SUBSTANCE EVALUATION REPORT

Public Name: **2,2',2"-NITRILOTRIETHANOL (TEA)**

EC Number(s): **203-049-8**

CAS Number(s): **102-71-6**

Submitting Member State Competent Authority: UK REACH CA

Year of evaluation (as given in the CoRAP): **2014**

VERSION NUMBER: 1.1 **DATE: August 2015**

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	✓
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other:	

**Include details in the executive summary.*

DISCLAIMER

The Substance evaluation report has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Executive summary

Grounds for concern

Initial concerns

The following initial concerns were identified in the justification document.

- Human health: suspected CMR, suspected sensitiser. 2,2',2"-Nitrilotriethanol (TEA) has been identified in a list of agents associated with occupational asthma by the CSST (Commission de la santé et de la sécurité du travail) (updated April 2010). [The CSST is an organisation mandated by the Quebec government to oversee health and safety at work.] The justification document also noted that animal studies had indicated a potential of the substance to induce skin sensitisation and an increase in the incidence of liver tumours in female mice.
- Human exposure: wide dispersive use, consumer use and aggregated tonnage. TEA has a large production volume, widespread use in manufacturing with the potential for high exposure in workers, wide dispersive use with high release for the environment and is widely used in consumer products.

Procedure

Initial assessment period: evaluation of existing information 26th March 2014 to 25th March 2015

The evaluation focused on the information provided in the registration dossiers and additional information provided informally by the Registrants to support their proposed mode of action and human relevance for the human health effects of TEA. The evaluating member state competent authority (eMSCA) met with the Registrants in April 2014 to discuss the substance evaluation procedure. At various stages, the Registrants provided information following informal requests. The lead Registrant updated the lead CSR in May 2014.

Chemistry

Analytical information provided in the dossiers was assessed to confirm substance identity and composition.

The physico-chemical data was screened, paying particular attention to those endpoints important to other parts of the evaluation, specifically water solubility, partition coefficient and vapour pressure.

Human health

The initial ground for concern was the main focus of the human health assessment. Skin and respiratory sensitisation were listed as concerns because of TEA's inclusion on the CSST's (Commission de la Santé et de la Sécurité du Travail) list of agents causing occupational asthma (updated April 2010). The Registrants provided (publicly-available) information additional to that in the registration dossier to inform on the skin and respiratory sensitisation potential of TEA. Carcinogenicity was listed as a concern because of a reported increased incidence of liver tumours in female mice. Additionally, a brief review of all the information in the registration dossier was undertaken to identify other potential areas of concern.

A literature search conducted by the eMSCA in September 2014 identified some new information on the potential of TEA to induce skin and respiratory sensitisation, which was included in the evaluation.

Environment and environmental exposure

As TEA was not prioritised for environmental concerns, only a brief review of all of the relevant environmental fate, behaviour and toxicity data was performed. The evaluation was based on information contained in the IUCLID 5 file and the Registrants' CSRs.

A literature search conducted in April 2014 did not identify any new information.

Human exposure

For the human health exposure assessment, all the data provided by the Registrants in the IUCLID 5 file and CSR were reviewed.

Conclusions

Initial assessment period: evaluation of existing information 26th March 2014 to 25th March 2015

Based on the evaluation of the information in the registration dossiers, supplemented with information provided informally by the Registrants, the following conclusions are reached.

Human health

The initial concern for sensitisation was clarified. Based on the available animal and human data, the eMSCA concluded that TEA did not meet the criteria for classification for skin or respiratory sensitisation. No further information is requested.

The initial concern for carcinogenicity was clarified. An increased incidence of hepatocellular adenoma in female B6C3F1 mice was reported in one dermal study; however, given the high susceptibility of this strain of mouse to spontaneous liver tumours, this finding does not represent a hazard in humans. In the same study, an increased incidence of haemangiosarcomas in the livers of male mice of the mid-dose group was reported, which was outside the historical control range. Taking into account that the increased incidence occurred only in one sex of one species in one study and was not dose-related, the eMSCA concluded that this is most likely a chance finding that was unrelated to treatment. No information to further clarify this concern is requested.

Human exposure

TEA does not have a harmonised classification in Annex VI of CLP, nor have the Registrants concluded that it meets the criteria for classification for any human health end-points. As no hazard was identified from the Registrants' chemical safety assessment, in accordance with REACH Annex I (5.0), an exposure estimation is not necessary.

Environment and environmental exposure

The low environmental hazard profile of the substance was confirmed. TEA is rapidly degradable, does not bioaccumulate and exhibits only limited ecotoxicity. It is not considered to be vP/vB or PBT. Given this profile, a review of the environmental exposure assessment was not undertaken.

Overall, the eMSCA concluded that, following the evaluation during the initial assessment period, further information was not required to clarify any concerns.

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TABLES

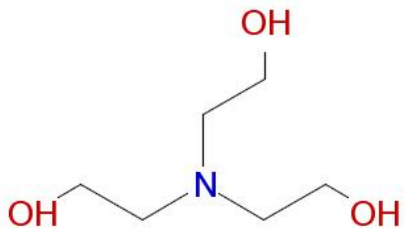
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	2,2',2"-nitrilotriethanol
EC number:	203-049-8
EC name:	2,2',2"-nitrilotriethanol
CAS number (in the EC inventory):	102-71-6
CAS number:	102-71-6
CAS name:	Ethanol, 2,2',2"-nitrilotris-
IUPAC name:	2,2',2"-nitrilotriethanol
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	$C_6H_{15}NO_3$
Molecular weight range:	149.1882
Synonyms:	TEA

Structural formula:



1.2 Composition of the substance

Name: 2,2',2"-Nitrilotriethanol.

Description: The substance 2,2',2"-nitrilotriethanol is a mono constituent substance (origin: organic).

Degree of purity: > 80%

Generally the information provided by the registrants was sufficient to confirm the identity of the registered substance. However, it is noted that not all are compliant with the information requirements of REACH Annex VI 2.3.5. Those spectra submitted were consistent between the different registrations. Further detail is provided in the confidential annex.

In their dossiers registrants were able to characterise the composition of their substances using standard analytical methods; Infra-Red (IR), Proton/Carbon nuclear magnetic resonances (^{1}H NMR & ^{13}C NMR including 2D-COSY and HSQC), Mass Spectrometry (MS) and Ultra violet spectrometry (UV/VIS), although UV spectrometry is less useful in this instance due to the chemical structure of TEA. The UV/VIS-spectrums submitted have no strong absorption bands in the near UV and Visible regions. The tail of the strong absorption below 200 nm is observed in the spectra, as expected for an aliphatic compound.

Gas chromatography (GC) and/or HPLC were used to determine purity however often very limited information was provided. No validation information such as recovery rates, limit of detection or quantitation were given. Registrants are reminded that sufficient information to be able to reproduce the analysis should be included in their dossiers.

Registrants are also reminded that they should provide analytical data from each separate manufacturing source. In this instance it does not appear to be the case that each registrant has provided information for their specific source. For example companies with different manufacturing sites seem to have provided the same analysis in all their registrations. The analysis should be relevant for the source registered.

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
2,2',2''-nitrilotriethanol	≥85.0 - ≤100 % (w/w)	≥80 - ≤ 100 % (w/w)	For further information, see confidential annex for individual compositions.

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
See confidential annex for individual compositions.			

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
See confidential annex for individual compositions.			

1.3 Physico-chemical properties

The physico-chemical properties reported in the registration dossiers are summarised in Table 5.

For most endpoints a number of endpoint records have been provided which includes information from various literature sources/industry databases and some measured data. Where a weight of evidence approach is taken the registrants are reminded that the summary record should include some discussion regarding which is the key record and which is being taken forward, especially when there is a range of values presented.

Generally the results provided are sufficiently consistent between the sources provided. However to support the vapour pressure endpoint several different results, measured at different temperatures are given and the values are too inconsistent to propose an overall conclusion. It is recommended that the registrant provides a justification as to which value is considered the most robust or conducts a study.

Additionally it is noted that the registrants have provided a waiving argument for not measuring the surface tension, however given the properties and uses of the substance surface activity could be expected. It is recommended that the registrants provide information on surface tension.

Table 5: Overview of physicochemical properties

Property	Value	Remarks
Physical state	The substance is an organic, viscous, colourless to plate-yellow liquid with slight ammonia odour.	Value used for CSA: liquid at 20ºC and 101.3 kPa Reliability 2 (reliable with restrictions)
Melting/freezing point	20.5 °C	Value used for CSA: 20.5ºC at 101.3 kPa Range of values from different registrants based on peer reviewed literature data was 20.5 ºC - 21.6ºC, no record of pressure. One registrant presented experimental data based on Test procedure ASTM E 737-76, which resulted in a Melt./Freez. Pt. of 17ºC at 101 kPa. Reliability 2 (reliable with restrictions)
Boiling point	336.1 °C at 1013.25 hPa	336.1ºC at 101.3 kPa. Substance decomposes when being heated. Some registrant's data observed decomposition (product turning brown) at ca. 290ºC. Data obtained *via* DSC indicates a boiling point of 320ºC at 101 kPa. Differences in experimentally derived boiling points may be due to differences in the purity of the substance. The boiling point given in literature that has been quoted is 335.4ºC at 101.3 kPa.
Relative Density	1.125 g/cm^3 at 20 °C	Reliability 2 (reliable with restrictions)
Vapour pressure	< 0.0003 hPa at 21 °C	An estimated vapour pressure derived by calculation was < 0.0003 hPa at 21 °C. A vapour pressure measures according to ASTM-D 2879 was 0.03 mBar (equivalent to 0.03 hPa) at 38ºC. The literature indicates a vapour pressure value of 0.00005 hPa at 40ºC. Another literature source indicates a vapour pressure of 0.019 hPa at 20ºC. It is noted that the vapour pressure data provided by the registrants suggests several different values at different temperatures, and is too inconsistent to propose an overall conclusion.
Surface tension	No data.	Waiver - expert judgment "*the surface activity does not need to be tested as based on chemical structure no surface activity is to be expected*". It is noted that the chemical structure and high water solubility would infer that low surface activity is to be expected; however given that 2,2',2''-nitrilotriethanol is used as a surfactant and emulsifier, surface tension measurements should have been made. A brief search of public domain information gives values of surface tension of 48.42 dyne/cm (ChemSpider). An information sheet on Dow's website gives the surface tension as 48.9 dynes/cm at 25ºC.
Water solubility	>1000 g/l at 20 °C	Miscible in all proportions Registrants provided a mixture of values from peer reviewed literature and data determined using ASTM 1148-02 method as well as BASF internal standard DIN 19267. All registrants support water

		solubility >1000g/l at 20 °C. Reliability 2 (reliable with restrictions).
Partition coefficient n-octanol/water (log value)	-2.3 at 25 °C / pH = 7.1	Value used for CSA: Log Kow (Pow):-2.3 at 25ºC. Registrants provided data obtained from shake-flask methods (e.g. OECD 107) which gave results of -2.3 (pH 7.1) and -1.9 (pH 7.1-pH 7.3) and 1.34 (pH 9.5). Literature values of -1 and -1.75 to -1.32 were submitted. There is no information on temperature of pH for literature data. One registrant used Episuite V.4. to predict log Kow -2.48. All values demonstrate there is no potential for accumulation in fat/bioaccumulation. Reliability 2 (reliable with restrictions).
Flash point	179 °C at 1013.25 hPa	Value used for CSA: 179ºC at 1013 hPa. A flash point of 179 °C at 1013.25 hPa was obtained from two separate literature references. A flash point of 193 °C at 1013.25 hPa was obtained from data generated using a method utilising the Pensky-Martins closed cup apparatus. Reliability 2 (reliable with restrictions).
Flammability	Non flammable liquid. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.	Value used for CSA: non-flammable. Waiver - Based on chemical structure pyrophoric properties and flammability in contact with water are not to be expected.
Explosive properties	No explosive properties	Value used for CSA: non explosive Waiver - There are no chemical groups associated with explosive properties present in the molecule. Furthermore, the oxygen balance of the compound calculated by eMS of -177%, when considered in conjunction with a lack of structural triggers, is indicative of no explosive properties.
Self ignition temperature/ Auto flammability	324 °C at 1013.25 hPa	Value used for CSA: 324 °C at 1013.25 hPa Registrants provided two literature values of 324 °C and 325ºC at 1013.25 hPa. One registrant provided data according to ASTM E 659, which determined a self-ignition temperature of 332ºC at 101 kPa. Reliability 2 (reliable with restrictions).
Oxidising properties	No oxidising properties	Value used for CSA: Oxidising: no. Waiver - Substance is incapable of reacting exothermically with combustible materials. An oxygen balance calculation made by eMS resulted in a value outside the region where there may be potential for the test substance to be an oxidiser (-177%), which along with structural considerations of the chemical, supports the statement made by the registrants that the substance is not an oxidiser.
Granulometry	Not applicable	
Stability in organic solvents and identity of relevant degradation products		Waiver - "In accordance with column 1 of REACH Annex IX, the stability in organic solvents does not need to be tested, because the stability of the substance is not considered as critical".
Dissociation constant	7.86 at 25 °C	Value presented is based on titrimetric data from one registrant, and is supported by literature values submitted by two further registrants. Reliability 2 (reliable with restrictions).

Viscosity	934 mPa/s at 20 °C	Value used for CSA: Viscosity at 20ºC: 934 mPa/s (dynamic). Registrants provided viscosity measurements as follows: 934 mPa/s at 20ºC and 204 mPa/s at 40ºC (OECD 114) 911 mPa/s at 20ºC and 202 mPa/s at 40.5ºC (DIN 53019) 590.5 mPa/s at 25ºC (literature value) 607 mPa/s at 25ºC (literature value) The measured viscosity at 40 ºC confirms that the substance is not an aspiration hazard.

2 MANUFACTURE AND USES

2.1 Quantities

The aggregated tonnage as given on the ECHA dissemination site (http://echa.europa.eu/web/guest/information-on-chemicals/) is 100,000 to 1,000,000 tonnes per annum.

2.1.1 Manufacturing processes

The following manufacturing processes have been identified:

1. Manufacture of the substance
2. Production of chemical
3. Formulation of mixtures

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

The following industrial uses have been identified:

1. Formulation of mixtures
2. Formulation of products containing TEA
3. Formulation of TEA
4. Formulation of preparations
5. Use as an intermediate
6. Use in construction chemicals (e.g., cement and concrete)
7. Gas treatment
8. Water treatment
9. Use in metal-working fluids
10. Use as additive or processing aid in leather, textile or paper
11. Use in detergents and cleaners
12. Use as a laboratory chemical
13. Industrial use resulting in manufacture of another substance
14. Processing aid for paper, textile, leather

15. Use of TEA in electroplating
16. Use of TEA in detergents, cleaners and ink removers
17. Use of TEA as additive in plastic, e.g. rubber
18. Use of TEA as additive in fuel
19. Use of fuel
20. Use as additive in wood protection formulations
21. Use in Cleaning Agents
22. Use in gas scrubbing/treatment
23. Water treatment chemicals, including anti-corrosion treatment
24. Use as additive in PU systems
25. Use as additive in plastic (eg rubber) , wood protection formulations , catalyst in polymerisation reactions

2.2.2 Use by professional workers

The following professional uses have been identified:

1. Formulation of mixtures
2. Use in construction chemicals (e.g. cement and concrete)
3. Use in metal working fluids
4. Use in PU-systems
5. Use in detergents and cleaners
6. Use as a laboratory chemical
7. Use as additive in concrete and cement
8. Processing aid for paper, textile, leather
9. Use of TEA in metal working fluids
10. Use of TEA in detergents, cleaners and ink removers
11. Use of TEA as additive in plastic, e.g. rubber
12. Use of TEA as a laboratory chemical
13. Use of fuel
14. Use in Cleaning Agents
15. Metal working fluids / rolling oils
16. Use as additive in PU systems

17. Use in biocidal products (non-active)
18. Use as additive in concrete, cement, coating, adhesives, catalyst in polymerisation reactions

2.2.3 Uses by consumers

The following consumer uses were identified:

1. Use in PU-systems
2. Use in detergents and cleaners
3. Personal care products
4. Use of concrete and cement
5. Use of TEA in detergents and cleaners
6. Use of TEA in wood protection formulations
7. Use in Cleaning Agents

2.3 Uses advised against

None.

2.3.1 Uses by workers in industrial settings advised against

None.

2.3.2 Use by professional workers advised against

None.

2.3.3 Uses by consumers advised against

None.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

TEA does not have a harmonised classification in Annex VI of the CLP Regulation.

3.2 Self-classification

The Registrants consider that TEA does not meet the criteria for classification for any human health or environmental end-points and thus do not apply any self-classifications.

4 ENVIRONMENTAL FATE PROPERTIES

Although TEA was not nominated as an environmental priority for the CoRAP, available environmental fate and hazard studies from the REACH registration have been reviewed. The data are summarized briefly with key studies highlighted.

A literature search was undertaken in May 2014, and relevant information is also included.

Measured and estimated dissociation constants for TEA are in the range 7.46 to 7.92 (information from registration dossier; Perrin, 1965.). Assuming the lower value, it is anticipated TEA will exist as a cation at environmentally relevant pH (e.g. 3% ionised at pH 6, 25% ionised at pH 7, 78% ionised at pH8 and 92% ionised at pH8.5).

4.1 Degradation

A summary of key information on the fate of TEA is presented in Table 6.

