SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2,2'-Iminodiethanol (DEA)

EC number 203-868-0

CAS RN 111-42-2

Evaluating Member State(s): Germany

Dated: 18 November 2021

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Decision to request further information was issued on: 25 February 2014.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document 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.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, 2,2'-Iminodiethanol (diethanolamine, 'DEA') was originally selected for substance evaluation in order to clarify concerns about:

- Potential formation of CMR transformation products (Suspected CMR)
- Wide dispersive use, high aggregated tonnage

During the evaluation, reproductive toxicity of DEA was identified as an additional concern.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

DEA is included in Annex VI of Regulation (EC) No 1272/2008 (CLP regulation).

According to Annex II (entries 410 and 411) of the European Cosmetics Regulation No 1223/2009, secondary alkyl- and alkanolamines [and their salts] including DEA and nitrosamines such as 2,2'-(nitrosoimino)bisethanol (N-nitroso-diethanolamine; 'NDELA'; EC number 214-237-4; CAS RN 1116-54-7) are prohibited in cosmetic products. Annex III (entries 60–61) of the EU Cosmetics Regulation 1223/2009/EU restricts the maximum secondary amine content (including DEA) in the ready for use preparation to 0.5%. In addition, the entries 60–62 restrict the maximum nitrosamine content in the ready for use preparation to 50 µg/kg.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions *(As per Entry 30 of Annex XVII in case of Repr. 1B)*	*(X)
Other EU-wide measures	X
No need for regulatory follow-up action at EU level	

*(X) depending on possible outcomes from CLH

4. FOLLOW-UP AT EU LEVEL

4.1 Need for follow-up regulatory action at EU level

4.1.1 Harmonised Classification and Labelling

Based on the existing and newly generated information on DEA, the evaluating member state competent authority (eMSCA) considers that an update of the harmonised classification of the substance is necessary. This concerns the need to classify DEA as carcinogenic (Carc. 2) and as a reproductive toxicant (Repr. 1B), hazard classes for which DEA currently neither possesses a harmonised classification or for which it is self-classified

by the majority of C&L notifiers. The eMSCA considers an update of the harmonised classification with regard to carcinogenicity and reproductive toxicity as the most important measure to drive further risk management for DEA.

A proposal for an update of the CLP Annex VI entry for DEA will be submitted by the eMSCA.

4.1.2 Identification as a substance of very high concern, SVHC (first step towards authorisation)

In case a classification as Repro. 1B will be added to its Annex VI CLP entry, it would formally fulfil the criteria for identification as an SVHC according to Article 57(c) and subsequent authorisation. However, the eMSCA currently does not regard DEA as a suitable candidate for authorisation. The identified risk to consumers and industrial/professional users may currently be more suitably addressed by a restriction (cf. 4.1.3), if necessary, and establishment of a lower occupational exposure limit (OEL) (cf. 4.1.4), respectively, following the establishment of a more protective harmonised classification. Listing in the candidate list alone could have side effects and through awareness and information duties linked to the SVHC identification may reduce the intended uses in articles.

4.1.3 Restriction

A classification of DEA as Repr. 1B would mean that it would eventually be subject to the existing restriction entry no. 30 of Annex XVII REACH on reprotoxic substances. Its placing on the market or use as substance or constituent or in mixtures for supply to the general public above the relevant generic concentration limit (GCL, i.e. 0.3% for Repro. 1B substances) or specific concentration limit (SCL) will be forbidden.

The DNEL derived by the eMSCA is lower than the DNEL derived in the registration dossiers. According to the risk characterisation performed by the eMSCA, worst-case assumptions point towards a potential risk for consumers if products or mixtures containing DEA in concentrations even below 0.3% DEA (in case no SCL is derived during the CLH process) continue to be used. Due to the changes in the market which are expected as a consequence of the envisaged stricter harmonised classification, it is however unclear whether such mixtures intended for use by consumers will remain relevant in the future. This also applies to the use of substances which currently may contain DEA as an impurity.

