (no scores reported).

Anonymous (1976a) applied 0.1ml triethylamine in the conjunctival sac of both eyes of each of three albino rabbits. One eye of each animal was washed with flowing water initiated fifteen seconds after instillation and continued of one minute; the contralateral eye remained unwashed. The test substance was corrosive without washing and irritant with washing (no further details).

For a TSCA submission Anonymous (1986a) the results of an eye irritation test are available. 0.1ml trimethylamine was placed in the conjunctival sac of both eyes of three albino rabbits. One eye of each rabbit was washed 15 seconds after instillation. The irritant reactions were scored periodically for 7d. In unwashed

eyes the cornea began to opacify immediately and was almost completet in 10min. severe conjunctival inflammation developed promptly. Tissue necrosis appeared within minutes. The reaction persisted through the 7th day without change and appeared to be irreversible. In washed eyes slight corneal clouding appeared at 4h and moderate clouding 3d after instillation persisting through the 7th day. Conjunctival inflammation was also seen but signs of recovery were evident when observations were discontinued. The scores are presented in the following table.

Table 14: Mean scores (Anonymous, 1986a).

	unwashed				washed			
Time	Cornea	Iris	Conjunctivae redness	Conjunctivae chemosis	Cornea	Iris	Conjunctivae redness	Conjunctivae chemosis
10min	3	?	3	1	0	<1	3	1
1h	4	?	3	1	0	<1	3	1
2h	4	?	3	1	0	<1	3	1
4h	4	?	3	1	1	<1	3	1
24h	4	?	3	1	1	<1	3	1
48h	4	?	3	1	1	<1	3	1
72h	4	?	3	1	<2	<1	3	1
4d	4	?	3	1	<2	<1	3	1
5d	4	?	3	1	<2	<1	2	1
6d	4	?	3	1	<2	<1	<1	1
7d	4	?	3	1	<2	<1	<1	1

Several further citations are mentioned in the registration dossier indicating severe irritating properties of trimethylamine but no further details are available to further substantiate these statements.

10.5.2 Comparison with the CLP criteria

Category 1	A substance that produces: (a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3 and/or

	(ii) iritis > 1,5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.
Category 2	Substances that produce in at least in 2 of 3 tested animals, a positive response of: (a) corneal opacity ≥ 1 and/or (b) iritis ≥ 1, and/or (c) conjunctival redness ≥ 2 and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

For comparison with the given classification criteria only limited data is available. Two studies describing severe irritating and corrosive effects are available. No scores are reported.

10.5.3 Conclusion on classification and labelling for eye corrosion/irritation

Triethylamine showed severe effects in the eyes of rabbits (severe irreversible corneal opacity, bleeding of the nictating membrane, conjunctival edema, chemosis and redness, necrosis, etc.). Anonymous (1986a) reported cornea scores of 4 for unwashed rabbit eyes and irreversibility within the observation periode of 7 days.

However the substance is classified as Skin Corr 1A and according to the CLP guidance (ECHA, 2017) serious damage to eyes is implicit indicated as Eye Dam 1, which is supported by the severe effects seen in the study by cornea scores of 4 (Anonymous, 1986a) and described effects in Anonymous (1960) and Anonymous (1997).

RAC evaluation of serious eye damage/eye irritation

Summary of the Dossier Submitter's proposal

Due to the classification of triethylamine for Skin Corrosion Category 1, serious damage to the eyes is implicit, as reflected in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage). However, studies and information on eye irritation/corrosion are available and presented by the DS. There are 9 studies for this endpoint.

In one study (Unnamed, 1960, no scores reported) using 2 rabbits, one drop (≈50 µl) of triethylamine caused severe corneal opacity, bleeding of the nictating membrane, conjunctival oedema, chemosis and redness after 10 minutes. The symptoms persisted for the next 2 weeks; the corneal opacity was not regarded to be reversible.