Table 6: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Calculation using AOPWIN v1.92 (US EPA, 2012a) Registrant Reliability: 2	DT_{50} 3.5 hours		Registration dossier
Indirect photolysis estimation Registrant Reliability: 2	DT_{50} ~ 342 days (14 m water column)		Schwarz (1982)
Ready biodegradation measured by CO_2 evolution No guideline Registrant Reliability: 2	~100% degradation after 5 days with 5.7 mg/l test item, 164 mg/l suspended solids (SS) ~100% degradation after 1 day with 0.6 mg/l test item, 164 mg/l SS <u>Mineralisation half- life:</u> 0.36 days with 0.6 mg/l test item, 164 mg/l SS 0.67 days with 5.7 mg/l test item, 164 mg/l SS 0.24 days with 0.6 mg/l test item, 818 mg/l SS 0.41 days with 5.7 mg/l test item, 818 mg/l SS	Not GLP	West and Gonsior (1996)
Ready biodegradation considered similar to OECD Test Guideline 301E Registrant Reliability: 2	96% degradation after 19 days (DOC removal)	Not GLP	Gerike and Fischer, (1979)
Biodegradation in seawater considered similar to OECD Test Guideline 306 Registrant Reliability: 2	19.6% degradation after 28 days (O_2 consumption)	Not GLP	Eide-Haugmo *et al* (2012)
Simulation study using ^{14}C Registrant Reliability: 2	River water only DT_{50}: 1.0 to 7.2 days River water with sediment DT_{50}: 1.2 to 1.9 days Based on pseudo first order for mineralisation.	Not GLP	West and Gonsior (1996)
Soil simulation study using ^{14}C and sandy loam Registrant Reliability: 2	DT_{50}: ≥1.4 to ≤5.4 days Based on pseudo first order for mineralisation.	Not GLP	West and Gonsior (1996)

4.1.1 Abiotic degradation

4.1.1.1 Hydrolysis

TEA does not contain any functional groups. Therefore hydrolysis is not anticipated. Furthermore, the substance is considered readily biodegradable. The Registrant has submitted an argument to justify the waiving of this end point. The evaluating Member State competent authority (eMSCA) does not see the need for requesting further information.

4.1.1.2 Phototransformation/photolysis

4.1.1.2.1 Phototransformation in air

A predicted half-life (DT_{50}) of 3.5 hours using AOPWIN v1.92 (information in the registration dossier) is available in the REACH Registration.

Neither a QSAR Prediction Reporting Format (QPRF) or QSAR Model Reporting Format (QMRF) are presented. The eMSCA recommends these are completed to fully validate the QSAR.

4.1.1.2.2 Phototransformation in water

Limited details are available but the results from the Schwarz, 1982 study of indirect photolysis are considered by the Registrant as reliable. The author considered indirect photolysis by OH-radicals of TEA in surface water with a resulting rate constant of 1.3 $x10^{-11}$ cm^3/(molecule*sec). Considering a mean 14 metre water column, this results in a DT_{50} of around 342 days.

4.1.1.2.3 Phototransformation in soil

No data available. As TEA is rapidly degradable on the basis of ready biodegradation testing, the Registrant has submitted a justification to request that this endpoint be waived. The eMSCA does not see the need for requesting further information.

4.1.2 Biodegradation

4.1.2.1 Biodegradation in water

4.1.2.1.1 Estimated data

No data available.

4.1.2.1.2 Screening tests

Various literature studies are available and discussed below. A GLP Ready Biodegradation study is not available.

A study (West and Gonsior, 1996) investigating the biodegradation of TEA is available in the literature. The study used a CO_2 evolution method but was not run following a specified guideline or to GLP. Two test concentrations were employed (0.6 and 5.7 mg/l TEA) with a suspended solid concentration of 164 mg/l and 818 mg/l activated sludge. Rapid biodegradation was observed with 100% mineralisation by 5 days for both concentrations. The eMSCA notes that the study employed

test concentrations significantly below the OECD test guideline 301 CO_2 method of 10-20 mg DOC/l and suspended solids from a mixed liquor activated sludge (secondary effluent) far exceeding the guideline equivalent of ≤30mg SS/l. The study also calculated mineralisation half-lives as follows:

- 0.36 days with 0.6 mg/l test item, 164 mg/l SS
- 0.67 days with 5.7 mg/l test item, 164 mg/l SS
- 0.24 days with 0.6 mg/l test item, 818 mg/l SS
- 0.41 days with 5.7 mg/l test item, 818 mg/l SS

Overall, the eMSCA considers the study is useful supporting evidence that TEA undergoes biodegradation but it cannot be used to quantify the process.

A study (Gerike and Fischer, 1978 and 1979) broadly following OECD Test Guideline 301E is available in the literature. The study used non adapted sludge from a waste water treatment plant and 20 mg/l test item. After 19 days 96% degradation was observed based on DOC removal. The study was not run to GLP and there are no details regarding the suspended solids concentration.

Overall, the eMSCA considers that this study is useful supporting evidence that TEA undergoes biodegradation but it cannot be used to quantify the process.

A study (Eide-Haugmo *et al* (2012)) investigating the degradation of TEA in seawater is available. The study broadly followed OECD Test Guideline 306 but was not to GLP. TEA was tested at 2 mg/l and 19.6% degradation was observed at day 28.

4.1.2.1.3 Simulation tests (water and sediments)

The aforementioned West and Gonsior (1996) literature reference includes a radio labelled aerobic simulation study using river water and river water with river sediment. The study did not follow a recognised test guideline and was not to GLP. Degradation of TEA at 100 mg/l was investigated with water and sediment from 2 river systems in the USA.

Based on test item analysis and assuming pseudo first order for mineralisation, half-lives were calculated by the authors for water (1.0 to 7.2 days) and water with sediment (1.2 to 1.9 days).

4.1.2.1.4 Summary and discussion of biodegradation in water and sediment

TEA is not anticipated to undergo hydrolysis owing to the lack of functional groups. In various literature studies, significant biodegradation was observed with quoted DT_{50} values for mineralisation less than 16 days. Therefore TEA is considered by the Registrant to be rapidly degradable.

4.1.2.2 Biodegradation in soil

The West and Gonsior (1996) literature reference included degradation in soil simulation using ^{14}C test material at 1.4, 201 and 2,000 mg/kg dry weight. The study did not follow a recognised test guideline and was not to GLP.

Based on test item analysis and assuming pseudo first order for mineralisation, half-lives were calculated by the authors to be ≥1.4 to ≤5.4 days.

4.1.3 Summary and discussion on degradation

TEA is considered by the Registrant to be rapidly degradable on the basis a weight of evidence from literature. Therefore, it is not anticipated to persist in the environment. The eMSCA agrees with this assessment.

Neither a QPRF nor QMRF were presented for degradation half-life in air estimate. The eMSCA recommends these are completed to fully validate the QSARs.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

Experimental data are not available.

Predicted adsorption coefficient values are used to fulfil the endpoint in the REACH registration dossier. TEA has pKa in the range 7.46 to 7.91 (Perrin, 1965; information in the registration dossier) and it is anticipated TEA will partially exist as a cation at an environmentally relevant pH.

Table 7 shows a summary of REACH Registration predicted values. The charged molecule prediction is based on a predicted log K_{ow} value of -2.46 and not the measured value of -2.3. The US EPA KOCWIN methods based on log K_{ow} and MCI are just outside the model domain (see table overleaf).

Neither a QPRF nor QMRF were presented. The eMSCA recommends these are completed to fully validate the QSAR.

Overall, the Registrant considers that the predicted log K_{oc} values are low and the substance is anticipated to have a limited adsorption potential. The eMSCA notes that TEA is likely to exist in the environment as a cation which may increase adsorption potential. As the substance is considered rapidly degradable the Registrant considers an experimental value is not required at this time. The eMSCA agrees with this assessment.

Table 7: Adsorption QSAR predictions

Model	K_{oc} l/kg	Log K_{oc}	Remarks
Calculation based on Franco A. and Trapp S. (2008, 2009 and 2010) cited in registration dossier Registrant Reliability: 2	pH 5: 18 pH 7: 17 pH 8: 12	pH 5: 1.27 pH 7: 1.23 pH 8: 1.06	Charged molecule pH 5-8, 25°C Using predicted log K_{ow} -2.48 Registration dossier
US EPA KOCWIN v.2.00 MCI method (US EPA, 2012a) Registrant Reliability: 2	10	1	Uncharged molecule Substance outside model domain given more than 2 aliphatic alcohol (-COH) groups

US EPA KOCWIN v.2.00 (US EPA, 2012a) estimated from log K_{ow} method using experiment log K_{ow} -2.3 at 25°C	0.0581	-1.24	Uncharged molecule Substance outside model domain given lower range of log K_{ow} -2.11 (Registration dossier)

4.2.2 Volatilisation

The REACH Registration for TEA includes predicted Henry's Law Constants from various models. Following REACH Guidance (ECHA, 2008), the Henry's Law constant range at 25°C is: 5.16E-10 Pa*m^3/mol at pH5; 4.6E-8 Pa*m^3/mol at pH7; and 3.88E-7 Pa*m^3/mol at pH 9 (information in registration dossier).

Using US EPA EPI Suite HENRYWIN v.3.20, the Henry's Law Constant is 4.23E-7 Pa*m^3/mol at 25°C (information in registration dossier).

Neither a QPRF nor QMRF were presented. The eMSCA recommends these are completed to fully validate the QSAR.

The Registrant notes TEA is not anticipated to partition from the aquatic environment to the atmosphere. The eMSCA agrees with this assessment.

4.2.3 Distribution modelling

The REACH Registration dossier includes a distribution modelling study using experimental water solubility, vapour pressure, log K_{ow} and Mackay Level 1 v.3.00 calculation. The results predict TEA will partition to the aquatic environment (100%).

4.2.4 Summary and discussion of environmental distribution

TEA is predicted to partition exclusively to the aquatic environment (100%) where it will remain and with little adsorption to suspended solids / sediment or partitioning to the atmosphere. In the aquatic environment, TEA is considered rapidly degradable.

This scenario is supported by the literature paper Davis and Carpenter, 1987 which reviewed information on the environmental fate of alkanolamines. It considered that alkanolamines would partition primarily to the aquatic environment where available data reflected rapid biodegradation.

Neither a QPRF nor QMRF were presented for adsorption coefficients or Henry's Law coefficients. The eMS recommends these are completed to fully validate the QSARs.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

TEA is considered miscible in water. The experimental log K_{ow} is -2.3 at 25°C, pH 7.1 following OECD Test Guideline 107 (information in registration dossier).

The REACH Registration includes measured and calculated bioconcentration factors which are summarised in Table 8. The data suggests that the fish BCF is likely to be below 10 l/kg. Values outside of the model domain are not included.

Table 8: Bioaccumulation QSAR predictions

Method	BCF l/kg wet wt	Log BCF	Remarks
Japanese guideline considered similar to OECD Test Guideline 305 Flow-through for 6 weeks with nominal 0.25 and 2.5 mg/l test item. Registrant Reliability: 2	<0.4 and <3.9 for whole fish (unclear if wwt or dw)	-0.4 and 0.6	Information in registration dossier
Data collected for BCFBAF v.3.01 validation and included in Arnot BCF database. No further details available. Flow-through for 42 days with nominal 0.25 mg/l test item. Registrant Reliability: 2	0.59 whole fish wwt	-0.23	Registration dossier; US EPA, (2012a); US EPA (2012c).
Estimation using BCF Read-Across model v.1.0.2 (VEGANIC v.1.1.1) Registrant Reliability: 2	0.68	-0.17	Registration dossier; Mario Negri Institute of Pharmacological Research, (2013a).
Estimation using USE EPA EPI Suite v.4.11 (US EPA, 2012a) and measured log Kow -2.3 Registrant Reliability: 2	3.162 steady state	0.5	Registration dossier
Estimation using OASIS Catalogic v5.11.9.13 Registrant Reliability: 2	2.4	0.36	All mitigating factors applied; within domain applicability (Registration dossier)
	9.2	0.96	Without mitigating factors; within domain applicability (Registration dossier)
Estimation using T. E. S. T. v4.1 (US EPA, 2012d) Registrant reliability: 2	0.46	-0.33	Average of applied models (Registration dossier)

Estimation using VegaNIC v.1.1.1 BCF Meylan model v.1.0.2 and log Kow of -1 Registrant reliability: 2	3-3.89	0.5-0.59	Registration; Mario Negri Institute of Pharmacological Research (2013b and 2013c); Meylan *et al*, (1999);
Estimation using VegaNIC v.1.1.1 BCF CAESAR v.2.1.13 and log Kow of -0.94 Registrant reliability: 2	3.02-3.89	0.48-0.59	Registration dossier; Mario Negri Institute of Pharmacological Research (2013d); Zhao *et al* (2008); Lombardo *et al* (2010)

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

TEA is considered hydrophilic with a low log K_{ow} value of -2.3. Predicted and measured BCFs are significantly below bioaccumulation trigger values for classification (500 l/kg) and PBT (2,000 l/kg) assessment. Overall, TEA is considered by the Registrant to have low bioaccumulation potential. The eMSCA agrees with this assessment.

4.4 Secondary poisoning

TEA has a low bioaccumulation potential and is considered rapidly degradable. It is not currently considered to meet relevant human health classification criteria for carcinogenicity, mutagenicity, reproduction or STOT RE. Given the low potential for bioaccumulation, exposure of predators is considered low. On this basis, a secondary poisoning scenario is not considered necessary by the Registrant. The eMSCA agrees with this assessment.

5 HUMAN HEALTH HAZARD ASSESSMENT

The areas of focus for the human health evaluation of TEA were sensitisation and CMR (carcinogenicity: liver tumours). A review of the information in the registration dossier on the other human health end-points did not identify any additional concerns.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No ADME data following oral and inhalation exposure are available so no estimate of absorption via these routes can be made. The default values of 100% for oral and inhalation absorption will be used in the calculation of the DNELs.

Based on *in vitro* studies in human skin, dermal absorption values from the exposure model were 10% and 6% for 1 and 5% TEA, respectively, at pH 7.0 (Kraeling and Bronaugh, 2003). The value of 10% will be used for humans. For rats, a value of 30% will be used from an NTP (2004) study.

5.2 Acute toxicity

The registrants concluded that the substance is not acutely toxic by the oral, dermal or inhalation routes. Based on the available information, the eMSCA can support this conclusion.

5.3 Irritation

The registrants concluded that the substance is not irritating to skin or eyes. Based on the available information, the eMSCA can support this conclusion.

5.4 Corrosivity

The registrants concluded that the substance is not corrosive. Based on the available information, the eMSCA can support this conclusion.

5.5 Sensitisation

One of the grounds for concern for TEA was the potential for it to induce skin sensitisation, based on its inclusion by the CSST (Commission de la santé et de la sécurité du travail) (updated April 2010) in a list of occupational asthmagens. The CSST is an organisation mandated by the Quebec government to oversee health and safety at work.

The justification for CSST considering TEA to be a skin and respiratory sensitiser was based on the following reports.

One study reported two cases of respiratory sensitisation (shortness of breath, cough, chest tightness, rhinitis) in two workers in the metal industry exposed to cutting oils containing triethanolamine. The symptoms disappeared at weekends and reappeared when returning to work. A bronchial provocation test was performed. One of the workers was tested with a cutting oil without triethanolamine then with another which contained it. The oil that contained triethanolamine was then tested as such, and also heated. In both cases, the response was positive, and more pronounced with the heated oil. The second worker was tested with heated cutting oil, and had an immediate positive response. Skin tests (prick) were performed and one worker gave a positive response.

A study in the metalworking industry (230 workers) showed that 20.4% of workers had skin sensitisation caused by triethanolamine (contained in cutting oils) following closed skin test (patch). However, the product was tested at a 10% dilution in water, therefore at a concentration which can cause irritation.

A few isolated cases of skin sensitisation are also reported in workers using cutting oils in their work. Positive responses were obtained after closed skin tests.

A maximization test (GPMT) performed in guinea pigs showed no positive response.

The CSST document concluded that triethanolamine seemed to show irritant properties when present with other products that facilitated its absorption.

5.5.1 Skin

5.5.1.1 Non-human information

The registration dossier reported a Guinea Pig Maximisation Test conducted to OECD 406, in which TEA was non-sensitising. Based on the results of a pre-test, animals were dermally injected twice with 0.1 mL 2% TEA on day 1, followed by an epicutaneous induction (occlusive) with 0.5 mL undiluted TEA for 48 hours starting on day 9, and a dermal challenge (occlusive) with 0.5 mL 10% TEA for 24 hours on day 22. Dermal reactions were evaluated according to Draize 48 and 72 hours after the start of the dermal challenge. No clinical signs were noticed and all readings were negative.

The Registrants provided additional, publicly-available, information to inform on the skin sensitisation potential of TEA. Additionally, the eMSCA conducted a literature search for papers on TEA and contact allergy (on Medline in Web of Science published during the period 1980-2014). This search retrieved ca 68 papers, one of which was in addition to those provided by the Registrants.

Search criteria
Search on Medline from 1/1/1980. (Originally conducted from 1/1/2000 but few paper identified so search date extended. Substance: , 2', 2"-nitrilotriethanol (syn. Triethanolamine, Triethanolamin, Tris(2-hydroxyethyl)amine) CAS Number 102-71-6 Contact allergy, Skin sensitisation Skin sensitization dermal sensitisation dermal sensitization Dermatitis Eczema

The additional paper described a series of *in vivo* studies in the mouse (Anderson *et al*. 2009). Skin irritancy in BALB/c mice was assessed by measurement of ear thickness following exposure to the test item, whilst a local lymph node assay was used to asses sensitisation potential. The formulation

of the test item with the most potential for irritancy and sensitisation was then determined, before further analysis of its constituent parts. Nine metal-working fluids (MWFs) were examined for skin irritancy and sensitisation potential. The most potent was found to contain TEA. TEA was subsequently found to test positive for both skin irritancy and sensitisation in the mouse.

Table 9. Summary of additional publications on the skin sensitisation potential of TEA

Method	Results	Comments	Conclusion
Guinea pig maximization test Induction- 1.5% triethanolamine Challenge- 10, 5 and 1% Note: challenge with technical and pro-analysis quality TEA	No positive reactions were noted in any of the guinea pigs (0/20) at all challenge doses.	There was no positive control data. Induction with 1.5%. There is no data on highest concentration and skin irritation presented here but based on other reports this concentration should be acceptable.	Negative but no positive controls Boman *et al*, 1993
GPMT with MEA, DEA or TEA and determination of cross reactivity. Adjuvant test following method from Boman *et al* 1993. TEA Induction- intradermal 1.5%, topical 25% Challenge- 10, 5 and 1%	TEA- max score 2/15 after challenge. Max score for cross-reactivity with other ethanolamines: 3/15 after induction with MEA in water (exp 1) then challenge with TEA (5%). When the vehicle is changed to saline for MEA induction, max score was 2/15 after challenge with DEA (7%).	Based on these results TEA is not a sensitiser, i.e. positive results were below the 30% cut-off value for a positive result in an adjuvant test.	Negative Wahlberg and Boman 1996

5.5.1.2 Human information

Information on the potential of TEA to induce skin sensitisation following exposure in humans, identified by the eMSCA and registrant but not included in the registration dossier, is provided below.