The eMSCA considers that the establishment of a harmonised classification of DEA as Repro. 1B is an important first step towards restricting the substance for use by the general public (i.e. consumers) at least in concentrations above the Repr. 1B GCL of 0.3% (or the respective SCL). Based on the outcome of the CLH process and possible new information on the occurrence of DEA, the eMSCA considers that a specific restriction might be warranted in the future in case an EU-wide risk persists for DEA in consumer products at concentrations below 0.3%. However, a restriction proposal on e.g. limiting the percentage in mixtures with intended consumer uses would require further review once the classification procedure and derived concentration limit for the Annex VI entry of DEA is completed. Therefore, this is not part of or further elaborated in this conclusion.

4.1.4 Other EU-wide regulatory risk management measures

The risk characterisation ratios for DEA are above 1 for a number of occupational exposure scenarios using the DNEL derived by the eMSCA based on the newly submitted information. Thus, the setting of an EU-wide OEL should be envisaged as well.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1 No need for regulatory follow-up at EU level

Not applicable.

5.2 Other actions

Not applicable, cf. section 4.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP Follow-up action	Date for intention	Actor
CLH Dossier	2021	DE CA
Amendment of OEL	N/A	RAC/SCOEL

Part B. Substance evaluation

7. EVALUATION REPORT

7.1 Overview of the substance evaluation performed

The Substance, 2,2'-Iminodiethanol ('DEA') has been proposed for substance evaluation based on Article 44(1) of REACH.

The Substance is produced at high tonnage (> 100 000 tons per year) and its registered uses are wide spread. A large variety of identified uses was found in the registration dossier prior to the start of the evaluation. DEA was chosen for substance evaluation especially to gain information on the carcinogenic transformation product 2,2'-(nitrosoimino)bisethanol (*N*-nitroso-diethanolamine; NDELA; EC number 214-237-4; CAS RN 1116-54-7) and to assess its exposure conditions in order to decide on the necessity for further risk management measures.

This substance evaluation did not encompass environmental endpoints.

DEA was originally selected for substance evaluation in order to clarify concerns about:

- Potential formation of CMR transformation products (Suspected CMR)
- Wide dispersive use, high aggregated tonnage

During the evaluation, reproductive toxicity of DEA was identified as an additional concern.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Potential formation of CMR transformation products	Concern refuted. Information by the registrant was provided on this endpoint following information requirements specified in the substance evaluation decision. Measurement values for inhalation exposure during manufacture of DEA have been provided, demonstrating that inhalation exposure to the transformation product NDELA does not lead to unacceptable risks. However, no measurements from downstream uses have been included.
Occupational exposure	Concern confirmed. An examination of the updated registration showed that the registrants have essentially complied with the exposure requests specified in the decision. However, for a number of exposure situations the risk characterisation ratios for DEA are still significantly above 1 by using the lower DNEL derived by the eMSCA. The eMSCA concludes that an amendment of the OEL for DEA is necessary.
Reproductive Toxicity	Concern confirmed. An Extended-One Generation Reproductive Toxicity Study (EOGRTS) according to OECD TG 443 was provided by the registrants. Based on the new information, the eMSCA considers a stricter classification of DEA, e.g. Repr. 1B, as necessary.
Carcinogenicity	Concern confirmed. Based on available information, classification of DEA as Carc. 2 is considered appropriate by the eMSCA.
Repeated-Dose Toxicity	Concern confirmed. Available data supports the existing harmonised classification of DEA as STOT RE 2.
Consumer exposure	Concern confirmed. Based on the DNEL derived by the eMSCA, a risk for consumers arising from the handling of exemplary mixtures containing DEA in concentrations below the generic concentration limit of 0.3% for substances classified as Repr. 1B cannot be excluded. No information could be gathered on consumer risks from degradation of DEA to NDELA in consumer mixtures. In response to the decision, the registrant provided information on DEA and NDELA in consumer textiles, leather and paper articles. Evaluation of this

	information, together with additional information on DEA in textiles provided by industry associations, resulted in no indication of unacceptable health risks.

7.2 Procedure

DEA was included in the first Community Rolling Action Plan (CoRAP) for evaluation by Germany in 2012. The evaluation process was started in March 2012 and evaluation was concluded within 12 months with the issuing of a draft decision requesting further information from the registrants. The decision[2] was finalised by the Member State Committee at the 33rd meeting in November 2013 and subsequently taken by ECHA. It required the registrants to conduct an Extended One Generation Reproductive Toxicity (EOGRT) study in rats via the oral route (OECD TG 443) including the developmental neurotoxicity and immunotoxicity cohorts but without the extension of Cohort 1B to mate the F1 animals to produce an F2 generation. Furthermore, the registrants were required to perform an exposure assessment and risk characterisation for NDLEA, the carcinogenic transformation product of DEA for manufacturing, particular downstream and consumer uses.

