Committee for Risk Assessment

RAC

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

Adopted

10 June 2021

10 June 2021

CLH-O-0000007001-91-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **triethylamine**
EC Number: **204-469-4**
CAS Number: **121-44-8**

The proposal was submitted by **Austria** and received by RAC on **19 December 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **3 February 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 April 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anna Biró**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **10 June 2021 by consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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 **Add** Eye Dam 1 **Retain** Flam. Liq. 2 Skin Corr. 1A	**Modify** H331 H311 H302 **Add** 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%	
RAC opinion	612-004-00-5	triethylamine	204-469-4	121-44-8	**Modify** Acute Tox. 3 Acute Tox. 3 Acute Tox. 3 **Add** Eye Dam 1	**Modify** H331 H311 H301 **Add** H318	**Modify** GHS05 GHS06 Dgr	H331 H311 H301 H314		**Add** Oral: ATE = 100 mg/kg Dermal: ATE = 300 mg/kg Inhal: ATE = 7.2 mg/L STOT SE 3; H335: C ≥ 1%	
Resulting Annex VI entry if agreed by COM	612-004-00-5	triethylamine	204-469-4	121-44-8	Flam. Liq. 2 Acute Tox. 3 Acute Tox. 3 Acute Tox. 3 Skin Corr. 1A Eye Dam 1	H225 H331 H311 H301 H314 H318	GHS02 GHS05 GHS06 Dgr	H225 H331 H311 H301 H314		Oral: ATE = 100 mg/kg Dermal: ATE = 300 mg/kg Inhal: ATE = 7.2 mg/L STOT SE 3; H335: C ≥ 1%	

GROUNDS FOR ADOPTION OF THE OPINION

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.

HUMAN HEALTH HAZARD EVALUATION

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

Method, reliability	LD_{50}	Test substance	Dose levels	Mortalities	Study
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 % dispersion of triethylamine in 1 % "Tergitol"	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) 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	> 60 mg/animal < 300 mg/animal	Triethylamine No information on purity	Doses not specified, but inclusive of 60		Unnamed US EPA TSCA submission, 1965

Method, reliability	LD_{50}	Test substance	Dose levels	Mortalities	Study
information on numbers Reliability (DS): 3		No information on source	and 300 mg/animal		Not similar to guideline GLP: no
ouse, strain not specified No information on animal numbers or sex Reliability (DS): 4	500 mg/kg bw	Triethylamine No information on purity No information on source	No information		Liot and Filov (1964) 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 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 2.0 mL/kg bw: all animals	Unnamed study report (1989) and Smyth *et al.* (1951) Similar to 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 6 males/dose 14 days post-exposure observation Reliability (DS): 3	10.9 mg/L (reported as 2600 ppm)	Triethylamine as vapour No information on purity No information on source	2000, 4000 ppm 4 h exposure	2000 ppm: 1/6 4000 ppm: 6/6	Myers and Ballantyne, 1997 Similar to OECD 403 GLP: no
Rat, strain not specified 6 animals/ dose	> 4.1 mg/L & < 8.2 mg/L (reported as > 1000 ppm & < 2000 ppm)	Triethylamine as vapour No information on purity	500, 1000, 2000 ppm 4 h exposure	1000 ppm: 1/6 2000 ppm: 6/6	Smyth *et al.* 1951 Similar to OECD 403

Method, reliability	LC_{50}	Test substance	Dose levels, duration of exposure	Mortalities	Study
sex not specified Reliability (DS): 3		No information on source			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 1 h exposure	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 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

Method, reliability	LC_{50}	Test substance	Dose levels, duration of exposure	Mortalities	Study
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.**

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 N=3 Observation 7 days	0.1 ml	Corrosive Scoring not reported	Unnamed, 1976b 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**.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).