Table 10. Summary of human data on the skin sensitisation potential of TEA

Method	Results	Comments & conclusion
Human Volunteer Study Test Substance: TEA (Purity=98.9%) 10/sex in test group Vehicle= physiological saline No information on purity. Lessmann *et al.*, 2009	A 2009 published study analysed patch test data from 85,098 patients who had been tested with TEA 2.5% petrolatum by Information Network of Departments of Dermatology (IVDK) to identify particular exposures possibly associated with an elevated risk of sensitization. Assessment of IVDK data 1992-2007: 0.3% of patients tested (n=85 098) were positive, 0.9% questionable, 0.1% irritant. Metalworkers within this cohort were positive but at low percentage (1.5% with wbMWF, 0.79% in metal industry).	The authors concluded that, although used widely, no exposure associated with an increased risk of TEA sensitisation was identified

Method	Results	Comments & conclusion
	The study authors concluded that the profile of patch test reactions indicates a slightly irritant potential rather than a true allergic response in many cases. The paper also reviews case reports for patients presumed to be sensitised to TEA through the use of various products applied topically (sun creams, topical anti-pruritic lotion, cosmetics and various topical pharmaceutical products). Group sizes range from single patients to several thousand patients. Positive results were noted in most groups tested with rates from 0-100%.	
Retrospective analysis of metal workers that were patch tested as part of the IVDK in 2002-2003. A total of 251 were acceptable from the IVDK database. 206 of these were patch tested for current MWF allergens. Geier et al, 2004	TEA produced 1.1% positive reactions of metal workers. The authors noted that TEA may be less frequently used by metal-workers compared to DEA and MEA. TEA is more commonly found in cosmetics and creams.	The authors concluded that MEA was a more potent sensitiser than TEA in this study

5.5.2 Respiratory system

5.5.2.1 Non-human information

No relevant information provided in the registration dossier.

5.5.2.2 Human information

The eMSCA identified two published reports for TEA.

In the first, Makela *et al*. (2011) examined 20 female cleaners with occupational asthma. Diagnosis was based on patient history and lung function tests in response to specific challenge with the suspected products, and to pure TEA in one instance. Of the 20 patients diagnosed with occupational asthma, 5 were attributed to wax-removing detergents that contained ethanolamines. One case of occupational asthma was confirmed to be caused by TEA, in the single patient who was challenged with pure TEA. Exposure to pure MEA (2-aminoethanol) was not conducted. The author concluded that ethanolamines in the tested products were the likely cause of the reaction in all cases.

In the second report (Savonious *et al.,* 1994), diagnosis of 3 cases of occupational asthma (OA) was linked to exposure to ethanolamines. Two patients were confirmed only to have been exposed to triethanolamine (TEA), and the third was exposed to a detergent product containing 8% 2-aminoethanol (MEA) and 9% sodium metasilicate.

5.5.3 Summary and discussion of sensitisation

Skin sensitisation

One of the grounds for concern for TEA was the potential for it to induce skin sensitisation. The justification for CSST considering TEA as an agent for causing skin sensitisation was based on case reports in metal workers. The CSST concluded that TEA had irritant properties when present with other products that facilitated its absorption. There it is unlikely that TEA alone can induce skin sensitisation. The CSST also noted that in terms of prevalence, although this product is present in many formulations of cosmetics, few cases of skin sensitisation were reported in the literature.

The current review conducted by the eMSCA has identified sensitisation studies with TEA in animal models in the published literature that gave predominantly negative results.

In a published study provided by the registrant(Lessman, 2009), the authors analysed patch test data from 85,098 patients who had been tested with TEA (2.5% petrolatum) by Information Network of Departments of Dermatology (IVDK) (note: it is likely that the data on metal workers considered in Geier *et al*, 2004 formed part of this study). Of these patients 0.3% tested were positive, 0.9% questionable, and 0.1% displayed an irritant response. It notable that the cohort tested included metal-workers (likely to be a high exposure group). For workers using water-based metal working fluids 1.5% tested positive and of the general group of metal-workers 0.79% tested positive. The paper also reviewed case reports for patients presumed to be sensitised to TEA through the use of various products applied topically (sun creams, topical anti-pruritic lotion, cosmetics and various topical pharmaceutical products). Group sizes ranged from single patients to several thousand patients. Positive results were noted in most groups tested, but with highly variable rates (from 0-

100%, with higher percentages in those studies with few individuals). The eMSCA does not consider that these case reports provide robust evidence of TEA being a skin sensitiser in humans.

Furthermore, the eMSCA considers that care is required when interpreting these data, as ethanolamines in solution often have a high pH value>10 and this in itself may cause irritation which could have been misinterpreted for sensitisation.

The human evidence demonstrates that TEA induces sensitisation in humans in only a very low proportion of those exposed, even when exposure is high, as is the case with those workers who use water-based metal working fluids (1.5% tested positive). These workers are also likely to have a compromised skin barrier owing to the nature of the work. Furthermore, despite this product being present in many formulations of cosmetics, few cases of skin sensitisation from exposure to such products have been reported in the literature.

Therefore, based on human data, including in a highly exposed population (workers using water-based metal working fluids), and animal data, TEA has a low potential to induce skin sensitisation and does not meet the criteria for classification. The concern has been clarified and no further information is requested.

Respiratory sensitisation / occupational asthma

No information on respiratory sensitisation was included in the registration dossier. Two case reports of TEA being associated with occupational asthma have been reported in the literature. However, considering the very high tonnages of TEA used in a wide variety of applications and over a long period of time and the absence of other reports, the eMSCA concludes that TEA is not a respiratory sensitiser. The concern has been clarified and no further information is requested.

5.6 Repeated dose toxicity

Since carcinogenicity was identified as an area of concern, the data on repeated-dose toxicity presented in the registration dossier are provided below.

5.6.1 Non-human information

The registrant has provided the following studies with TEA: a 91 day study in Cox CD rats, two 90 day dermal toxicity studies (one in Fischer rats and another in B6C3F1 mice) and a 28 day inhalation toxicity (OECD 412 compliant) in Wistar rats.

5.6.1.1 Repeated dose toxicity: oral

Table 11. Summary of oral repeated-dose toxicity studies

Method	Dose Levels	Remarks
Rat: Cox CD 20/sex/dose Oral (diet) Similar to OECD Guideline 408, non-GLP	0, 250, 500 and 1000 mg/kg bw/day TEA (purity 88.5%)	**Clinical signs** No treatment related effects. **Bodyweights and food consumption** No treatment related effects. **Organ weights** No treatment related effects.

Method	Dose Levels	Remarks
No clinical chemistry performed EPA (1989b) Original study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary in IUCLID and the CSR.		**Haematology** No treatment related effects. **Gross examination and histopathology** No treatment related effects. **eMSCA Conclusion** NOAEL established to be 1000 mg/kg bw/day, the highest dose tested

5.6.1.2 Repeated dose toxicity: inhalation

Table 12. Summary of inhalation repeated-dose toxicity studies

Method	Dose Levels	Remarks
Species: Wistar rats **Group size**: 5/sex/dose **Test Substance**: TEA (no vehicle) **Purity**=98.9% **Exposure period**: 28 days 6 hours/day and 5 days/week (nose only) **Guideline**: OECD 412 , GLP compliant Information in registration dossier	0, 0.02, 0.1 or 0.5 mg/litre TEA (analytical; concentration- no method of analysis stated) No details of Droplet size analysis provided.	The dose levels for this study were based on a range finding study (detail not given). Very limited information was provided on this study. **Mortalities and Clinical signs** No mortality was observed. Red crusting around nasal edges in top dose animals noted (from day 14 in females and day 21 in males). **Bodyweights and food consumption** No treatment related effects. **Organ weights** No treatment related effects. **Haematology** No treatment related effects. **Neurobehaviour** Some differences in grip strength observed were judged not substance-related because of a lack of concentration- or time-related effect. No other abnormalities were observed during neuro-functional testing. **Gross examination and histopathology** Local effects observed histopathologically included focal inflammatory changes in the submucosa of the larynx, with a concentration-dependent increase in incidence and severity. At the low dose no similar effects were seen in females but in males minimal to slight effects were noted. Findings in the larynx Note: No findings in controls.

Inflammation, focal	0.02 mg/litre (m/f)	0.1 mg/litre (m/f)	0.5 mg/litre (m/f)

Method	Dose Levels	Remarks
		<table><tr><td>**Grade 1**</td><td>**2/0**</td><td>**1/1**</td><td>**0/2**</td></tr><tr><td>**Grade 2**</td><td>**1/0**</td><td>**1/1**</td><td>**3/2**</td></tr><tr><td>**Grade 3**</td><td>**0/0**</td><td>**0/0**</td><td>**1/0**</td></tr></table>Grade 1:minimal, Grade 2: slight, Grade 3: moderate Grade 4: marked severe **eMSCA Conclusion** The LOAEC (local effects) was established to be 0.02 mg/litre (equivalent to 23 mg/kg bw/day), based on the minimal to slight effects seen in the larynx of males. The NOAEC (systemic effects) was established to be 0.5 mg/litre (equivalent to 575 mg/kg bw/day), based on the absence of effects at the highest dose tested.

5.6.1.3 Repeated dose toxicity: dermal

Table 13. Summary of dermal repeated-dose toxicity studies

Method	Dose Levels	Remarks
Species: Fischer 344 rats **Group size**: 20/sex/dose 10 designated for periodic urinalysis, haematology, and clinical chemistry determinations 10 designated for the collection of clinical observations data, sperm morphology and vaginal cytology evaluations, necropsy with gross examination and tissue collection, and histopathologic examination **Test Substance**: TEA (acetone) **Purity**=98.9% **Exposure period**: 90 days 5 days/week **Guideline**: OECD 411 , GLP	0, 125, 250, 500; 1000, 2000 mg/kg bw/day.	**Mortalities and Clinical signs** No mortality was observed. Discoloration at the application site was noted in all groups. Skin irritation was noted at 500 mg/kg bw/day and above, with a dose-related increase in incidence and decrease to time of onset. Scaling occurred a 1000 mg/kg bw/day and above and crusting and ulceration at the top dose. **Bodyweights and food consumption** A significant decrease in bodyweight gain was seen at the top dose. **Clinical Chemistry** Dose-related increases in serum alanine and aspartate aminotransferase at the top dose. In females at the top dose serum urea nitrogen and albumin were increased. An increase in the incidence of crystals in the urine was also noted for females at 1000 mg/kg bw/day and above. **Urinalysis** Males exhibited decreased urinary protein excretion from 500 mg/kg bw/day and females from 250 mg/kg bw/day. **Organ weights** Kidney weights (Absolute and relative) were increased in male and female rats at 1000 mg/kg bw/day and above. Relative weights were also increased at 250 mg/kg bw/day in males. Males <table><tr><td>**Kidney weights**</td><td colspan="6">**Dose Group (mg/kg bw/day)**</td></tr><tr><td></td><td>**0**</td><td>**125**</td><td>**250**</td><td>**500**</td><td>**1000**</td><td>**2000**</td></tr><tr><td>**Abs (g)**</td><td>1.187</td><td>1.134</td><td>1.188</td><td>1.264</td><td>1.366**</td><td>1.366**</td></tr><tr><td>**% control**</td><td></td><td>95.5%</td><td>100.1%</td><td>106.5%</td><td>115.1%</td><td>115.1%</td></tr><tr><td>**Relative[a]**</td><td>3.97</td><td>4</td><td>4.16</td><td>4.41*</td><td>4.65**</td><td>5.58**</td></tr><tr><td>**% control**</td><td></td><td>100.8%</td><td>104.8%</td><td>111.1%</td><td>117.1%</td><td>140.6%</td></tr></table>[a] Relative to bodyweight * Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

Method	Dose Levels	Remarks
compliant Information in registration dossier		** P≤0.01 Females

Kidney weights	Dose Group (mg/kg bw/day)					
	0	125	250	500	1000	2000
Abs (g)	0.744	0.745	0.758	0.810*	0.847**	0.891**
% control		100.1%	101.9%	108.9%	113.8%	119.8%
Relative[a]	4.31	4.41	4.37	4.66*	4.98**	5.67**
% control		102.3%	101.4%	108.1%	115.5%	131.6%

[a] Relative to bodyweight
* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01

Haematology

RBC parameters: In top dose males and females there were significant decreases in MCV, in females only hematocrit.

WBC parameters: In top dose males there were significant increases in WBC counts , segmented neutrophils and eosinophils (both relative and absolute), and a decrease in relative lymphocytes counts. In top dose females there were significant increases segmented neutrophils (both relative and absolute), and a decrease in relative lymphocytes counts. These changes are likely a consequence of the marked inflammatory response in these animals.

Gross examination and histopathology

Treatment related skin lesions were noted in males at 250 mg/kg bw/day and above and females at 500 mg/kg bw/day and above. Lesions at the site of application ranged from no discernible change, through minimal to mild epidermal thickening (acanthosis), to chronic active inflammation, erosion, and ulceration. The dermis was also thickened with inflammation and fibrosis at the higher doses.

There was increased incidence of nephropathy from low to high dose in female rats; the severity of this lesion did not vary between dose groups.

LESION	Dose Group (mg/kg bw/day)					
	0	125	250	500	1000	2000
Number of animals	10	10	10	10	10	10
regeneration (nephropathy)	2 (1.0)	3 (1.0)	5 (1.0)	7* (1.0)	10** (1.4)	8* (1.4)
mineralization	3 (1.0)	9** (1.1)	6 (1.0)	7 (1.6)	9** (1.9)	9** (1.4)

*Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test
**P≤0.01
[a]Average severity of lesions in affected rats: 1=minimal; 2=mild; 3=moderate; 4=marked

It is notable (given the results of the 2 year study) that there were no effects on reproductive organs

eMSCA Conclusion

The NOAEL (local effects) was established to be 125 mg/kg bw/day, based on skin lesions in males.

<table>
<tr><th>Method</th><th>Dose Levels</th><th>Remarks</th></tr>
<tr><td></td><td></td><td>The NOAEL (systemic effects) was established to be 250 mg/kg bw/day, based on evidence of effects on the kidneys in males (increased organ weights and nephropathy).</td></tr>
<tr><td>Species: B6C3F1 mice
Group size: 20/sex/dose

10 designated for periodic urinalysis, haematology, and clinical chemistry determinations
10 designated for the collection of clinical observations data, sperm morphology and vaginal cytology evaluations, necropsy with gross examination and tissue collection, and histopathologic examination

Test Substance: TEA (acetone)
Purity=98.9%

Exposure period: 90 days
5 days/week

Guideline: OECD 411 , GLP compliant

Information from registration dossier</td><td>0, 250, 500, 1000, 2000 or 4000 mg/kg bw/day.</td><td><u>Mortalities and Clinical signs</u>
No mortality was observed. At 4000 mg/kg bw group skin lesions were noted including scaliness, irritation, and discoloration at the application site for males and females, and skin erosion in one male.

<u>Bodyweights and food consumption</u>
No treatment related effects.

<u>Clinical Chemistry</u>
Dose related significant decreases in sorbital dehydrogenase were observed in all treated males. A similar change was seen in all treated females as well as increased serum protein and albumin in top dose females.

<u>Urinalysis</u>
There were some sporadic increases in urine volume in females at 4000 mg/kg bw/day but these changes lacked consistency over the study.

<u>Organ weights</u>
The absolute kidney and liver weights were increased in top dose animals; relative kidney weights of males administered 1000 mg/kg bw and females in all dosed groups were also increased, although with no evident dose response apart from the top dose.

<u>Males</u>
<table><tr><th>Kidney weights</th><th colspan="6">Dose Group (mg/kg bw/day)</th></tr><tr><th></th><th>0</th><th>250</th><th>500</th><th>1000</th><th>2000</th><th>4000</th></tr><tr><td>Abs (g)</td><td>0.320</td><td>0.306</td><td>0.311</td><td>0.326</td><td>0.325</td><td>0.347*</td></tr><tr><td>% control</td><td></td><td>95.6%</td><td>97.2%</td><td>101.9%</td><td>101.6%</td><td>108.4%</td></tr><tr><td>Relative[a]</td><td>9.37</td><td>9.93</td><td>9.73</td><td>10.07*</td><td>10.17*</td><td>10.85**</td></tr><tr><td>% control</td><td></td><td>106.0%</td><td>103.8%</td><td>107.5%</td><td>108.5%</td><td>115.8%</td></tr></table>[a] Relative to bodyweight
* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01

<u>Females</u>
<table><tr><th>Kidney weights</th><th colspan="6">Dose Group (mg/kg bw/day)</th></tr><tr><th></th><th>0</th><th>250</th><th>500</th><th>1000</th><th>2000</th><th>4000</th></tr><tr><td>Abs (g)</td><td>0.217</td><td>0.234*</td><td>0.230</td><td>0.231</td><td>0.230</td><td>0.253**</td></tr><tr><td>% control</td><td></td><td>107.8%</td><td>106.0%</td><td>106.5%</td><td>106.0%</td><td>116.6%</td></tr><tr><td>Relative[a]</td><td>7.69</td><td>8.32</td><td>8.03*</td><td>8.22*</td><td>8.41**</td><td>8.95**</td></tr><tr><td>% control</td><td></td><td>108.2%</td><td>104.4%</td><td>106.9%</td><td>109.4%</td><td>116.4%</td></tr></table>[a] Relative to bodyweight
* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01

<u>Haematology</u>
No significant findings.

<u>Gross examination and histopathology</u>
Microscopic examination of the skin of dosed mice indicated acanthosis and inflammation at the site of application. Acanthosis occurred in all dosed groups and in one vehicle control female; the severity increased with</td></tr>
</table>

Method	Dose Levels	Remarks
		increasing dose in males and females. Inflammation was only observed in males and females in the 4000 mg/kg bw groups and in one female in the 2000 mg/kg bw group. **eMS Conclusion** The LOAEL (local effects) was established to be 250 mg/kg bw/day , based on skin lesions. The LOAEL (systemic effects) was established to be 2000 mg/kg bw/day based on the magnitude of the kidney weight changes at the top dose, noting the absence of any histopathological findings associated with these changes at any dose level.