On 20 May 2016 the lead registrant informed the eMSCA that most of the decision´s information requirements regarding exposure and risks of NDELA and DEA in consumer products were no longer considered because consumer uses of DEA and use of DEA in the production of plastic and rubber were not supported any more. As uses of DEA in the production of textile, leather and paper were continued, the lead registrant forwarded to the eMSCA additional chemical safety reports (CSRs) with exposure and risk assessments for DEA and NDELA from consumers´ use of paper, leather and textile articles. Submission of the requested EOGRT study was delayed until January 2018.

[2] 'Decision on substance evaluation pursuant to article 46(1) of Regulation (EC) No 1907/2006 for 2,2'-Iminodiethanol, CAS No 111-42-2 (EC number 203-868-0)' accessible via https://echa.europa.eu/documents/10162/8db2d5d8-6383-44cb-96cf-ff6009361b01

7.3 Identity of the substance

Table 4

SUBSTANCE IDENTITY		
Public name:	2,2'-Iminodiethanol	
EC number:	203-868-0	
CAS number:	111-42-2	
Index number in Annex VI of the CLP Regulation:	603-071-00-1	
Molecular formula:	$C_4H_{11}NO_2$	
Molecular weight range:	105.14 g/mol	
Synonyms:	Diethanolamine 2,2'-Dihydroxydiethylamine 2,2'-Iminobis[ethanol] 2,2'-Iminobisethanol 2,2'-Iminodi-1-ethanol 2,2'-iminodietanol 2,2'-Iminodiethanol 2-[(2-Hydroxyethyl)amino]ethanol	Di(2-hydroxyethyl)amine Di(β-hydroxyethyl)amine DIAETHANOLAMIN Diethanolamine 80 Diolamine Ethanol, 2,2'-iminobis- Ethanol, 2,2'-iminodi- Iminodiethanol N,N-Bis(2-hydroxyethyl)amine

	Bis(2-hydroxyethyl)amine Bis(hydroxyethyl)amine Dabco DEOA-LF 2,2'-Iminodiethanol 80 2,2'-Iminodiethanol O-LF	N,N-Di(2-hydroxyethyl)amine N,N-DIETHANOLAMINE N,N'-Iminodiethanol Niax DEOA-LF NSC 4959

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:

7.4 Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Organic, colourless solid, sometimes a sirupy liquid, with an ammonia like odour
Melting/freezing point	27 °C
Boiling point	269.9 °C @ 1013.25 hPa; decomposition at >200 °C The eMSCA would like to indicate that the registration is missing a statement on whether decomposition occurs at 200 °C or whether the substance boils at 269.9 °C at ambient pressure. The short study summaries provided and the available literature data could not be conclusively evaluated in this endpoint.
Vapour pressure	0.00008553 hPa @ 20 °C
Surface tension	Based on its chemical structure, no surface activity is predicted for DEA.
Water solubility	DEA is totally miscible (22 °C, pH 6.8) (ASTM E 1148-02, flask method) 1000 g/L @ 20 °C (literature data)
Partition coefficient n-octanol/water (Log Kow)	–2.18 (25 °C, pH 7.15) (OECD Guideline 107 Partition Coefficient (n-octanol/water), Shake Flask Method)
Granulometry	Substance is marketed or used in a non-solid or granular form: Substance is a waxy solid at 20 °C and a syrupy liquid above 30 °C.
Stability in organic solvents and identity of relevant degradation products	The stability of the substance is not considered critical
Dissociation constant	8.99 @ 25 °C
Viscosity	390.9 mPa·s (dynamic) @ 30 °C (capillary method)

7.5 Manufacture and uses

7.5.1 Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☒ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

DEA is produced in an aggregated tonnage between 100 000 and 1 000 000 tpa. There are currently 30 active registrants in the joint registration.[3] Additionally, there is a separate registration of DEA as an intermediate with a single registrant.[4]