In a second study (titled Anonymous, 1997 in the CLH dossier) triethylamine (0.005ml) was applied into eyes of five rabbits. After 18-24 h the treated eye was rinsed with water and stained with fluorescein. The test material produced severe corneal opacity, iritis, necrosis and hemorrhage of the eyelids, and chemosis (no scores reported, observation period 24 hours).

In the third (Unnamed US EPA TSCA submission, 1976a) study 0.1ml triethylamine was applied in the conjunctival sac of both eyes of albino rabbits. One eye of each animal was washed with flowing water after fifteen seconds, the contralateral eye remained unwashed. The test substance was corrosive without washing and irritant with washing (no further details).

For the "Unnamed US EPA TSCA submission, 1986a" study the results of an eye irritation test are available. 0.1ml trimethylamine was placed in the conjunctival sac of both eyes of three albino rabbits. One eye of each rabbit was washed 15 seconds after instillation. The irritant reactions were scored periodically for 7d. In unwashed eyes the cornea began to opacify immediately and was almost complete in 10 minutes, and severe conjunctival inflammation developed promptly. Tissue necrosis appeared within minutes. The reaction (cornea score of 4 and conjunctivae redness score of 3) persisted through the 7th day without change and appeared to be irreversible. In washed eyes slight corneal clouding appeared at 4h and moderate clouding 3d after instillation persisting through the 7th day. Conjunctival inflammation was also seen but signs of recovery were evident when observations were discontinued. The mean scores (24/48/72h) are presented in the table.

The dossier submitter concluded that the substance is classified as Skin Corr 1A and according to the CLP guidance (ECHA, 2017) serious damage to eyes is implicitly indicated as Eye Dam 1, which is supported by the severe effects seen in a study with cornea scores of 4, and the described severe effects (severe corneal opacity (irreversible), iritis, bleeding of the nictating membrane, conjunctival oedema, chemosis and redness) in two other studies.

***Table**: Studies on eye corrosion/irritation*

Method	**Dose levels, duration of exposure**	**Results**	**Study**
Rabbit N=2 Observation 19 days	1 drop (≈50 µl) not washed	Severe corneal opacity (irreversible) bleeding of the nictating membrane, conjunctival oedema, chemosis and redness Scoring not reported	Unnamed, 1960 Similar to OECD 405 GLP: no
Rabbit, New Zealand White N=5 Observation 18-24 hours	0.005 ml (5 µl) directly on the cornea washed after 18-24 hours	Severe corneal opacity, iritis Scoring not reported	Myers and Ballantyne, 1997 GLP: unknown
Rabbit, albino N=3	0.1 ml one eye washed, other unwashed	Corrosive without washing Irritating with washing Scoring not reported	Unnamed US EPA TSCA submission, 1976a GLP: no
Rabbit, New Zealand White	0.1 ml	Corrosive	Unnamed, 1976b

N=3 Observation 7 days		Scoring not reported	Not similar to guideline GLP: no
Rabbit, albino N=3 Observation 7 days	0.1 ml one eye washed, other unwashed	Cornea score (unwashed) Mean 24/48/72h = 4 Conjunctivae redness (unwashed) Mean 24/48/72h = 3 Conjunctivae chemosis (unwashed) Mean 24/48/72h = 1 Cornea score (washed) Mean 24/48/72h = ~1 Conjunctivae redness (washed) Mean 24/48/72h = 3 Conjunctivae chemosis (washed) Mean 24/48/72h = 1	Unnamed US EPA TSCA submission, 1986a GLP: unknown
Rabbit	triethylamine 1% and 5% solution in propylene glycol/water (conflicting statements)	5% strongly irritating, in contrast to 1% Grade 9 according to Carpenter	Myers and Ballantyne, 1997 Unnamed US EPA TSCA submission, 1987 GLP: unknown
Rabbit		Irritating	Unnamed, 1960 GLP: no
Rabbit	50 ppm	Grade 9 score according to Carpenter "severe"	Smyth H.F. *et al.*, 1951 GLP: no
Rabbit	250 µg 24 hours	Severe irritant	Unnamed, 1986b GLP: unknown

Comments received during consultation

Two MSCAs agreed that the substance fulfils the criteria for classification as Eye Dam. 1; (H318) based on the studies presented in the CLH report, but also implicit as the substance is already classified as Skin Corr. 1A. One of the MSCAs also commented that as the substance is already classified for Skin Corrosion, the classification for serious eye damage will not be indicated in the label.