5.6.1.4 Repeated dose toxicity: other routes

No information available.

5.6.2 Human information

No information available.

5.6.3 Summary and discussion of repeated dose toxicity

Dermal exposure

In a sub-chronic dermal toxicity study in rats (20 animals/sex/dose) there were significant decreases in bodyweight gain at 2000 mg/kg bw. There were clear local effects at the application site: epidermal thickening (acanthosis), to chronic active inflammation, erosion, and ulceration; the dermis was also thickened with inflammation and fibrosis at the higher doses. Changes in WBC count and differential counts were consistent with the presence of skin inflammation. There were slight but dose-related increases in serum alanine and aspartate aminotransferase activities. Although there were no other changes consistent with effects on the liver. There were dose related increases in kidney weights in both sexes in all treatment groups accompanied by nephropathy in females only.

In a second sub-chronic dermal toxicity in mice findings were similar to those in the rat study. Local findings included scaliness, irritation, and discoloration at the application. Kidney weights were increased but with no histopathological correlates.

Oral exposure

In a sub-chronic dietary toxicity study in rats up to 1000 mg/kg bw/day (91 days), there were no significant adverse findings.

Inhalation exposure

In a sub-acute 28-day inhalation toxicity study (OECD 412), rats exposed to TEA for 6 hours/day and 5 days/week displayed concentration-dependant focal inflammatory changes in the submucosa of the larynx. There were no systemic findings.

5.7 Mutagenicity

Mutagenicity was not identified as an area of concern for TEA. However, carcinogenicity was; therefore, the available information on mutagenicity was evaluated.

5.7.1 Non-human information

5.7.1.1 In vitro data

The results of *in vitro* studies on mutagenicity are summarised in the following table.

Table 14. Summary of *in vitro* genotoxicity data

In vitro data			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
Bacterial reverse mutation assay Guideline: JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) **Environ. Mutagenesis, 8, Suppl.7,1-119, (1986)**	*S. typhimurium*,: TA98, TA97, TA100, TA1535, T and TA1537	TEA (purity not stated) Test concentrations: up to 1000 µg/plate (Conducted with and without metabolic activation)	**Conclusion: Negative** Evidence of cytotoxicity with and without activation, but evaluated up to limit concentrations No data on results of positive and negative controls.
mammalian cell gene mutation assay OECD Guideline 476 (In *vitro* Mammalian Cell Gene Mutation Test) EU Method B.17 Mutagenicity - *In Vitro* Mammalian Cell Gene Mutation Test Information in registration dossier	mouse lymphoma L5178Y cells (TK+/-)	TEA (purity not stated) Test concentrations: up to 1500 µg/ml (Conducted with and without metabolic activivation)	**Conclusion: Negative** Evidence of cytotoxicity with and without activation, but evaluated up to limit concentrations Valid positive and negative controls.

In vitro data			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
Bacterial reverse mutation assay Guideline: JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) **Mut.Res. 153, 57-77 (1985)**	*S. typhimurium*,: TA98, TA1538, TA100, TA1535, T and TA1537 *E. coli*, WP2 *E. coli* WP2 uvr A	TEA (purity 88.2%) Test concentrations: up to 4000 µg/plate (Plate incorporation) (Conducted with and without metabolic activivation)	**Conclusion: Negative** No data on results of positive and negative controls. Supplementary data
Bacterial reverse mutation assay Guideline: None **Mut.Res. 101, 305-313 (1982**	*S. typhimurium*,: TA98, and TA100 *E. coli*, WP2	TEA (purity not stated) Test concentrations: up to 20000 µg/plate (Plate incorporation) (Conducted with and without metabolic activivation) Positive control substance: 4-nitroquinoline-N-oxide;benzo(a)pyrene;N-dimethylnitrosamine	**Conclusion: Negative** Limited design supplementary data.
Bacterial reverse mutation assay Guideline: Following Ames, B.N. et al., Mutation Res., 31, 347-364, 1975 Information in registration dossier	*S. typhimurium*,: TA98, TA100, TA1535, TA1537 and TA1538 *E. coli*, WP2 and *E. coli* WP2 uvr A	TEA (purity 88.18%) Test concentrations: up to 2000 µg/plate (Plate incorporation) (Conducted with and without metabolic activivation)	**Conclusion: Negative** Valid positive and negative controls.
***In vitro* mammalian cytogenetics assay (chromosome aberration test)** Guideline: equivalent or similar to OECD Guideline 473 (*In vitro* Mammalian Chromosome Aberration Test) **Environ.Molec.Mutag. 10 Suppl.10,|1-175 (1987)**	Chinese hamster Ovary (CHO)	TEA (purity not stated) Doses were chosen for the aberration test based on a preliminary test of cell survival 24 hr after treatment. 100 - 2520 µg/ml (without S9) 330 - 10100 µg/ml (with S9) In the first SCE test with each chemical, cells were exposed to a range of doses spanning four to five orders of magnitude, in half-log increments, up to a maximum dose of 5-10 mg/ml or to the limits of solubility in culture medium. In some cases, test	**Conclusion: Negative** No data on the validity of positive and negative controls

In vitro data			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
		chemical precipitate was observed at the higher dose levels. Dose selection for repeat trials involved a range of doses based on observations from the first trial.	
Sister chromatid exchange assay in mammalian cells (DNA damage and/or repair) Guideline: Following Environ. Mutagen. 7, 1-51 **Environ.Molec.Mutag. 10 Suppl.10,|1-175 (1987)**		TEA (purity not stated) Test concentrations: 100 - 2520 µg/ml (without S9) 330 - 10100 µg/ml (with S9) In the first SCE test with each chemical, cells were exposed to a range of doses spanning four to five orders of magnitude, in half-log increments, up to a maximum dose of 5-10 mg/ml or to the limits of solubility in culture medium. In some cases, test chemical precipitate was observed at the higher dose levels. Dose selection for repeat trials involved a range of doses based on observations from the first trial.	**Conclusion: Negative** No data on the validity of positive and negative controls

5.7.1.2 In vivo data

No *in vivo* studies on mutagenicity have been provided.

5.7.2 Human information

No information available.

5.7.3 Summary and discussion of mutagenicity

The *in vitro* genotoxicity of TEA has been investigated in four bacterial reverse mutation assays, a chromosome aberration assay in Chinese hamster Ovary (CHO) cells, mammalian gene mutation and a sister chromatid exchange assay in mammalian cells.

Negative results were reported in all studies. The available data are sufficient to conclude that TEA is not an *in vitro* mutagen.

5.8 Carcinogenicity

One of the areas of concern for the human health evaluation of TEA was carcinogenicity, specifically liver tumours in rats.

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

Table 15. Summary of oral carcinogenicity studies

<table>
<tr><th>Method</th><th>Dose Levels</th><th>Remarks</th></tr>
<tr>
<td>Test species: Rat Fischer 344/DuCrj

Route: Oral

Group Sizes: 50/sex/dose

Test material: TEA (purity ca 99% quoted in study but later found to contain ca 2% DEA)

Route: Oral (drinking water)

Guideline: None

Groups of rats were dosed (in drinking water) for 104 weeks, and thereafter tap water was given to animals in all groups, observation being continued until wk 113 when all survivors were sacrificed. Moribund or dead animals were autopsied completely and examined pathologically for the development of tumours.

J. Toxicol. Environ. Health, 19, 345-357 (1986)</td>
<td>1 % and 2 % TEA in drinking water (ca. 667 and 1333 mg/kg kg/bw/day), (from week 69: 0.5 % and 1 %, in females, ca. 333 and 667 mg/kg bw/day)

(estimates provided by registrant)</td>
<td>Study designed to investigate carcinogenicity; other parameters investigated were limited to clinical signs, organ weights, bodyweights, and pathology.

The dose levels in females were reduced by half from wk 69, because of associated nephrotoxicity.

There was a dose-related decrease in bodyweight gains. In males final bodyweights were 98 and 90% of control values in low and high dose groups respectively. In females final bodyweights were 93 and 86% of control values in low and high dose groups respectively.

A variety of tumours developed in all groups, including the control group, and all tumours observed were histologically similar to spontaneous tumours in this strain of rats.

There were statistically significant dose related increases in kidney weight (relative and absolute) in both sexes. There was an increase in nephrotoxicity, which appeared to have an adverse effect on the life expectancy of the treated animals, especially of females.

No statistically significant increase of the incidence of any tumour was observed in the treated groups of both sexes by the chi-square test.

The mortality rates in males were unaffected by treatment, however in females there was a clear dose dependency.

<table>
<tr><th colspan="6">% mortality rate at 2 years</th></tr>
<tr><th colspan="3">Males</th><th colspan="3">females</th></tr>
<tr><th>control</th><th>1%</th><th>2%</th><th>control</th><th>1%</th><th>2%</th></tr>
<tr><td>32</td><td>32</td><td>34</td><td>16</td><td>32</td><td>42</td></tr>
</table>

Therefore, an age-adjusted statistical analysis on incidences of main tumours or tumour groups of both sexes was also done by methods recommended by Peto et al. (1980).

The results of this analysis showed that a positive trend ($p < 0.05$) was noted in the occurrence of hepatic tumours (neoplastic nodule/hepatocellular carcinoma) in males and of uterine endometrial sarcomas and renal-cell adenomas in females. The study authors note that these tumours were observed spontaneously in this strain of rats, and their incidences in the control group of the present study were lower than those of the laboratory's historical controls (no actual historical control data were presented in the paper).

See Table 17 for summary of hepatic, uterine and renal tumours.

Increased incidence of renal tumours in the female high-dose group may have been connected with renal damage. Histological examination of renal damage observed in the treated groups, especially in the female high-dose group, revealed acceleration of 'chronic nephropathy'. In addition, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis</td>
</tr>
</table>

Method	Dose Levels	Remarks
		with or without papillary necrosis were also observed. **<u>eMSCA Conclusion</u>** The eMSCA concludes that there was no clear evidence of carcinogenic potential of TEA in Fischer 244 rats. It is noted that the IARC Monograph for TEA concluded that there was no evidence for treatment related tumours. It was not possible to set a NOAEL for chronic toxicity because of effects seen in the kidneys at the lowest dose and mortality rates in females.

Table 16. Hepatic, uterine and renal tumours in 2 year rat study (TEA administered via drinking water)

Organ/Lesion	Treatment Group					
	Males			Females		
	Control	1% TEA	2% TEA	Control	1% TEA	2% TEA
Number of rats Examined	48	49	48	50	48	47
<u>Uterus</u>						
Endometrial-stromal polyp	-	-	-	14	7	7
Adenoma	-	-	-	2	3	3
Adenocarcinoma	-	-	-	3	7	5
Endometrial-stromal sacoma[a]	-	-	-	0	3	3
<u>Liver</u>						
Neoplastic nodule[a]	1	2	5	0	0	1
Hepatocellular carcinoma[a]	0	0	1	0	0	0
<u>Kidney</u>						
Renal cell adenoma	0	1	0	0	0	2

[a] A positive trend ($p<0.05$) was noted in the occurrence of hepatic tumours (neoplastic nodule/hepatocellular carcinoma) in males and of uterine endometrial sarcomas and renal-cell adenomas in females by Peto trend analysis tests (Peto *et al* 1980).

Table 17. Summary of oral carcinogenicity studies

Method	Dose Levels	Remarks
Test species: mouse (B6C3F1) **Route**: Oral **Group Sizes**: 50/sex/dose **Test material:** TEA (purity not stated) **Route**: Oral (drinking water)	1, 2% in drinking water (ca. 1600; 3200 mg/kg) (estimates provided by registrant)	Study designed to investigate carcinogenicity; other parameters investigated were limited to clinical signs, bodyweights, organ weights and pathology. There were slight effects on bodyweight gains in both sexes, which were dose related. There were no significant effects on organ weights. In males final bodyweights were 97 and 89% of control values in low and high dose groups respectively. In females final bodyweights were 93 and 86% of control values in low and high dose groups respectively. Neoplasms developed in all groups, including the control group, but no dose-related increase of the incidence of any tumour was observed in treated groups of both sexes. There were no adverse effects as regards survival of the mice, organ weights, and specific incidence of neoplasms in the treated, compared to the control group. This chronic toxicity test provides no evidence of carcinogenic potential of TEA in B6C3F1 mice

Guideline: None Groups of mice were dosed (in drinking water) for 82 weeks, After 82 weeks, surviving mice were deprived of food overnight and then killed under aneasthesia and exsanguinated. Organs were weighed and/or sampled for further examination of tumours. **Fundam. Appl. Toxicol. 18, 25-29** Original study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary in IUCLID and the CSR.		The ECHA Guidance on the Application of the CLP Criteria lists B6C3F1 mice as having a high spontaneous tumour incidence in the liver. **<u>eMSCA Conclusion</u>** There was no evidence of carcinogenicity at the top dose tested. The NOAEL for chronic toxicity was the 1% drinking water level (equivalent to approx. 1600 mg/kg bw/day), based on the reductions seen in bodyweight gain in females at the top dose, although it is noted that the study is of limited design in terms of chronic toxicity assessment. .

Method	**Dose Levels**	**Remarks**
Test species: ICR-JCL mice **Group Sizes**: 40/sex/dose for 2 years **Test material:** TEA (stated as analytical grade) treated as follows; An acidic reaction mixture consisting of equal volumes of TEA (1 g/ml) and sodium nitrite (1 g/ml) solutions in	0 (Control animals received untreated diet), 0.03 or 0.3% (w/w) TEA ($NaNO_2$ reaction mixture see methods). .	This study was obtained by the eMSCA since it was referenced in the IARC Monograph for TEA, but not provided by the registrant. The study is unusual in that the mice were exposed in the diet to TEA which had been reacted with sodium nitrite at 37ºC under acidic conditions. This methodology was apodted after it was noted by the authors that TEA was not mutagenic to *Bacillus subtilis* by itself, but it became mutagenic after reacting with sodium nitrite under acidic conditions or when the mixture was heated. The study authors note that although N-nitrosodiethanolamine, a known carcinogen and mutagen, was detected in the reaction mixture by TLC, it may not be the main mutagenic product, because the product was a stable and direct mutagen and its mutagenic activity was destroyed by liver enzymes, unlike N-nitrosodiethanolamine. The compound causing cytotoxic and mutagenic effects in bacteria was therefore unidentified. The survival rates were unaffected by treatment There was a statistically significant ($p < 0.05$, test unspecified) increase in the

0.1 M acetic acid buffer (pH 3.5). The mixture was incubated for 8 hr at 37°Cand then neutralized with 1 N NaOH. For the heating reaction the mixture of TEA and sodium nitrite (without buffer) was autoclaved for 20 min at 120°C. **Route**: Oral (diet) **Guideline**: None Groups of mice were dosed (in drinking water) for 82 weeks, After 82 weeks, surviving mice were deprived of food overnight and then killed under aneasthesia and exsanguinated. Organs were weighed and/or sampled for further examination of tumours. **Cancer Research 38, 3918-3921, November 1978**		incidence of lymphomas in female mice (controls, 1/36; low dose, 7/37; high dose, 9/36), but no increase in the incidence of tumours at any site in male mice. No HC data were provided for the incidence of lymphomas in this strain of mouse. **eMSCA Conclusion** The eMSCA considers this study of limited value given the uncertainty over the exact nature of the compounds the mice were exposed to, which could be reaction and/or degradation products (produced by the heat treatment).

5.8.1.2 Carcinogenicity: inhalation

No relevant information available.