7.5.2 Overview of uses

Table 7

USES	
	Uses
Uses as intermediate	Use as intermediate
Formulation	Formulation of products containing DEA Formulation of Mixtures (industrial and professional)
Uses at industrial sites	Use as additive in plastic, e.g. rubber Use as laboratory chemical Intermediate Gas treatment Use as additive in PU-systems Processing aid for paper, textile, leather Use in metal working fluids Use in wood protection formulations Catalyst in polymerisation reactions Use in construction chemicals (e.g. cement and concrete) Solvent Paper - finishing and coating Use of fuel
Uses by professional workers	Use as additive in PU-systems Formulation of mixtures Use in construction chemicals (e.g. cement and concrete) Processing aid for paper, textile, leather Use as laboratory chemical Use of fuel Use in metal working fluids Use in detergents and cleaners Textile use Use as additive in plastic, e.g. rubber
Consumer Uses	fuel Use of concrete and cement Use in detergents and cleaners

[3] Dissemination site for DEA (https://echa.europa.eu/de/substance-information/-/substanceinfo/100.003.517) accessed and data retrieved on 7 January 2021.

[4] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/30435

	Use in wood protection formulations
Article service life	Paper service life: indoor Leather service life: indoor and outdoor Textile service life: indoor and outdoor Use in concrete and cement Cutting of paper

The registrations for DEA do not contain uses advised against.

7.6 Classification and Labelling

7.6.1 Harmonised Classification (Annex VI of CLP)

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC number**	**CAS No**	**Classification** **Hazard Class and Category Codes**	**Hazard statement codes**	**Spec. Conc. Limits, M-factors**	**Notes**
603-071-00-1	2,2'-iminodiethanol	203-868-0	111-42-2	Acute Tox. 4* STOT RE 2 * Skin Irrit. 2 Eye Dam. 1	H302 H373** H315 H318		
* For certain hazard classes, including acute toxicity and STOT repeated exposure, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification. ** The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation, but with a general hazard statement not specifying the route of exposure as the necessary information is not available.							

7.6.2 Self-classification

- In the registration(s):

Table 9

CLASSIFICATION ACCORDING TO REGULATION (EC) NO 1272/2008 AS PROVIDED BY THE REGISTRANTS[1]	
Hazard class and category	**Hazard statement**
Acute Tox. 4 Skin Irrit 2 Eye Dam. 1 Repr. 2 STOT RE 2 (Aquatic Acute 2) (Aquatic Chronic 3)	H302 H315 H318 H361 H373 (H401) (H412)
[1]Classes in brackets are not used by all registrants and they are not included in Annex VI of Regulation (EC) 1272/2008.	

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Table 10

NOTIFIED CLASSIFICATION ACCORDING TO CLP CRITERIA	
Hazard class and category	**Hazard statement**
Acute Tox. 3	H301
Skin Sens. 1	H317
Repr. 2	H361
STOT RE 1	H372
STOT SE 3	H336
Carc. 2	H351
Repr. 2	H361

7.7 Environmental fate properties

Not assessed in the course of this evaluation.

7.8 Environmental hazard assessment

Not assessed in the course of this evaluation.

7.9 Human Health hazard assessment

7.9.1 Toxicokinetics

DEA is readily absorbed following oral administration (57 %). In skin penetration studies, absorbed percentages varied between 3-16 % and 27-58 % in rats and mice. With increasing doses higher absorption takes place (Mathews et al. 1997). Therefore, systemic availability of DEA is considered to be equal after oral and dermal exposure.

A comparison of permeability constants among species tested generally suggests that the rank order of skin penetration for DEA is mouse > rabbit > rat > human skin. However, for undiluted DEA the permeability constants were slightly higher in humans compared to rats (Sun et al., 1996). Therefore, the dermal bioavailability is considered equal between humans and rats.

Distribution to the tissues is similar for all administration routes with the highest concentrations in liver and kidney. The half-life for clearance from the tissues is approximately 6 days; thus, DEA shows a potential for accumulation with repeated exposure. Urine is the primary route of excretion for unchanged DEA (Mathews et al. 1995).