In response to the comment on labelling, the DS replied that the correct labelling is given in Table 6 of the CLH Dossier.

Assessment and comparison with the classification criteria

There are 9 studies for this endpoint; none of them conform to GLP or the current OECD test guideline studies. Only one study has an observation period (19 days) similar to that required in OECD Guideline 405 (21 days) and only one study reports scoring values.

In one study (Unnamed, 1960, 2 rabbits, dose of ≈50 µl, scoring not reported, observation period 19 days) triethylamine caused severe corneal opacity, bleeding of the

nictating membrane, conjunctival oedema, chemosis and redness. The corneal opacity was not regarded to be reversible.

One study (Unnamed US EPA TSCA submission, 1986a, 3 rabbits, 0,1 ml test substance, one eye washed, other eye unwashed, 7 days observation) reported results of an eye irritation test in which the scores for the cornea, conjunctivae redness and conjunctivae chemosis in unwashed and washed rabbit eye are listed. In the unwashed eyes a mean 24/48/72h score of 4 was given for cornea, persisting for 7 days, conjunctivae redness score for 24/48/72h was 3, which also persisted for 7 days.

In another study (titled Anonymous, 1997 in the CLH dossier and REACH registration, but because of the unique protocol, and wording of the findings, it is identified as Myers and Ballantyne, 1997) severe corneal opacity and iritis was found after 24 hours. Contrary to what the CLH dossier and REACH registration contains, in the original study there is no mention of "necrosis and hemorrhage of the eyelids, and chemosis" describing the effects of triethylamine. The study used 0.005 ml (5 µl) directly on the cornea and washed the eyes after 18-24 hours.

The remaining studies also indicate corrosive/irritating effects for triethylamine but give even less details.

A substance warrants classification as Eye Damage Category 1, if it produces:
(a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of:
(i) corneal opacity $\geqslant$ 3 and/or
(ii) iritis > 1,5
calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

In one study triethylamine caused severe corneal opacity, bleeding of the nictating membrane, conjunctival oedema, chemosis and redness, and the corneal opacity was not regarded to be reversible. In another study the mean scores following grading at 24, 48 and 72 hours for corneal opacity was 4. These findings warrant classification as Eye Dam. 1; H318, which is also implicit as the substance is already classified as Skin Corr. 1A; H314 (Causes severe skin burns and eye damage).

RAC proposes that triethylamine should be classified as **Eye Dam. 1; H318**.

10.6 Respiratory sensitisation

Not performed for this substance.

10.7 Skin sensitisation

Not performed for this substance.

10.8 Germ cell mutagenicity

Not performed for this substance.

10.9 Carcinogenicity

Not performed for this substance.

10.10 Reproductive toxicity

Not performed for this substance.

10.11 Specific target organ toxicity-single exposure

Not performed for this substance.

10.12 Specific target organ toxicity-repeated exposure

Not performed for this substance.

10.13 Aspiration hazard

Not performed for this substance.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not performed for this substance.

12 EVALUATION OF ADDITIONAL HAZARDS

Not performed for this substance.

13 ADDITIONAL LABELLING

Not applicable for this substance.

14 REFERENCES

Anonymous (1960). REACH registration data. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=8c45bc7d-f563-4754-9b4a-086aa14c48fe

Anonymous (1997). REACH registration data. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=4e0550cf-85c7-49c5-ac36-e7d18a17fa1b

Anonymous (1976a). REACH registration data. (https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=faa70077-ada7-4ef8-9bcd-e00e91d1e7b2; OTS0001118

Anonymous (1976b). REACH registration data. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=a32de0ef-8830-4bc5-ac70-475f4e5259b0

Anonymous (1986a). REACH registration data https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=dc05c19e-7051-42c6-9230-78a66d789ef0 OTS 0513613

Anonymous (1986b). REACH registration data. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14938/7/4/3/?documentUUID=d10be1a5-1741-40d3-a09f-896d2cfcee35

ACGIH, American Conference of Governmental Industrial Hygienists (2001). Triethylamine. In: Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Ed., 2011, Cincinnati, OH, 4p.