5.8.1.3 Carcinogenicity: dermal

Table 18. Summary of dermal carcinogenicity studies

Method	Dose Levels	Remarks
Test species: Rat Fischer 344/DuCrj	0, 32, 63, or 125 mg/kg bw/day (males) and 0, 63, 125, or 250 mg/kg	Doses based on the presence of acanthosis and inflammation at the site of application at the higher doses in the 13-week study. **Mortalities and clinical signs**

Method	Dose Levels	Remarks
Study Duration: 103 weeks (5 days per week). **Group Sizes**: 60/sex/dose Ten male and ten female rats from each group were evaluated at 15 months for organ weights and histopathology **Test material:** TEA (purity ca 99%) **Vehicle**: Acetone **Route**: Dermal **Guideline**: None **NTP (1999)**	bw/day (females)	The survival rate of females in the 250 mg/kg group was slightly less than that of the vehicle controls. Male and female rats receiving TEA had irritated skin at the site of application; in dosed females, the site of application also had a crusty appearance. The number of animals in which these findings were observed increased with increasing dose. **Bodyweights** The mean body weight of females administered 250 mg/kg ranged from 9% to 12% less than that of the vehicle controls between weeks 73 and 93. **Organ weights** At the 15-month interim evaluation, the absolute left and right kidney weights and relative right kidney weight of females administered 250 mg/kg were significantly greater than those of the vehicle controls. **Pathology** The incidence of acanthosis at the site of application in males administered 125 mg/kg and the incidences of acanthosis, inflammation, and ulceration in dosed females were greater than in the vehicle controls at the 15-month interim evaluation and at the end of the 2-year study. Males in the 125 mg/kg group also had greater incidences of inflammation and ulceration than the vehicle controls, and females receiving 125 or 250 mg/kg had greater incidences of epidermal erosion than the vehicle controls at 2 years. There were no skin neoplasms at or away from the site of application that were considered related to treatment with triethanolamine. At the end of the study, renal tubule adenomas were observed in 7 dosed males and in one vehicle control female and one female in the 63 mg/kg group. One male in the 125 mg/kg group and one female in the 250 mg/kg group had renal tubule hyperplasia. Extended (step-section) evaluation of the kidneys of all male rats revealed additional renal tubule adenomas in one vehicle control male, one male in the 32 mg/kg group, two males in the 63 mg/kg group, and three males in the 125 mg/kg group (including one male from the 15-month interim evaluation). An oncocytoma was also identified in one male in the 32 mg/kg group. Hyperplasia was identified in eight additional vehicle control males and in 19 additional dosed males. The total incidences (combined standard and extended evaluations) of renal tubule adenoma in dosed male rats were slightly greater than the vehicle control incidence (vehicle control, 1/50; 32 mg/kg, 2/50; 63 mg/kg, 6/49; 125 mg/kg, 4/50), though none reach statistical significance. The total incidence of hyperplasia in dosed and vehicle control males was similar (9/50, 8/50, 7/49, 6/50). There was no clear dose relationship in the severity of hyperplasia in males. Summary of pathology findings presented in Table 20. **eMSCA Conclusion** The eMSCA concludes there was equivocal evidence of carcinogenic activity of TEA in male rats based on a slight increase in the incidences of renal tubule

Method	Dose Levels	Remarks
		cell adenoma. There was no evidence of carcinogenic activity in female rats. The NOAEL for systemic toxicity was 125 mg/kg bw/day based on the reduced bodyweights in females. The NOAEL for local effects was 63 mg/kg bw/day based on skin lesions at the site of application. It is noted that based on this study IARC (2000) concluded that there was no significant increase in the incidence of tumours at any site.
Test species: Mouse B6C3F1 **Study Duration:** 104 (males) or 105 (females) weeks (5 days per week) **Group Sizes**: 60/sex/dose Ten male and ten female mice from each group were evaluated at 15 months for organ weights and histopathology **Test material:** TEA (purity ca 99% 2% DEA) **Vehicle**: Acetone **Route**: Dermal **Guideline**: None **NTP (1999)**	100, 300, 1000 mg/kg bw/day (dermal doses (females)) 200, 630, 2000 mg/kg bw/day (dermal doses (males))	Doses based on a 13-week study. This study was compromised by the presence of an infection with *Helicobacter hepaticus*. An increased incidence of hepatocellular neoplasms in male mice has been shown to be associated with *H. hepaticus* infection when hepatitis is also present. **eMSCA Conclusion** Although this study was compromised by the *H. hepaticus* infection it is still worth noting the in incidence of liver tumours seems to be exacerbated by TEA.
Test species: Mouse B6C3F1 **Study Duration: 104 (males) or 105 (females) weeks (5 days per week)** **Group Sizes: 50/sex/dose** **Test material: TEA (**purity	100, 300, 1000 mg/kg bw/day (dermal doses (females)) 200, 630, 2000 mg/kg bw/day (dermal doses (males))	The 1999 NTP study in $B6C3F_1$ mice was considered inadequate due to the presence of *H. hepaticus* infection, which complicated interpretation of the relationship between TEA administration and liver neoplasms. It was considered that evaluating the role of TEA in the development of liver neoplasms in uninfected mice is necessary to complete the characterisation of the carcinogenic hazard of TEA. Therefore a second dermal mouse study was conducted. **Mortalities and clinical signs** Survival of all dosed groups was similar to that of the vehicle control groups. Treatment-related clinical findings included skin irritation at the site of application, which increased with increasing dose and was more severe in

Method	Dose Levels	Remarks
greater than 99% less than 0.1% DEA) **Vehicle: Acetone** **Route: Dermal)** **Guideline: None** **NTP (2004c)** **NTP (2004b)**		males than in females **Bodyweights** Body weights of 2,000 mg/kg males were less than those of the vehicle controls from weeks 17 to 37 and at the end of the study; body weights of dosed groups of females were similar to those of the vehicle controls throughout the study. **Organ weights** Not undertaken **Pathology** Liver: Gross lesions observed at necropsy included nodules and masses of the liver in dosed females. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends in females, and the incidences of these neoplasms in all dosed groups of females were significantly increased. The incidence of hepatocellular adenoma in 300 mg/kg females was at the upper end of the historical control range, and the incidences of hepatocelluar adenoma in 1000 mg/kg females and of hepatocellular adenoma or carcinoma (combined) in all dosed groups of females exceeded the historical ranges in controls (all routes) given NTP-2000 diet. The incidences of multiple hepatocellular adenoma were significantly increased in the 300 and 1000 mg/kg females. Historically, approximately 18% (31/170) of female control mice that developed hepatocellular adenomas had multiple adenomas. Adenomas weren't found in the vehicle controls; multiple adenomas occurred in 3 (17%), 7 (35%), and 17 (52%) of the females in the 100, 300, and 1000 mg/kg groups, respectively, that developed hepatocellular adenomas. The incidences of hepatocellular neoplasms in males were similar to those in the vehicle controls. The incidences of hepatoblastoma were slightly increased in 630 and 2000 mg/kg males, but the incidences were within the historical control range and were not considered treatment-related. The incidence of hemangioma in 2000 mg/kg males was greater than that in the vehicle controls, and the incidence of hemangiosarcoma in 630 mg/kg males was significantly increased; the incidences of these lesions in these groups exceeded the historical control ranges. Two 630 mg/kg males had multiple hemangiosarcomas of the liver. The pathology report states that the hepatocellular adenomas were nodular, expansile lesions that occupied an area greater than one liver lobule. They were well demarcated from surrounding parenchyma by a zone of compression or lack of continuity between the hepatic cords within the nodule and those of the surrounding parenchyma. There was loss of normal lobular architecture, with a lack of portal triads and haphazardly arranged hepatic cords, often with areas of atypia. Neoplastic cells were generally large, with abundant eosinophilic and variably vacuolated cytoplasm, increased nuclear to cytoplasmic ratio, and nuclear atypia and with an increased mitotic index. The report notes that hepatoblastomas are uncommon neoplasms in mice. Histologically, they have a characteristic appearance of small, dark, ovoid- to spindle-shaped cells with round to oval nuclei and scant amounts of eosinophilic cytoplasm arranged in compact sheets, islands, or trabeculae. Hepatoblastomas almost always occur within an existing proliferative lesion,

Method	Dose Levels	Remarks
		most often a hepatocellular carcinoma. The report states that avoid duplicate diagnoses, NTP studies make no separate diagnosis for the lesion within which the hepatoblastoma occurs. The haemangiosarcomas seen in this study were characterised by pleomorphic, proliferative endothelial cells forming irregular vascular spaces, occasionally with areas of thrombosis. The haemangiomas were characterised by irregular vascular spaces lined by a single layer of flattened, mature appearing endothelial cells. Haemangiosarcoma also occurred in the spleen in two males from each of the vehicle control, 200, and 630 mg/kg groups, and the aorta of one male in the 2000 mg/kg group. In one male in each of the vehicle control and dosed groups, haemangiosarcoma metastasized from the spleen or aorta to the liver, and haemangiosarcoma metastasized from the spleen to the bone marrow in one vehicle control and one 630 mg/kg male. The incidence of haemangiosarcoma in all organs was significantly increased in the 630 mg/kg group and exceeded the historical control range; this increase was attributed to the high incidence of hemangiosarcoma in the liver of mice in this group. The study states that spontaneous hemangiosarcomas occur in 3.0% of male B6C3F1 mice and 3.6% of females and that haemangiosarcomas may occur at a variety of sites, but the liver and spleen are the most common sites in male B6C3F1 mice, and the spleen and subcutis are the most common sites in females. The study states that for 20 NTP chemical studies for which there was a chemical-related increased incidence in vascular neoplasms, the increased incidences occurred most commonly at a specific site, and less commonly at two or more specific sites. In general, the vasculature as a whole is not affected; rather the vasculature within a specific organ/tissue is affected. The most common site of chemically induced vascular neoplasms in NTP studies is the liver. In this study the incidence of vascular neoplasms in the liver was notable given that it’s statistically significant, outside of historical control ranges in some instances, and only in the 630 mg/kg group. The incidences of haemangiomas of the liver were low in each group and not significantly different between groups, although they did exceed historical control ranges. The study authors note that unlike liver and kidney tumours biological continuum between benign and malignant neoplasm is not strong for between haemangioma and haemangiosarcomas. Also, in the majority of NTP studies with chemical-related increases in the incidences of vasculature neoplasms have involved haemangiosarcomas without an increase in haemangiomas, but not all studies. The incidences of eosinophilic focus in all dosed groups of males and in 300 and 1000 mg/kg females were significantly increased. The incidences of mixed cell focus in dosed groups of females were greater than that in the vehicle controls, and the incidence in the 300 mg/kg group was significantly increased. Foci of cellular alteration were defined as sharply demarcated clusters of cells with altered cytoplasmic tinctoral properties. Eosinophilic and mixed foci were variably sized and ranged from approximately one hepatic lobule to several hepatic lobules, generally causing little compression of the adjacent parenchyma. There was little or no alteration of normal hepatic architecture within the focus, and cellular atypia was generally absent. Component cells of the eosinophilic foci were large with abundant eosinophilic cytoplasm. In the mixed foci, the eosinophilic cells were admixed with a second population of cells with prominent fine to coarse cytoplasmic vacuolation.

Method	Dose Levels	Remarks
		Skin: Gross lesions observed at necropsy included visible crusts at the site of application in all dosed groups of mice. Treatment-related epidermal hyperplasia, suppurative inflammation, ulceration, and dermal chronic inflammation occurred at the site of application in most dosed groups of mice, and the incidences and severities of these lesions generally increased with increasing dose. Summary of Pathology finding in Table 21. **eMSCA Conclusion** The eMSCA considers that there was equivocal evidence of carcinogenic activity of TEA in male mice based on the occurrence of liver hemangiosarcoma. There was some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular adenoma. Exposure to TEA by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related non-neoplastic lesions at the site of application The LOAEL for systemic toxicity was 200 mg/kg bw/day based on the significantly increased incidence of hepatocellular adenoma or carcinoma (combined) in all dosed groups of females. The ECHA Guidance on the Application of the CLP Criteria lists B6C3F1 mice as having a high spontaneous tumour incidence in the liver. The NOAEL for local effects was 100 mg/kg bw/day based on skin lesions at the site of application in males.

Table 19: RENAL TUBULE LESIONS: Summary of Pathology Findings from 2 year Dermal Carcinogenicity Study in the Rat

Note: The standard evaluation of the kidneys in these studies included microscopic examination of a longitudinal section of the central portion of the left kidney and a cross section of the central portion of the right kidney. Step sections were made from the residual kidney wet tissue from all male rats because microscopic examination of the original kidney sections showed increased incidences of proliferative lesions. Kidneys were sectioned in increments of 0.5 mm to produce four additional sections per kidney, or eight sections per animal.

SEX/TIME POINT/LESION	NUMBER OF ANIMAL AFFECTED (Ave severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked)			
MALES	**0 mg/kg**	**32 mg/kg**	**63 mg/kg**	**125 mg/kg**
15-MONTH INTERIM EVALUATION				
Single Sections (Standard Evaluation)				
Number Examined Microscopically	**10**	**10**	**10**	**10**
Nephropathy, Chronic[a]	10 (2.0)	9 (2.0)	10 (2.0)	10 (1.6)
Step Sections (Extended Evaluation)	**10**	**10**	**10**	**10**
Adenoma	0	0	0	1
Single Sections and Step Sections (Combined)				
Number Examined Microscopically	**10**	**10**	**10**	**10**
Nephropathy, Chronic	10 (2.0)	9 (2.0)	10 (2.0)	10 (1.6)
Adenoma	0	0	0	1
2-YEAR STUDY				
Single Sections (Standard Evaluation)				
Number Examined Microscopically	**50**	**50**	**50**	**50**
Hyperplasia[a]	1 (3.0)	0	1 (1.0)	1 (3.0)
Nephropathy, Chronic	48 (2.6)	49 (2.6)	49 (2.6)	50 (2.7)
Adenoma[b]	0	1	4	2
Step Sections (Extended Evaluation)				
Number Examined Microscopically	**50**	**50**	**50**	**50**
Hyperplasia	8 (1.5)	8 (2.6) [c]	6 (1.2)	5 (2.4)
Adenoma	1	1	2	2
Oncocytoma	0	1	0	0
Single Sections and Step Sections (Combined)				
Number Examined Microscopically	**50**	**50**	**50**	**50**
Hyperplasia[a]	9 (1.7)	8 (2.6)	7 (1.5)	6 (2.5)
Nephropathy, Chronic	48 (2.6)	49 (2.6)	49 (2.6)	50 (2.7)
Adenoma[b]	1	2	6	4
Oncocytoma	0	1	0	0
FEMALES	**0 mg/kg**	**32 mg/kg**	**63 mg/kg**	**125 mg/kg**
15-MONTH INTERIM EVALUATION				
Number Examined Microscopically	**10**	**10**	**10**	**10**
Nephropathy, Chronic	9 (1.0)	8 (1.0)	8 (1.0)	4* (1.3)
2-YEAR STUDY				
Number Examined Microscopically	**50**	**50**	**50**	**50**
Hyperplasia	0	0	0	1 (1.0)
Nephropathy, Chronic	45 (1.7)	44 (1.5)	41 (1.7)	42 (1.5)
Adenoma	1	1	0	0

[a]Includes hyperplasia and renal tubule hyperplasia

[b]Historical incidence for 2-year NTP dermal studies with acetone vehicle control groups (mean ± standard deviation): 0/100. Historical incidence for 2-year NTP feed studies with untreated control groups: 9/1,200 (0.8% ± 1.5%); range, 0%-6%.

[c] Severity grade was not given for one animal in this group.

2 Year Dermal Carcinogenicity Study in the Mouse (NTP 2004 c, b)

Table 20: LIVER: Summary of Pathology Findings from 2 year Dermal Carcinogenicity Study in the Mouse

SEX/TIME POINT/LESION	NUMBER OF ANIMAL AFFECTED			
MALES	**0 mg/kg**	**200 mg/kg**	**630 mg/kg**	**2000 mg/kg**
Number Examined Microscopically	**50**	**50**	**50**	**50**
Eosinophilic Focus[a]	9	20*	31**	30**
Hemangioma[b]	0	1	0	2
Hemangiosarcoma, Multiple	0	0	2	0
Hemangiosarcoma (includes multiple)[c]				
Overall rate[d]	1/50 (2%)	0/50 (0%)	6/50 (12%)	1/50 (2%)
Adjusted rate[e]	2.1%	0.0%	13.5%	2.2%
Terminal rate[f]	1/37 (3%)	0/43 (0%)	3/34 (9%)	1/40 (3%)
First incidence (days)	726 (T)	- [h]	517	726 (T)
Poly-3 test[g]	P=0.587	P=0.501N	P=0.047	P=0.7
Hepatocellular Adenoma	19	18	23	20
Hepatocellular Carcinoma	17	14	14	11
Hepatocellular Adenoma or Carcinoma	33	27	33	25
Hepatoblastoma[i]	1	1	2	3
FEMALES	**0 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
Number Examined Microscopically	**50**	**50**	**50**	**50**
Eosinophilic Focus	16	22	28*	32*
Mixed Cell Focus	5	8	14*	11
Hepatocellular Adenoma, Multiple	0	3	7*	17**
Hepatocellular Adenoma (includes multiple)[j]				
Overall rate	9/50 (18%)	18/50 (36%)	20/50 (40%)	33/50 (66%)
Adjusted rate	19.9%	41.0%	43.5%	72.4%
Terminal rate	6/35 (17%)	16/34 (47%)	18/41 (44%)	25/32 (78%)
First incidence (days)	617	665	444	604
Poly-3 test	P<0.001	P=0.024	P=0.012	P<0.001
Hepatocellular Carcinoma	6	8	4	5
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	12/50 (24%)	23/50 (46%)	24/50 (48%)	34/50 (68%)
Adjusted rate	26.3%	51.0%	51.7%	74.6%
Terminal rate	7/35 (20%)	17/34 (50%)	21/41 (51%)	26/32 (81%)
First incidence (days)	595	601	444	604
Poly-3 test	P<0.001	P=0.011	P=0.009	P<0.001

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test

** P≤0.01

(T) Terminal sacrifice

[a] Number of animals with lesion

[b] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 2/1,159 (0.2% ± 0.6%), range 0%-2%

[c] Historical incidence: 28/1,159 (2.5% ± 1.4%), range 0%-4%

[d] Number of animals with neoplasm per number of animals with liver examined microscopically

[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[f] Observed incidence at terminal kill

[g] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by N.

[h] Not applicable; no neoplasms in animal group

[i] Historical incidence: 16/1,159 (1.5% ± 2.6%), range 0%-10%

[j] Historical incidence: 179/1,152 (16.3% ± 6.6%), range 6%-28%

[k] Historical incidence: 250/1,152 (22.8% ± 9.4%), range 8%-40%

Table 21: HEMANGIOMA AND HEMANGIOSARCOMA: Summary of Pathology Findings from 2 year Dermal Carcinogenicity Study in the Mouse (MALES)

SEX/TIME POINT/LESION	NUMBER OF ANIMALS AFFECTED			
MALES	**0 mg/kg**	**200 mg/kg**	**630 mg/kg**	**2000 mg/kg**
Number Examined Microscopically	**50**	**50**	**50**	**50**
Hemangioma, Liver[a]	0	1	0	2
Hemangiosarcoma, Liver	1	0	6*	1
Hemangiosarcoma, Liver, Metastatic, Aorta	0	0	0	1
Hemangiosarcoma, Liver, Metastatic, Spleen	1	1	1	0
Hemangiosarcoma, Aorta	0	0	0	1
Hemangiosarcoma, Bone Marrow, Metastatic, Spleen	1	0	1	0
Hemangioma, Spleen	1	0	0	0
Hemangiosarcoma, Spleen	2	2	2	0
Hemangiosarcoma (All Organs)[b]				
Overall rate[c]	3/50 (6%)	2/50 (4%)	9/50 (18%)	2/50 (4%)
Adjusted rate[d]	6.3%	4.3%	20.1%	4.3%
Terminal rate[e]	1/37 (3%)	2/43 (5%)	5/34 (15%)	1/40 (3%)
First incidence(days)	624	726 (T)	517	618
Poly-3 test[f]	P=0.442N	P=0.508N	P=0.046	P=0.513
Hemangioma or Hemangiosarcoma (All Organs)[g]				
Overall rate	4/50 (8%)	3/50 (6%)	9/50 (18%)	4/50 (8%)
Adjusted rate	8.4%	6.4%	20.1%	8.6%
Terminal rate	2/37 (5%)	3/43 (7%)	5/34 (15%)	3/40 (8%)
First incidence (days)	624	726 (T)	517	618
Poly-3 test	P=0.550	P=0.509N	P=0.092	P=0.628

* Significantly different (P#0.05) from the vehicle control group by the Poly-3 test (T)Terminal sacrifice

[a] Number of animals with lesion

[b] Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ± standard deviation): 59/1,159 (5.3% ± 3.4%), range 0%-14% Number of animals with neoplasm per number of animals necropsied

[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[e] Observed incidence at terminal kill

[f] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by N.