Under favourable conditions (e.g., low pH and heat) DEA can be converted to a carcinogenic nitrosamine, in this case to N-nitrosodiethanolamine (2,2'-(nitrosoimino)bisethanol; EC number 214-237-4; CAS RN 1116-54-7), a hepatocarcinogen. Nitrosamine formation *in vivo* is thought to occur as a result of a non-enzymatic reaction between an amine and nitrous acid, formed from nitrate in the acid environment of the stomach.

7.9.2 Acute toxicity and Corrosion / Irritation

DEA shows acute oral toxicity (LD_{50} of 1600 mg/kg bw) leading to the harmonised classification as Acute Tox. 4, H302. The eMSCA supports this conclusion.

No standard guideline tests for acute inhalation toxicity are available for DEA. In acute screening studies (Foster, 1971; Hartung et al., 1970) aerosol concentrations between 0.13 and 6.4 mg/L (30-1476 ppm) DEA with exposure for 80 minutes up to 4 hours were tested in Sprague-Dawley rats. After exposure to 6.4 mg/L of DEA aerosol for 80 minutes, 3/4 rats died 2-4 hours post exposure. After an exposure time of 105 minutes, 2/4 rats died 80-90 minutes post-treatment with the same concentration. No mortality occurred in rats after exposure up to 3.35 mg/L (768 ppm) for 4 hours. Clinical signs at this dose were

increased respiration rate and increased systolic blood pressure. Furthermore congestion in lung, liver, and spleen as well as discoloured kidneys and thymus were seen in gross pathology, and pulmonary oedema was noted in histopathology.

The available results from inhalation studies in rats have pointed out that DEA induced adverse effects following inhalation exposure to a single dose. Therefore, the eMSCA considers DEA acutely toxic after inhalation.

For the dermal route, no reliable data are available.

DEA has a harmonised classification as irritating to skin and severely damaging to the eyes. The eMSCA supports this conclusion.

7.9.3 Sensitisation

The registrants concluded the substance is not sensitising, and based on the available information. The eMSCA can support this conclusion.

7.9.4 Repeated dose toxicity

Table 11

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, ORAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
OECD TG 443 (EOGRTS), GLP **2,2'-iminodiethanol** (99.9 %) (CAS 111-42-2/EC 203-868-0) oral (drinking water), no vehicle 0, 100, 300, 1000 ppm (nominal) (approx. 0, 6.8, 21.5, 73.4 mg/kg bw/d mean dose in parental M; approx. 0, 10.2, 29.4, 103.9 mg/kg bw/d mean premating dose in parental F) 2 weeks prior to breeding and continuing through mating period (up to two weeks), approximately 4 additional weeks (M) or gestation (three weeks) and lactation (three weeks) for F, daily until sacrifice **Rat**(Crl:WI(Han) Wistar) 30 M/30 F per dose group (P) Samples from 10 M/10 F per group (P) at termination for haematology and clinical chemistry	Significant effects in parental animals ≥ 100, 300, 1000 ppm: **Blood (*microcytic anaemia*):** decreased MCV: -**2.9**, -4.4, -6.4 % (M) and at 1000 ppm -5.4 % (F) decreased RBC at 1000 ppm: *-12.94 %* (m), *-10.41 %* (f) decreased HGB from 300 ppm: -5.7, ***-21.1 %*** (M), -3.2, *-14.8 %* (F) **Glandular stomach (F):** Erosion/ulcer (0/20, 2/21, 4/21), increased oedema with inflammatory cell infiltrates (6/20, 12/21, 10/21 compared to 2/20 in control) **Liver:** ↑ abs. wt. (F: + 9, 12, 15 %), ↑ rel. wt. (M: + **4**, 7, 24 % and F + 9, 15, 25 %) centrilobular hypertrophy (M: 4/30, f: 10/30 at 1000 ppm) enzyme activities M ≥ 300 ppm: ALT: - 14 %, n.s.; AST: n.s., + 66 % and ALP: + 41 %, +54 % **Kidney:** ↑ abs. wt. (F + 13, 16, 14 %), ↑ rel. wt. (M: + **5**, 12, 18 % and F: + 13, 19, 24 %) Nephrotoxicity: tubular degeneration/regeneration (M/F: ≥ 300/1000 ppm), ↑ multifocal mineral depositions (M/F: ≥ 1000/300 ppm)	Key study experimental study (reliable without restriction) RDT **LOAEL (F0 parental animals):** 100 ppm (**6.8** mg/kg bw/d in M, 10.2 mg/kg bw/d in F) based on ↓ MCV, ↑ abs. (F) + rel. (M/F) kidney/liver weight, higher incidences of inflammation of glandular stomach (F) (Note: No histological findings in brain, cervical, thoracic, and lumbar cord (only high dose of 144 mg/kg investigated)	(TL, 2018a)