Ashland Chemical Company (1970). Comparative Toxic Effects of Exposure of Male Rats to Vapors of Dimethyl Ethyl Amine and Triethylamine with cover letter dated 072287. OTS0515467 submitted to Office of Toxic Substances, US Environmental Protection Agency, Washington, D.C.

BASF AG (1960). Industrial hygiene orientating investigation, Report Nr. VI/389

Bio Dynamics Inc. (1987). Acute Dermal Toxicity of Triethylamine in Rabbits. OTS0515253 submitted to Hoechst-Celanese Corporation, Summit, New Jersey.

Carpenter C.P., Smyth H.F., Shaffer C.B. (1948). The acute toxicity of ethylene imine to small animals

Journal of Industrial Hygiene and Toxicology, 30, 2-6.

ECHA Dissemination (2019). Information on Chemicals - Registered Substances. European Chemicals Agency. Online: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Gagnaire F., Azim S., Bonnet P., Simon P., Guenier J.P., De Ceaurriz J. (1989). Nasal irritation and pulmonary toxicity of aliphatic amines in mice. Journal of Applied Toxicology, 9, 301-304.

Greim H. (1996). Triethylamin. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 22. Lfg, DFG, Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag GmbH & Co. KGaA. https://doi.org/10.1002/3527600418.mb12144d0022.

IRDC (1995). Acute Inhalation Toxicity Evaluation on Triethylamine in Rats, with cover letter dated 02/07/95. OTS0557602 sponsored by Air Products and Chemicals, Allentown, PA 18195.

Kagan G.Z. (1965). The determination of the maximum permissible concentrations of diethyl- amine and triethylamine in bodies of water. Hygiene and Sanitation, 30, 351-356.

Kocketkova T.A., Kulagina N.K. (1964). Toxicity triethylamine. Toksikologija novych promyšlennych chimičeskich veščestv, 7, 56-76.

Loit A.O., Filov V.A. (1964). Toxicity of Aliphatic amines and its modification in homologous series

Gigiena Truda i Professional'nye Zabolevanija, 8, 23-28.

Myers R.C., Ballantyne B. (1997). Comparative acute toxicity and primary irritancy of various classes of amines. Toxic Substance Mechanisms, 16, 151-194.

NTP, National Toxicology Program (1998). Testing Status of Triethylamine. 11038-A http://ntp.niehs.nih.gov/testing/status/agents/ts-11038-a.html#Short-Term-Toxicity

NTP, National Toxicology Program (2018). Technical Report on the Toxicity Studies of Triethylamine Administered by Inhalation to F344/N Rats and B6C3F1/N Mice. Toxicity Report Series 78. U.S. Department of Health and Human Services; Public Health Service. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox078_508.pdf

Sax N.I., Lewis R.J. (1989). Dangerous Properties of Industrial Materials. 7th ed., Van Nostrand Reinhold New York.

Schmidt P., Burck D., Weigmann H.J. (1974). Zur akuten Toxizitat einiger für die Kunststoffindustrie bedeutsamer Amine [Acute toxicity of some for plastic processing industry important amines]. Zeitschrift für die gesamte Hygiene und ihre Grenzgebiete, 20, 393-398.

Smyth H.F., Carpenter C.P., Weil C.S. (1951). Range-finding toxicity data: List IV. Archives of Industrial Hygiene and Occupational Medicine, 4, 119-122.

US EPA, Environmental Protection Agency (1987). Range Finding Tests on Triethylamine. OTS0515571. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0515571.xhtml