[g] Historical incidence: 73/1,159 (6.4% ± 3.3%), range 2%-14%

5.8.2 Human information

No relevant information available.

5.8.3 Summary and discussion of carcinogenicity

Rat (Oral Dosing via Drinking Water)

In an oral carcinogenicity study, Fischer rats were exposed daily to TEA via the drinking water for 2 years. In week 69, dose levels in females were reduced to 0.5 and 1% (corresponding to ca. 333 and 667 mg/kg bw/day), because of associated nephrotoxicity.

Although there was a positive trend towards increased occurrence of hepatic tumours in males and of uterine endometrial sarcomas and renal-cell adenomas in females, based on an age-adjusted statistical analysis, it was judged as not related to the treatment.

The eMSCA concludes that TEA was not carcinogenic under these conditions in the Fischer rat.

Mouse (Oral Dosing via Drinking Water)

In an oral carcinogenicity study B6C3F1 mice were exposed daily to TEA via the drinking water for 82 weeks. There was no evidence for carcinogenic potential of TEA in mice.

The eMSCA concludes that TEA was not carcinogenic under these conditions in the B6C3F1 mice.

Mouse (Oral Dosing via Diet with a containing TEA which had been reacted with sodium nitrite under acidic/heated conditions)

This study (Cancer Research 38, 3918-3921, November 1978) was considered of limited value owing to the unknown nature of the compounds to which the mice were exposed.

Mouse (Dermal Dosing (Acetone Vehicle))

These NTP studies used acetone as a vehicle which would likely markedly increase the dermal penetration of TEA.

Although an initial study NTP study (NTP 1999) was compromised by the *H. hepaticus* infection it is still worth noting the increased incidence of liver tumours seems to be exacerbated by TEA. The study used B6C3F1, a strain that is known to have a high spontaneous tumour incidence in the liver. This study was repeated in 2004 again in B6C3F1 mice.

In the second NTP 2004 study TEA was administered to mice 5 days per week for 2 years.

There was a slight increase in haemangiosarcomas in the livers of males exposed to TEA; although not dose-related, the increase was above historical control data. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all dosed groups of females.

Given the high spontaneous occurrence of liver tumours in B6C3F1 mice, the increased incidence of liver tumours in a single sex in this strain is not considered sufficient to conclude that TEA is carcinogenic. An increased incidence of haemangiosarcomas in the livers of male mice was also reported in the same study. Taking into account that the increased incidence occurred only in one sex of one species in one study and was not dose-related, the eMSCA concluded that this was most likely a chance finding that was not related to treatment.

The eMSCA concludes that the concern has been clarified and no further information is requested.

5.9 Toxicity for reproduction

Reproductive toxicity was not an initial concern for TEA and was not identified as an additional concern.

5.10 Endocrine disrupting properties

There are no concerns for endocrine disruption potential for TEA.

5.11 Other effects

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

No information available.

5.11.1.2 Immunotoxicity

No information available.

5.11.1.3 Specific investigations: other studies

The registrant has provided some mechanistic studies on tumour formation to further investigate the potential of TEA to induce tumour formation.

Table 22: Summary of studies to investigate the potential of TEA to induce tumour formation

Method	Dose Levels	Remarks
Study: Mechanistic (*in vivo*); Study in the transgenic Tg.AC mouse which carries an inducible v-Ha-ras oncogene that imparts the characteristic of genetically initiated skin to these animals. **Test species:** mouse (Tg.AC) female **Group Size**: 15/sex/dose **Exposure period**: 20 week (5 days/week) **Test Substance**: TEA (purity 99% two batches 0.04% DEA 0.45% DEA)) **Vehicle**: acetone **Route**: dermal **Toxicological Sciences 49, 241-254 (2000)**	0, 120, 400, 1200 mg/kg bw/day	Homozygous Tg.AC mice in the negative control groups treated with acetone developed a very low frequency of papillomas. The average papilloma incidence among animals treated 5 days per week with 3.0 to 30 mg of TEA was not significantly different from the incidence observed in animals treated with acetone, the negative control and solvent vehicle. There was no significant difference in weight gain among vehicle-control or TEA-treated groups. Survival was slightly reduced in the TEA-treated groups, but this was mainly due to removal of animals with odontomas from the study.
Study: Mechanistic (*in vivo*); The haplo-insufficient p53 knockout ($p53^{+/-}$) and zetaglobin v-Ha-ras (Tg.AC) transgenic mouse models	0, 120, 400, 1200 mg/kg bw	TEA was inactive in Tg•AC mice. The average incidence of mice bearing papillomas was uniformly high among all groups of the TEA-treated mice, as well as in the acetone control group. However, the average tumour multiplicity was less than 1.0 in every instance. There was no indication that this low multiplicity

Method	Dose Levels	Remarks
were compared to conventional two rodent species carcinogen bioassays by prospectively testing nine chemicals (including TEA which was only tested in Tg•ACmice). **Test species:** mouse (Tg.AC) female **Group Size:** 13-20/sex/dose **Exposure period**: 20 week (5 days/week) **Test Substance**: TEA (purity 99% two batches 0.04% DEA 0.45% DEA)) **Vehicle**: acetone **Route**: dermal The positive control agent was TPA 1.25 µg 3x/week or 1.5 µg, 2x/week for 20 weeks. **Toxicological Sciences 53, 213–223 (2000)**		was related to treatment, as the average multiplicity of papillomas forTg.AC mice was in the range observed for negative(vehicle) control groups (Toxicological Sciences 49, 241-254 (2000)).

Toxicological Sciences 49, 241-254 (2000)

A 1999 published study described the development of a transgenic mouse model for carcinogenesis bioassays. The induction of epidermal papillomas in the area of topically applied chemical agents, for duration of not more than 26 weeks, acts as a reporter phenotype that defines the activity of the test article. The study described here the activity of six chemicals, including TEA that had been previously characterized for activity in the standard 2 -year bioassay conducted by the National Toxicology Program (NTP).

The transgenic Tg.AC mouse carries an inducible v-Ha-ras oncogene that imparts the characteristic of genetically initiated skin to these animals. Homozygous female Tg.AC mice were treated with benzene (BZ), benzethonium chloride (BZTC), o-benzyl-p- chlorophenol (BCP), 2 -chloroethanol (2 -CE), lauric acid diethanolamine (LADA) and triethanolamine (TEA). BZ and LADA induced skin papillomas in a dose-dependent manner, while BCP induced papillomas only at the highest dose. BZTC, 2-CE, and TEA exhibited no activity.

Toxicological Sciences 53, 213–223 (2000)

The haplo-insufficient p53 knockout (p531/2) and zetaglobin v-Ha-ras (Tg.AC) transgenic mouse models were compared to the conventional two rodent species carcinogen bioassay by prospectively testing nine chemicals. TEA was administered to homozygous female mice. The application site was closely shaven prior to the first treatment, then shaved weekly or as needed prior to subsequent

treatments. The TEA in acetone was administered in 200-ml volumes 5x/week for 20 weeks. A 20-week dermal exposure period was the standard protocol used for studies in Tg.AC mice.

Table 23: Activity of TEA in the Tg.AC Transgenic Mouse Model

Treatment	Number of animals	Incidence (%)	Mean weeks to first tumour	Multiplicity (tumours/total animals/group)	Mean weeks to maximum tumour burden	Survival at 20 weeks (%)
3.0 mg	14	4/14 (28.6)	11.8	5/14 (0.36)	13.8	11/14 (78.6)
10.0 mg	13	5/13 (38.5)	13.4	10/13 (0.77)	14.8	12/13 (92.3)
30.0 mg	19	4/19 (21.1)	8.8	10/19 (0.53)	13.5	15/19 (78.9)
Acetone 200 ml	14	4/14 (28.6)	13.3	4/14 (0.29)	13.3	14/14 (100)
TPA 1.25 mg (2x/week)	20	19/20 (95.0)	7.6	390/20 (19.5)	12.4	9/20 (45.0)

TEA was inactive in Tg.AC mice. The average incidence of mice bearing papillomas was uniformly high among all groups of the TEA-treated mice, as well as in the acetone control group. However, the average tumour multiplicity was less than 1.0 in every instance. There was no indication that this low multiplicity was related to treatment, as the average multiplicity of papillomas forTg.AC mice was in the range observed for negative (vehicle) control groups.

5.11.2 Human information

Data on skin sensitisation provided see section (5.5).

5.11.3 Summary and discussion of specific investigations

5.12 Combined effects

No specific studies are available. There was no evidence found in the literature accessed to indicate that TEA can cause additional toxicity as part of a mixture. No additional concerns are identified.

5.13 Derivation of DNEL(s) / DMEL(s)

The registrant has derived long-term DNELs for worker exposure via inhalation routes. The registrant has proposed the use of the 28-day inhalation study (information in registration dossier) in rats in setting long-term DNEL – inhalation as no systemic effects were observed after inhalation exposure up to the highest concentration tested, 500 mg/m^3, for 28 days.

5.13.1 Overview of typical dose descriptors for all endpoints

Table 24: Available dose-descriptor(s) per endpoint for TEA as a result of its hazard assessment

Endpoint	Study	NOAEL	LOAEL	Associated effect and remarks
Acute toxicity	Acute oral			One reliable study give an LD_{50} values of 6400 mg/kg bw
	Acute Dermal			One published study gave LD_{50} values of > 2000 mg/kg bw.
	Acute inhalation			One study was provided which indicated an LC50 (6 h): > 1.8 mg/m^3 air however No analytical determination of the atmosphere concentrations was performed the nominal concentration quoted was based on theoretical calculation
	Skin irritation			In five studies dermal application TEA resulted indications of only very slight irritation. In a patch test study (limited

				information provided) with 6 human volunteers there was no evidence for irritation.
	Eye irritation			Available animal data demonstrated that TEA is a slight eye irritant, but not classifiable.
	Respiratory irritation	No Information	No Information	TEA is considered unlikely to be irritant to the respiratory tract given the lack of any significant irritancy seen in the eye irritation studies.
	Skin sensitisation	Not sensitising		A guinea pig maximisation study was included in the registration dossier which was negative. A review of published studies supported this conclusion. However data from patch test in human (exposed via cosmetic, pharmaceutical or industry uses) indicated the potential to produce positive responses.
	Respiratory sensitisation	No information		
Repeated dose toxicity	91 day oral toxicity study in rats	NOAEL 1000 mg/kg bw/day	Highest dose tested	

	28 day inhalation toxicity study in the rat (6 hours/day and 5 days/week)	The LOAEC (local effects) was established to be 0.02 mg/litre, based on the minimal to slight effects seen in the larynx of males. The NOAEC (systemic effects) was established to be 0.5 mg/litre, based on the absence of effects at the highest dose tested	LOAEC (local effects) was established to be 0.02 mg/litre (lowest dose tested) No evidence for systemic effects at the highest dose tested (0.5 mg/litre)	Local effects on larynx, trachea and lung including inflammation, hyperplasia and necrosis.
	90 day dermal toxicity study in rats	NOAEL (local effects) was established to be 125 mg/kg bw/day NOAEL (systemic effects) was established to be 250 mg/kg bw/day	LOAEL (local effects) skin lesions in males at 250 mg/kg bw/day LOAEL (systemic effects) evidence of effects on the kidneys in males at 500 mg/kg bw/day	Study used acetone as a vehicle.
	90 day dermal toxicity study in mice	LOAEL (local effects) was established to be 250 mg/kg bw/day LOAEL (systemic effects) was established to be 250	LOAEL (local effects) skin lesions (lowest dose tested) LOAEL (systemic effects) evidence of effects on the	Study used acetone as a vehicle

		mg/kg bw/day	kidneys (increased relative kidney weights) in females (lowest dose tested)	
Mutagenicity		N/A	N/A	Not mutagenic *in vitro*. No *in vivo* testing
Carcinogenicity	2 year oral study in the rat (via drinking water)	Study designed to investigate carcinogenicity other parameters investigated were limited to clinical signs, organ weights, bodyweights, and pathology. It was not possible to set a NOAEL for chronic toxicity due to effects seen in the kidneys at the lowest dose. Local effects (acanthosis and inflammation and ulceration, female rats had epidermal erosion) were seen in the lowest dose tested in females 63 mg/kg bw/day		The results of this analysis showed that a positive trend ($p < 0.05$) was noted in the occurrence of hepatic tumours (neoplastic nodule/hepatocellular carcinoma) in males and of uterine endometrial sarcomas and renal-cell adenomas in females. The study authors note that these tumours, were observed spontaneously in this strain of rats, and their incidences in the control group of the present study were lower than those of the laboratories historical controls. Increased incidence of renal tumours in the female high-dose group may have been connected with renal damage.

				Histological examination of renal damage observed in the treated groups, especially in the female high-dose group, revealed acceleration of 'chronic nephropathy'. In addition, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis with or without papillary necrosis were also observed. The IARC Monograph for Triethanolamine concluded that there was no evidence for treatment related tumours.
	2 year oral study in the mouse (via drinking water)	Study designed to investigate carcinogenicity other parameters investigated were limited to clinical signs, bodyweights, organ weights, and pathology. No evidence of carcinogenic potential of TEA in B6C3F1 mice. It was not possible to set a NOAEL for chronic toxicity due to effects seen		

		in the kidneys at the lowest dose and due to the limited study design		
	2 year dermal study in the rat	The eMSCA concluded there was equivocal evidence of carcinogenic activity of TEA in male rats based on a slight increase in the incidences of renal tubule cell adenoma. There was no evidence of carcinogenic activity in female rats. It is noted that based on this study IARC (2000) concluded that there was no significant increase in the incidence of tumours at any site. It was not possible to set a NOAEL for chronic toxicity due to effects seen in the kidneys at the lowest dose (hyperplasia).		Vehicle used was acetone
	2 year dermal studies in the mouse	In the 2004 NTP study there was equivocal evidence of carcinogenic activity of TEA in male mice based on the occurrence of liver hemangiosarcoma. There was some evidence of		Two 2 year dermal study in the mouse have been conducted by the NTP. The first 1999 NTP study in mice was considered inadequate due to the presence of *H. hepaticus* infection, which

		carcinogenic activity in female mice based on increased incidences of hepatocellular adenoma. Exposure to TEA by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related non-neoplastic lesions at the site of application		complicated interpretation of the relationship between TEA administration and liver neoplasms.
Reproductive/developmental toxicity	Reproduction/ Developmental Toxicity Screening Test	NOAEL (for systemic toxicity) (P): > 1000 mg/kg bw/day (male/female) (No adverse systemic effects were observed up to the highest dose tested) NOAEL (for reproductive performance and fertility) (P): > 1000 mg/kg bw/day (male/female) (No adverse effects were observed up to the highest dose tested) NOAEL (for developmental toxicity) (F1): 300 mg/kg bw/day (male/female) (Decreased numbers of implants and	NOAEL (for systemic toxicity) (P): No adverse systemic effects were observed up to the highest dose tested NOAEL (for reproductive performance and fertility) (P): No adverse effects were observed up to the highest dose tested LOAEL (for developmental toxicity) (F1): Decreased numbers of implants and delivered pups, and an increased post-implantation loss at 1000 mg/kg bw/day	Screening study

		delivered pups, and an increased post-implantation loss.)		
Developmental toxicity	Oral study in rats (MEA)	maternal NOAEL of 120 mg/kg bw/day a developmental toxicity NOAEL of 450 mg/kg bw/day	Maternal LOAEL of 450 mg/kg bw/day based on reduced food consumption, lower mean bodyweights and impaired bodyweight gain Developmental toxicity no LOAEL as no effect at the top dose tested 450 mg/kg bw/day	No evidence of an adverse effect on development
Developmental toxicity	Oral study in rats (MEA)	maternal NOAEL of 120 mg/kg bw/day a developmental toxicity NOAEL of 500 mg/kg bw/day	Maternal LOAEL of 300 mg/kg bw/day based on reduced food consumption, lower mean bodyweights and impaired bodyweight gain Developmental toxicity no LOAEL as no effect at the top dose tested 500 mg/kg bw/day	No evidence of an adverse effect on development
Developmental toxicity	Dermal study in rats (MEA)	maternal NOAEL of 75 mg/kg bw/day a developmental toxicity NOAEL of 225 mg/kg bw/day	Maternal LOAEL of 225 mg/kg bw/day based on Systemic effects: significantly reduced body weight gain. Local effects: dermal irritation followed a	No evidence of an adverse effect on development

			progression, beginning with erythema and leading to necrosis, scabs, and scar formation Developmental toxicity no LOAEL as no effect at the top dose tested 225 mg/kg bw/day	
Developmental toxicity	Dermal study in rabbits (MEA)	maternal NOAEL of 10 mg/kg bw/day a developmental toxicity NOAEL of 225 mg/kg bw/day	Maternal LOAEL of 25 mg/kg bw/day based on Systemic effects reduced body weight gain (↓38.3% during gestation days 0-29). Local effects: erythema, oedema, ecchymosis, necrosis, exfoliation, crusting. NOAEL for developmental toxicity was set at the highest dose level of 75 mg/kg bw/day Developmental toxicity no LOAEL as no effect at the top dose tested 225 mg/kg bw/day	No evidence of an adverse effect on development

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

Information on the repeated-dose toxicity of TEA was obtained from a 91-day oral toxicity study in rats, a 28-day inhalation study in rats, two 90-day dermal studies (one in rats, one in mice), several carcinogenicity studies and a reproduction / developmental toxicity screening study.

The toxicological profile of TEA that emerges from the available information is of a substance with low systemic toxicity. Following oral administration in the 91-day repeated-dose study and the reproduction / developmental screening study, no systemic toxicity was observed at 1000 mg/kg/d. Likewise, no systemic toxicity was observed following repeated inhalation exposure to a maximum concentration of 0.5 mg/L TEA (equivalent to a dose of 144 mg/kg/d when a respiratory volume of 08.L/minute/kg bw is applied). Local effects on the respiratory tract were recorded. Therefore, this study will be used to derive local inhalation effects, and systemic inhalation effects will be calculated from route-to-route extrapolation. It is notable that repeated dermal exposure consistently resulted in systemic toxicity with lower NOAELs than those obtained upon oral dosing (e.g., 250 mg/kg/d in a 90-day dermal repeated-dose study; 125 mg/kg/d in a two-year carcinogenicity study). Greater systemic toxicity via the dermal route compared with the oral and inhalation routes seems unlikely; the eMSCA notes that all the dermal studies employed acetone as a vehicle, which may have enhanced dermal penetration of TEA. For this reason, the NOAELs obtained from the dermal studies will not be used for route-to-route extrapolation. It is recognised that their use for dermal DNELs might be conservative.

There were no indications of acute toxicity and therefore acute DNELs will not be calculated. Therefore, the following DNELs were derived for workers and the general population:

- long-term inhalation exposure;
- long-term dermal exposure;
- long-term oral exposure (general population only).

Dermal absorption values of 10% for humans and 30% for rats will be used, based on experimental studies. In the absence of substance-specific information, default oral and inhalation absorption values of 100% will be used for rats and humans, except for extrapolation from the oral route to the inhalation route, in which case the worst-case scenario of 50% oral absorption and 100% inhalation absorption will be assumed.

5.13.2.1 Workers

Worker long-term systemic inhalation

Only local effects were observed in the 28-day inhalation study, in which rats were exposed to a maximum concentration that was equivalent to 144 mg/kg/d, which was below the NOAEL values obtained from the available oral studies; therefore this study will not be used for systemic effects. Systemic toxicity following oral administration of TEA was not reported in the 90-day repeated-dose study nor the reproduction / development screening study at the highest-tested dose of 1000 mg/kg/day. Therefore, the two-year oral carcinogenicity studies will be used to extrapolate to the inhalation route.

In one oral carcinogenicity study, TEA was administered in drinking water to rats (NOAEL for systemic effects 667/333 mg/kg/d); in the other, it was administered to mice (NOAEL 1600 mg/kg/d). Only two concentrations were tested in each study, thus limiting their usefulness for risk assessment. The doses administered in females in the rat study were reduced during the study, such that the low-dose-group animals received 667 mg/kg/d for 69 weeks then 333 mg/kg/d for the remainder of the study. Systemic toxicity, in the form of kidney effects and increased mortality, was reported in this group. Taking a conservative approach, a LOAEL of 333 mg/kg/d will therefore be used for the route-to-route extrapolation.

Inhalation NOAEC = oral NOAEL x (1/sRVrat) x (ABSoral-rat/ABSinh-human) x (sRVhuman/wRV)

= 333 x (1/0.38) x (50/100) x (6.7/10)

= 293.6 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	Chronic study used
Dose-response	1	Although a LOAEL was the starting point, there were no adverse effects in males at this dose. In another oral chronic study, a dose of 1600 mg/kg/d resulted in only slight changes in final bodyweights. Therefore a factor of 1 will be applied. Also, a NOAEL of 1000 mg/kg/d was obtained from a 90-day oral study.
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*12.5*	

Worker DNEL long-term inhalation - systemic = 293.6 mg/m^3 / 12.5 = **23.5 mg/m^3**

Worker long-term local inhalation

A LOAEC of 0.02 mg/L (=20 mg/m^3) for local effects was identified from the 28-day inhalation repeated-dose study.

In accordance with ECHA guidance chapter R.8, the exposure estimation should address the air concentration in workplaces and consumer uses, and so no modification of the starting concentration is needed. The concentration of TEA is assumed to drive the local effects.

Assessment factors:

Inter-species differences	2.5	No allometric scaling for local inhalation effects, 2.5 for remaining differences to take account of possible quantitative differences in deposition, airflow

		patterns, clearance rates and protective mechanisms (page 113-144 of ECHA guidance chapter R.8)
Intra-species differences	5	Default value for workers (page 113-144 of ECHA guidance chapter R.8)
Duration of exposure	1	For local irritation of the respiratory tract, the default position is to apply a factor of 6 for sub-acute to chronic extrapolation (page 29 of ECHA guidance). However, as the effect for TEA is considered to be concentration- rather than dose-dependent, a factor of 1 will be applied
Dose-response	3	LOAEC used as the starting point
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*37.5*	

Worker DNEL long-term inhalation - local = 20 mg/m^3 / 37.5 = **0.5 mg/m^3**

As an alternative to the use of a LOAEL / LOAEC as the starting point with an assessment factor for the dose-response, a BMDL can be used in place of a NOAEL. It is noted that, in the setting of a German MAK value, a benchmark calculation for the focal larynx effects led to a BMDL of 14.8 mg/m^3 for male and 14.1 mg/m^3 for female rats. Taking the lower value of 14.1 mg/m^3, the following assessment factors can be applied.

Inter-species differences	2.5	No allometric scaling for local inhalation effects, 2.5 for remaining differences to take account of possible quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms (page 113-144 of ECHA guidance chapter R.8)
Intra-species differences	5	Default value for workers (page 113-144 of ECHA guidance chapter R.8)
Duration of exposure	1	For local irritation of the respiratory tract, the default position is to apply a factor of 6 for sub-chronic to chronic extrapolation (page 29 of ECHA guidance). However, as the effect for MEA is considered to be concentration- rather than dose-dependent, a factor of 1 will be applied
Dose-response	1	BMDL used as the starting point
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*12.5*	

Worker DNEL long-term inhalation - local = 14.1 mg/m^3 / 12.5 = **1.1 mg/m^3**

The application of ECHA's recommended assessment factors results in a DNEL that is lower than the IOELV for MEA of **2.5 mg/m^3** (Directive 2006/15/EC), which has been used by the eMSCA as the worker DNEL long-term inhalation – local for that substance. As MEA is more reactive than TEA (it has a harmonised classification for skin corrosion category 1B), it appears counter-intuitive that TEA should have a lower DNEL than MEA for an effect that is based on irritancy. The IOELV for MEA will therefore also be used as the DNEL for TEA; this is considered to still be precautionary.

Worker long-term dermal systemic

Calculated from 90-day dermal study in rats (NOAEL for systemic toxicity 250 mg/kg/d)

As it is assumed that dermal absorption is not the same in rats and humans, modification of the starting dose is required.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 250 x (30 / 10)

= 250 x 3 = 750 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	2	Adjustment for sub-chronic to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

Worker DNEL long-term dermal - systemic = 750 / 100 = **7.5mg/kg/d**

Calculated from two-year study in rats (NOAEL for systemic effects 125 mg/kg/d)

Modification of the starting dose is required, as follows.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 125 x (30 / 10)

= 125 x 3 = 375 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for

		remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	Chronic study
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*50*	

Worker DNEL long-term dermal – systemic = 375 / 50 = **7.5 mg/kg/d**

Worker long-term dermal local

Local skin effects were apparent in the rat and mice 90-day dermal repeated-dose studies. A LOAEL of 250 mg/kg/d for local effects was established from the mouse study, whereas a NOAEL of 125 mg/kg/d for local effects was established from the rat study with a LOAEL of 250 mg/kg/d (minimal to mild epidermal thickening, chronic active inflammation, to erosion and ulceration at higher doses). The NOAEL from the rat study will thus be used to establish the DNEL long-term dermal local. This dose will be adjusted to mg/cm^2/d to enable comparison with human exposure.

Average weight of rats = 250 g.

Dose is applied over approximately 10% of the total body surface.

The total body surface area of rats is on average 445 cm^2 (ECHA guidance on information requirements, Chapter R.8, Appendix R.8.9).

The modification from $NOAEL_{test}$ in mg/kg of body weight to $NOAEL_{modified}$ in mg/cm^2/day is:

125 mg/kg x (0.25cm^2/44.5cm^2) = 0.7 mg/cm^2 = 700 µg/cm^2

Assessment factors:

Inter-species differences	1	No adjustment for direct chemical reactivity with membrane
Intra-species differences	5	Default value for workers
Duration of exposure	1	For local dermal effects, increasing the exposure duration does not increase the severity or incidence of effects
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*5*	

Worker DNEL long-term dermal – local = 700 µg/cm^2 / 5 = 140 µg/cm^2

Worker fertility and developmental toxicity, inhalation exposure

An oral screening study provided information on the reproductive toxicity of TEA. The NOAEL for fertility and developmental toxicity was 300 mg/kg/d.

Corrected NOAEC = 300 x (1/0.38) x (50/100) x (6.7/10)

= 264.5 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that might occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*12.5*	

Worker DNEL inhalation – fertility/development = 264.5 / 12.5 = **21.2 mg/m^3**

Worker fertility and developmental toxicity, dermal exposure

An oral screening study provided information on the reproductive toxicity of TEA. The NOAEL for fertility and developmental toxicity was 300 mg/kg/d. Modification of the starting dose is required, as follows.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 300 x (30 / 10)

= 300 x 3 = 900 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that might occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate

Overall assessment factor	*50*

Worker DNEL dermal – fertility/development = 900 / 50 = **18 mg/kg/d**

5.13.2.2 General population

General population long-term systemic inhalation

A LOAEL of 333 mg/kg/d from the two-year oral carcinogenicity study in rats will be used for the route-to-route extrapolation.

Inhalation LOAEC = oral LOAEL x (1/sRVrat) x (ABSoral-rat/ABSinh-human)

= 333 x (1/1.15) x (50/100)

= 144.8 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	Chronic study
Dose-response	1	Although a LOAEL was the starting point, there were no adverse effects in males at this dose. In another oral chronic study, a dose of 1600 mg/kg/d resulted in only slight changes in final bodyweights. Therefore a factor of 1 will be applied. Also, a NOAEL of 1000 mg/kg/d was obtained from a 90-day oral study.
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*25*	

General population DNEL long-term inhalation - systemic = 144.8 mg/m^3 / 25 = **5.8 mg/m^3**

General population long-term local inhalation

A LOAEC of 0.02 mg/L (=20 mg/m^3) for local effects was identified from the 28-day inhalation repeated-dose study.

In accordance with ECHA guidance chapter R.8, the exposure estimation should address the air concentration in workplaces and consumer uses, and so no modification of the starting concentration is needed. The concentration of MEA is assumed to drive the local effects.

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure nor local effects, 2.5 for remaining differences to take account of possible quantitative differences in

		deposition, airflow patterns, clearance rates and protective mechanisms
Intra-species differences	10	Default value for general population
Duration of exposure	1	For local irritation of the respiratory tract, the default position is to apply a factor of 6 for sub-acute to chronic extrapolation (page 29 of ECHA guidance). However, as the effect for MEA is considered to be concentration- rather than dose-dependent, a factor of 1 will be applied
Dose-response	3	LOAEC used as the starting point
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*75*	

General population DNEL long-term inhalation - local = 20 mg/m^3 / 75 = **0.3 mg/m^3**

As an alternative to the use of a LOAEL / LOAEC as the starting point with an assessment factor for the dose-response, a BMDL can be used in place of a NOAEL. It is noted that, in the setting of a MAK value, a benchmark calculation for the focal larynx effects led to a BMDL of 14.8 mg/m^3 for male and 14.1 mg/m^3 for female rats. Taking the lower value of 14.1 mg/m^3, the following assessment factors can be applied.

Inter-species differences	2.5	No allometric scaling for local inhalation effects, 2.5 for remaining differences to take account of possible quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms (page 113-144 of ECHA guidance chapter R.8)
Intra-species differences	10	Default value for general population (page 113-144 of ECHA guidance chapter R.8)
Duration of exposure	1	For local irritation of the respiratory tract, the default position is to apply a factor of 6 for sub-acute to chronic extrapolation (page 29 of ECHA guidance). However, as the effect for MEA is considered to be concentration- rather than dose-dependent, a factor of 1 will be applied
Dose-response	1	BMDL used as the starting point
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*25*	

General population DNEL long-term inhalation - local = 14.1 mg/m^3 / 25 =**0.6 mg/m^3**

This value is similar to the IOELV for MEA (Directive 2006/15/EC) adjusted for the general population (0.5 mg/m^3), which has been used as the general population DNEL long-term inhalation – local for that substance. As MEA is more reactive than TEA (it has a harmonised classification for skin corrosion category 1B), the DNEL of 0.6 mg/m^3 for TEA will be used by the eMSCA and is considered to be precautionary.

General population long-term dermal systemic

Calculated from 90-day dermal study in rats (NOAEL for systemic toxicity 250 mg/kg/d)

As it is assumed that dermal absorption is not the same in rats and humans, modification of the starting dose is required.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 250 x (30 / 10)

= 250 x 3 = 750 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	2	Adjustment for sub-chronic to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*200*	

General population DNEL long-term dermal - systemic = 750 / 200 = **3.75 mg/kg/d**

Calculated from two-year study in rats (NOAEL for systemic effects 125 mg/kg/d)

Modification of the starting dose is required, as follows.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 125 x (30 / 10)

= 125 x 3 = 375 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences

Intra-species differences	10	Default value for general population
Duration of exposure	1	Chronic study
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL long-term dermal – systemic = 375 / 100= **3.75 mg/kg/d**

General population long-term dermal local

Local skin effects were apparent in the rat and mice 90-day dermal repeated-dose studies. A LOAEL of 250 mg/kg/d for local effects was established from the mouse study, whereas a NOAEL of 125 mg/kg/d for local effects was established from the rat study with a LOAEL of 250 mg/kg/d (minimal to mild epidermal thickening, chronic active inflammation, to erosion and ulceration at higher doses). The NOAEL from the rat study will thus be used to establish the DNEL long-term dermal local. This dose will be adjusted to mg/cm^2/d to enable comparison with human exposure.

Average weight of rats = 250 g.

Dose is applied over approximately 10% of the total body surface.

The total body surface area of rats is on average 445 cm^2 (ECHA guidance on information requirements, Chapter R.8, Appendix R.8.9).

The modification from $NOAEL_{test}$ in mg/kg of body weight to $NOAEL_{modified}$ in mg/cm^2/day is:

125 mg/kg x (0.25cm^2/44.5cm^2) = 0.7 mg/cm^2 = 700 µg/cm^2

Assessment factors:

Inter-species differences	1	No adjustment for direct chemical reactivity with membrane
Intra-species differences	10	Default value for workers
Duration of exposure	1	For local dermal effects, increasing the exposure duration does not increase the severity or incidence of effects
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*5*	

General population DNEL long-term dermal – local = 700 µg/cm^2 / 10 = **70 µg/cm^2**

General population long-term oral systemic

A LOAEL of 333 mg/kg/d from the two-year oral carcinogenicity study in rats will be used for the long-term oral systemic DNEL, based on nephrotoxicity and increased mortality in females. No modification of the starting dose is required.

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	Chronic study used
Dose-response	1	Although a LOAEL was the starting point, there were no adverse effects in males at this dose. In another oral chronic study, a dose of 1600 mg/kg/d resulted in only slight changes in final bodyweights. Therefore a factor of 1 will be applied. Also, a NOAEL of 1000 mg/kg/d was obtained from a 90-day oral study
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL long-term oral = 333/100 = **3.33 mg/kg/d**

General population fertility and development, inhalation exposure

An oral screening study provided information on the reproductive toxicity of TEA. The NOAEL for fertility and developmental toxicity was 300 mg/kg/d.

Corrected NOAEC = 300 x (1/1.15) x (50/100)

= 130.4 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that might occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment	*25*	

factor		

General population DNEL inhalation – fertility/development = 130.4 / 25 = **5.2 mg/m^3**

General population fertility and development, dermal exposure

An oral screening study provided information on the reproductive toxicity of TEA. The NOAEL for fertility and developmental toxicity was 300 mg/kg/d. Modification of the starting dose is required as follows.

Corrected NOAEL = dermal NOAEL x (ABS derm-rat / ABSderm-human)

= 300 x (30 / 10)

= 300 x 3 = 900 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that might occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL dermal – fertility/development = 900 / 100 = **9 mg/kg/d**

General population fertility and development, oral exposure

An oral screening study provided information on the reproductive toxicity of TEA. The NOAEL for fertility and developmental toxicity was 300 mg/kg/d. Modification of the starting dose is not required.

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure

Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL oral – developmental toxicity = 300 / 100 = **3 mg/kg/d**

Summary of lowest DNELs for each exposure pattern calculated by eMSCA

The eMSCA identified the following DNELS as the lowest for each exposure pattern.

Table 25: Summary of the lowest DNELS for each exposure pattern

Exposure pattern	**Study**	**Modified NOAEL / NOAEC**	**AF**	**DNEL**
Worker DNEL long-term inhalation - systemic	Two-year oral carcinogenicity study in rats	293.6 mg/m^3	12.5	23.5 mg/m^3
Worker DNEL long-term inhalation - local	IOELV: 8-hour TWA	13 mg/m^3	5	2.5 mg/m^3
Worker DNEL long-term dermal - systemic	Two-year dermal carcinogenicity study in rats	375 mg/kg/d	50	7.5 mg/kg/d
Worker DNEL long-term dermal - local	90-day dermal repeated-dose toxicity study in rats	700 $\mu g/cm^2$	5	140 $\mu g/cm^2$
Worker DNEL inhalation – fertility, development	Reproduction/development screening study	264.5 mg/m^3	12.5	21.2 mg/m^3
Worker DNEL dermal – fertility, development	Reproduction/development screening study	900 mg/kg/d	50	18 mg/kg/d
General population DNEL long-term inhalation - systemic	Two-year oral carcinogenicity study in rats	144.8 mg/m^3	25	5.8 mg/m^3
General population DNEL long-term inhalation - local	28-day inhalation study	14.1 mg/m^3 (BMDL)	25	0.6 mg/m^3
General population DNEL long-term dermal - systemic	Two-year dermal carcinogenicity study in rats	375 mg/kg/d	100	3.75 mg/kg/d
General population DNEL long-term dermal - local	90-day dermal repeated-dose toxicity study in rats	700 $\mu g/cm^2$	10	70 $\mu g/cm^2$
General population DNEL	Two-year oral	333	100	3.3 mg/kg/d

long-term oral	carcinogenicity study in rats	mg/kg/d		
General population DNEL inhalation – fertility, development	Reproduction/development screening study	130.4 mg/m^3	25	5.2 mg/m^3
General population DNEL dermal – fertility, development	Reproduction/development screening study	900 mg/kg/d	100	9 mg/kg/d
General population DNEL oral – fertility, development	Reproduction/development screening study	300 mg/kg/d	100	3 mg/kg/d

The DNEL for local inhalation effects is protective of systemic effects. The general population DNELs obtained for systemic effects and fertility/development by the oral route were very close; therefore, the lowest value will be taken forward for the risk characterisation, which will be protective for both systemic toxicity and reproduction. The following DNELs will thus be used by the eMSCA in the risk characterisation.

Worker DNEL long-term inhalation – local/systemic	2.5 mg/m^3
Worker DNEL long-term dermal – systemic	7.5 mg/kg/d
Worker DNEL long-term dermal - local	140 µg/cm^2
General population DNEL long-term inhalation – local/systemic	0.6 mg/m^3
General population DNEL long-term dermal – systemic	3.75 mg/kg/d
General population DNEL long-term oral	3 mg/kg/d
General population DNEL long-term dermal – local	70 µg/cm^2

5.14 Conclusions of the human health hazard assessment and related classification and labelling

The area of focus for the human health evaluation of TEA was sensitisation and liver tumours in female mice.

With the exception of skin irritancy and contact sensitisation, the only information available to address the potential human health risks TEA comes from studies in animals.

Acute studies

The data provided on TEA demonstrate it is not acutely toxic via the oral, dermal or inhalational (to vapour) routes. TEA was found to produce only slight skin and eye irritation. Repeat dose inhalation studies did indicate that TEA could produce respiratory tract irritation.

Sensitisation

One of the grounds of concern for TEA was sensitisation (skin and respiratory). The eMSCA conducted a literature search for papers on TEA and contact allergy to supplement data provided by the registrant.

The current review has identified sensitisation studies with TEA in animal models in the published literature that gave largely negative results. Some human evidence is also available; even in a highly-exposed population (workers using water-based metal working fluids) the frequency of positive responses with TEA was very low. Considering the widespread use of TEA over a long period of time and scarcity of reports of occupational asthma, the eMSCA concludes that TEA is not a respiratory sensitiser. Therefore the concern has been clarified.

Sub-acute studies

In a sub-chronic dermal toxicity study in rats (20 animals/sex/dose) there were significant decreases in bodyweight gain at 2000 mg/kg bw. There were clear local effects at the application site; epidermal thickening (acanthosis), to chronic active inflammation, erosion, and ulceration, the dermis was also thickened with inflammation and fibrosis at the higher doses. Changes in WBC count and differential counts were consistent with the presence of skin inflammation. There were slight but dose-related increases in serum alanine and aspartate aminotransferase activities. Although there were no other changes consistent with effects on the liver. There were dose-related increases in kidney weights in both sexes in all treatment groups accompanied by nephropathy in females only.

In a second sub-chronic dermal toxicity in mice findings were similar to those in the rat study. Local findings included scaliness, irritation, and discoloration at the application. Kidney weights were increased but with no histopathological correlate.

In a sub-chronic dietary toxicity study in rats up to1000 mg/kg bw/day (91 days) there were no significant findings.

In a sub-acute 28 -day inhalation toxicity study (OECD 412) rats TEA for 6 hours/day and 5 days/week displayed concentration dependant focal inflammatory changes in the submucosa of the larynx. There were no systemic findings.

Genotoxicity

The *in vitro* genotoxicity of TEA has been investigated in four bacterial reverse mutation assays, a chromosome aberration assay in Chinese hamster Ovary (CHO) cells, mammalian gene mutation and a sister chromatid exchange assay in mammalian cells.

Negative results were reported in all studies.

Carcinogenicity

In an oral carcinogenicity study Fischer rats were daily exposed TEA via the drinking water for 2 years. In week 69, dose levels in females were reduced to 0.5 and 1% (corresponding to ca. 333 and 667 mg/kg bw/day), because of associated nephrotoxicity. Although there was a positive trend towards increased occurrence of hepatic tumours in males and of uterine endometrial sarcomas and renal-cell adenomas in females, based on an age-adjusted statistical analysis, it was judged as not related to the treatment.

In an oral carcinogenicity study B6C3F1 mice were daily exposed TEA via the drinking water for 82 weeks. There was no evidence for carcinogenic potential of TEA in mice.

A number of NTP studies via the dermal route were provided these used acetone as a vehicle which would likely markedly increase the dermal penetration of TEA.

Although an initial study NTP study (NTP 1999) was compromised by the *H. hepaticus* infection it is still worth noting the in incidence of liver tumours seems to be exacerbated by TEA. The study used B6C3F1 mice listed EHCA Guidance on the Application of the CLP Criteria lists B6C3F1 as having a high spontaneous tumour incidence in the liver. This study was repeated in 2004 again in B6C3F1 mice. In the second NTP 2004 study TEA was administered to mice 5 days per week for 2 years.

There was a slight increase in haemangiosarcomas in the livers of males exposed to TEA although not dose related the increase was above historical control data. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all dosed groups of females. The occurrence of liver tumours (hepatocellular adenoma or carcinoma) in a single sex in B6C3F1 mice is not considered sufficient to consider TEA carcinogenic. The occurrence of haemangiosarcoma, in the livers of male mice, although slightly above the historical control data, was not dose-related nor observed in other studies and is considered to be a chance finding. The eMSCA concludes that there was no evidence of carcinogenic activity of TEA.

Reproductive and developmental toxicity

A concern for reproductive toxicity was not identified in a screening reproduction/developmental toxicity study (OECD 421), in which TEA up to 1000 mg/kg/d. There was also no evidence of a teratogenic effect of TEA.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

TEA is a viscous, colourless to plate-yellow liquid with a boiling point of 336°C. It is non-flammable with a flashpoint of 179 °C, and does not possess explosive or oxidising properties. The viscosity data confirms that TEA is not an aspiration hazard, and Partition coefficient n-octanol/water (log value) demonstrates that there is no potential for accumulation in fat/bioaccumulation. Unfortunately the vapour pressure data is too inconsistent to de definitive for volatility. Based on the available data, TEA does not meet the criteria for classification for any physico-chemical end points.

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity data

Key and supporting aquatic toxicity information from the REACH registration is presented in Table 33 below. Studies which were disregarded in the REACH Registration (e.g. due to short study duration) are not included. Since the substance is of low intrinsic ecotoxicity, only a brief review is provided.

Table 26: Summary of relevant information on aquatic toxicity

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	End-point	Toxicity (mg/l)	
Acute toxicity to fish APHA method considered similar to OECD Test Guideline 203, not GLP Registrant reliability: 2	Fathead Minnow (*Pimephales promelas*)	Mortality	Flow-through; pH 7.8	96 hours	LC_{50}	11,800 mg/l (nominal given measured values within 20% nominal)	Information in registration dossier
Acute invertebrate immobilisation following NSW EPA ASTM Guideline E1129 considered similar to OECD Test Guideline, 202, not GLP Registrant reliability: 2	*Ceriodaphnia dubia*	Acute immobilisation	Static; no pH details	48 hours	EC_{50}	610 mg/l (nominal – no details of analytical support)	Warne and Schifko (1990)
Invertebrate Reproduction following German Federal Agency extended toxicity guideline considered similar to OECD Test Guideline 202 (1984), not GLP Registrant reliability: 2	*Daphnia magna*	Survival; reproduction; growth	Semi-static, pH 7	21 days	NOEC	16 mg/l (nominal given measured values within 20% nominal) Parental mortality	Information in registration dossier; Kuehn *et al* (1989)
Freshwater Algal Growth Inhibition following German Industrial Standard DIN 38412, part 9 considered similar to OECD Test Guideline 201, not GLP Registrant reliability: 2	*Desmodesmus subspicatus* (formerly *Scenedesmus subspicatus*)	Cell multiplication inhibition; growth rate	Static Non-neutralised media Neutralised media	72 hours	ErC_{50} ErC_{10} ErC_{50} ErC_{10}	216 mg/l 7.9 mg/l 512 mg/l 26 mg/l (values based on nominal - no details of analytical support)	Bayerisches Landesamt fuer Wasserwirtschaft (1989, 1986); Kommission Bewertung wassergefährdender Stoffe (1985); Federal Ministry of Justice (Germany) (2005)

Saltwater Algal Growth Inhibition following ISO 10253, not GLP Registrant reliability: 2 (supporting study)	*Phaedodactylum tricornutum*	Cell multiplication inhibition;	Static, non-neutralised seawater	72 hours	EC_{50} EC_{10} NOEC	204 mg/l >10 mg/l (calculated from graph) <28 mg/l (initial mean measured) calculated	Libralato *et al* (2010)
Saltwater Algal Growth Inhibition following ISO 10253, not GLP Registrant reliability: 2 (supporting study)	*Skeletonema costatum*	Cell multiplication inhibition;	Static, non-neutralised seawater	72 hours	EC_{50}	>107 to < 260 mg/l (values based on nominal - no details of analytical support)	Eide-Haugmo *et al* (2012) Eide-Haugmo *et al* (2009)

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

The Registrant uses an Assessment Factor of 50 as chronic data are available for two trophic levels, and the 21-d *Daphnia* NOEC of 16 mg/l to derive the freshwater aquatic PNEC as 0.32 mg/l.

Assuming an additional factor of 10, the marine aquatic PNEC is 0.032 mg/l.

The Registrant observed that non-neutralised media induced greater toxicity than neutralised media in toxicity testing with algae (Aman, 1989; Amam and Steinhaeuser, 1986; Kommission Bewertung wassergefährdender Stoffe, 1985; and German Federal Ministry of Justice, 2005): E_rC_{10} 26 mg/l neutralised media and E_rC_{10} 7.9 mg/l non-neutralised media. On this basis, the Registrant considered part of the observed toxicity resulted from the pH change due to the test substance and effects data based on neutralised media should be used for risk assessment. No further details about media preparation (e.g. the buffer used), the pH of controls or the pH of neutralised / non-neutralised media are available in the Registration. The Registrant is therefore asked to specify the test solution pH for control, neutralised and non-neutralised media.

The eMSCA notes that algae were the most acutely sensitive species and that the non-neutralised E_rC_{10} is the lowest available chronic value. There is currently insufficient detail in the algae RSS to demonstrate why these results can be disregarded for the aquatic PNEC derivation. The eMSCA recommends the Registrant updates the RSS and CSR clarifying the significance of the pH. This should consider the pH for controls, neutralised and non-neutralised media; whether the non-neutralised media was within an environmentally relevant range; and if the non-neutralised E_rC_{10} is valid for PNEC derivation.

7.1.2.2 PNEC sediment

The Registrant uses the Equilibrium Partitioning Method (EPM) to derive the freshwater sediment PNEC as 0.369 mg/kg wet weight (1.7 mg/kg dry weight), and the marine sediment PNEC as 0.0369 mg/kg wet weight (0.17 mg/kg dry weight).

7.2 Terrestrial compartment

7.2.1 Toxicity test results

No relevant data available. A human health genetic toxicology test using fruit fly, *Drosophila Melanogaster*, exposure by diet is available in the registration dossier, but has not been assessed by the eMSCA here.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC soil)

The Registrant uses the Equilibrium Partitioning Method (EPM) to derive the soil PNEC as 0.134 mg/kg wet weight (0.151 mg/kg dry weight).

7.3 Atmospheric compartment

TEA is not considered to be an ozone depleting or greenhouse gas so the eMSCA has not considered this compartment further.

7.4 Endocrine disrupting properties

Based on the structure, endocrine disrupting properties are not considered relevant.

7.5 Microbiological activity in sewage treatment systems

7.5.1 Toxicity to aquatic micro-organisms

From the REACH Registration, a 3 hour IC_{50} of >1,000 mg/l is available for domestic activated sludge following OECD Test Guideline 209 (Klecka *et al*, 1985).

7.5.2 PNEC for sewage treatment plant

Using as Assessment Factor of 10, the STP PNEC is 100 mg/l.

7.6 Non compartment specific effects relevant for the food chain (secondary poisoning)

7.6.1 Toxicity to birds

No data available.

7.6.2 Toxicity to mammals

No data available.

7.6.3 Calculation of PNECoral (secondary poisoning)

TEA has a low bioaccumulation potential and is rapidly degradable. It is not currently considered to meet relevant human health classification criteria for carcinogenicity, mutagenicity, reproduction or STOT RE. Given the low potential for bioaccumulation, exposure of predators is considered low. On this basis a secondary poisoning scenario is not considered to be necessary by the Registrant. The eMSCA agrees with this assessment.

7.7 Conclusion on the environmental hazard assessment and on classification and labelling

TEA does not have a harmonized environmental classification.

Considering available hazard data, there are no $L(E)C_{50}$ values < 1 mg/l so TEA does not meet Aquatic Acute classification criteria. There are no chronic NOECs <1 mg/l and TEA is considered rapidly degradable so TEA does not meet Aquatic Chronic classification criteria.

This reflects the majority of current REACH Registration self-classifications.

8 PBT AND VPVB ASSESSMENT

8.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

8.1.1 Persistence assessment

TEA is considered rapidly degradable and therefore is not considered persistent.

8.1.2 Bioaccumulation assessment

TEA has a measured logK_{ow} below 4.5 and BCFs below 2000. Therefore it is not considered bioaccumulative.

8.1.3 Toxicity assessment

Acute ecotoxicity data are available for TEA for three trophic levels. Chronic toxicity data are available for invertebrates and algae. Chronic NOECs are above the criteria of ≤ 0.01 mg/l.

TEA is not classified for human health as carcinogenic, mutagenic or reprotoxic or STOT RE.

Therefore TEA is not considered toxic.

8.1.4 Summary and overall conclusions on PBT and vPvB Properties

TEA is not considered by the Registrant to be PBT or vPvB. The eMSCA agrees with this assessment.

9 EXPOSURE ASSESSMENT

9.1 Human Health

TEA does not have a harmonised classification in Annex VI of CLP, nor have the Registrants concluded that it meets the criteria for classification for any human health end-points. As no hazard was identified from the Registrants' chemical safety assessment, in accordance with REACH Annex I (5.0) an exposure estimation was not conducted.

9.2 Environmental exposure assessment

TEA is a high production chemical (100,000 to 1,000,000 tpa) with widespread industrial applications such as water treatment , construction chemicals and processing aids for metal working, leather, textile and paper. TEA is also used in consumer products such as laundry detergents, cleaning agents and personal care products. As such release to the environment is anticipated.

TEA is rapidly degradable, not bioaccumulative and exhibits limited ecotoxicity. It is not considered vPvB or PBT or classified for environmental effects. On this basis an environmental exposure assessment has not been conducted by the Registrant.

Given TEA was a not an environmental CoRAP priority, further consideration of environmental exposure assessment has not be undertaken by the eMS.

9.3 Combined exposure assessment

Not conducted by the Registrants.

10 RISK CHARACTERISATION

Not assessed.

11 OTHER INFORMATION

A literature search was performed in April 2014 using the following search terms:

triethanolamine (TEA) CAS 102-71-6, EC 203-049-8
2,2',2'-nitrilotriethanol
Alkanolamines
Bioaccumulation
Bioconcentration
Persistence
Degradation
Biodegradation
Ecotoxicity
Fish
Invertebrate
Algae
Monitoring
Sewage treatment plant / works

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13 ABBREVIATIONS

AAF	acetylaminofluorene
ADI	acceptable daily intake
ai	active ingredient
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
bw	bodyweight
CHO	Chinese hamster ovary
CI	confidence interval
CLV	ceiling value
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
cv	coefficient of variation
DMSO	dimethyl sulfoxide
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECG	electrocardiogram
EHC	Environmental Health Criteria
eMSCA	evaluating Member State competent authority
FAO	Food and Agriculture Organization
FCAT	Freund's complete adjuvant test
FEF	forced expiratory flow
FEV	forced expiratory volume
FOB	functional observational battery
GDH	glutamate dehydrogenase
GEMS	Global Environmental Monitoring System
GI	gastrointestinal
GLC	gas-liquid chromatography
GLDH	glutamate dehydrogenase
GLP	good laboratory practice
cGMP	cyclic guanosine monophosphate
GOT	glutamic-oxaloacetic transaminase
GPMT	guinea-pig maximization test
GPT	glutamic-pyruvic transaminase
GST	glutathione-S-transferase
h	hour(s)
Hb	haemoglobin
HGPRT	hypoxanthine-guanine phosphoribosyltransferase

HPLC	high-performance liquid chromatography
HSE	Health and Safety Executive (UK)
IC	ion chromatography
Ig	immunoglobulin
im	intramuscular
IOELV	indicative occupational exposure limit
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
IU	international unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LI	labelling index
LOAEL	lowest-observed-adverse-effect level
LOD	limit of determination
LOEL	lowest-observed-effect level
LSC	liquid scintillation counter
MAC	maximum allowable concentration
MAK	maximum workplace concentration (Maximale Arbeitsplatzkonzentration)
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
mCi	millicurie
MCV	mean cell volume
mg/kg bw/day	milligram per kilogram bodyweight per day.
MRL	maximum residue limit
MS	mass spectrometry
MWF	metal-working fluid
ND	not detectable
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOLC	no-observed lethal concentration
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration (USA)
PCE	polychromatic erythrocytes
PCV	packed-cell volume
PEF	peak expiratory flow
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PT	prothrombin time
QA	quality assurance
QAP	quality assurance programme
QC	quality control
QSAR	quantitative structure-activity relationship

RBC	red blood cell
SC	suspension concentrate
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SEM	standard error of the mean; scanning electron microscopy
SPF	specific pathogen free
SS	suspended solids
TLC	thin-layer chromatography
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TWA	time-weighted average
UDS	unscheduled DNA synthesis
v/v	volume per volume
WWTP	waste water treatment plant
WBC	white blood cell
WG	water-dispersible granule
WHO	World Health Organization
WP	wettable powder
w/v	weight per volume

ANNEX: CONFIDENTIAL INFORMATION

This annex is confidential and not included in the public version of the report.