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, ORAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
	Brain: ↑ abs. wt. (F: + 2 %, 2 %, n.s.), ↑ rel. wt. ≥ 300 ppm (M: + 6, 11 % and F: + 5, 9 %) **Heart:** ↓ abs. wt. (M: -3, - 6, -10 % and F: -9 % at 1000 ppm)	No clinical signs of neurotoxicity)	
Equivalent or similar to OECD TG 408, NTP study: Test procedure in accordance with national standards (NTP), GLP **2,2'-iminodiethanol** (> 99 %) (CAS 111-42-2/EC 203-868-0) **Oral**: drinking water Vehicle: water 0, 320, 630, 1250, 2500, 5000 ppm (0, 25, 48, 97, 202, 436 mg/kg bw/d) in M; 0, 160, 320, 630, 1250, 2500 ppm (0, 14, 32, 57, 124, 242 mg/kg bw/d) in F 13 weeks (daily) **Rat** (Fischer 344) 10 M/10 F per dose group Effects on male reproductive system are reported in 7.9.7.	**Mortalities:** 2/10 M at 5000 ppm Significant effects ≥ 160, 320, 630, 1250, 2500 ppm: **Clinical examinations:** ↓ bwg≥10 % (M/F ≥ 630/320 ppm) ↓ water consumption (M/F ≥ 630/2500 ppm) tremors, emaciation, abnormal posture, rough hair coat (M/F ≥ 2500/1250 ppm) **Blood (*microcytic anaemia*):** decreased MCV: M: — , -1.9, -3.7, -7.4, -9.3 % F: -**1.8**, -3.6, -5.4, -8.9, -12.5 % decreased RBC from 320 ppm: M: n. s. , -6.71, -16.60, -27.19 % F: -6.67, -10.00, -19.29, -23.45 % decreased HGB from 320 ppm: M: **-3.4**, *-10.1, -14.9,* ***-33.8 %*** F: **- 8.6**, *-13.9,* ***-25.2, -30.5 %*** **Kidney:** ↑ abs. wt. F: + **30**, 27, 26, 32, 39 %, ↑ rel. wt. M: n.a., + 11, 13, 12, 25 % and F: + **36**, 39, 36, 53, 87 % Nephropathy: no effects on renal function observed ↑ incidence and/or severity of tubular necrosis and/or mineralization (M/F: ≥ 1250/160 ppm) **Brain (medulla) and spinal cord:** demyelination (minimal to mild, M/F: 10/10 ≥ 2500/1250 ppm)	Key study experimental study (reliable without restriction) RDT study **LOAEL:** 160 ppm in F (**14** mg/kg bw/d) based on ↓ MCV, nephrotoxicity, ↑ kidney wt. 320 ppm in M (25 mg/kg bw/d) based on ↓ MCV, ↓ HGB, ↑ rel. kidney wt. (note: ↓ renal function in 2 wk study/same reference: ≥ 158 mg/kg bw/d: ↑ lactate dehydrogenase activity in F, ≥ 371 mg/kg bw/d: ↑ urine conc. of urea nitrogen, glucose, protein in F	Study report 1992 (NTP, 1992; Melnick et al., 1994b)
Equivalent or similar to OECD TG 408, NTP study: Test procedure in accordance with national standards (NTP), GLP **2,2'-iminodiethanol** (> 99 %) (CAS 111-42-2/EC 203-868-0) **Oral**: drinking water Vehicle: water 0, 630, 1250, 2500, 5000, 10,000 ppm (0, 104, 178, 442, 807, 1674 mg/kg bw/d in M; 0, 142, 347, 884, 1154, 1128 mg/kg bw/d in F)	≥ 5000 ppm: all mice died before end of study Most sensitive significant effects ≥ 630, 1250, 2500 ppm: **Kidney:** Significant effects from 1250 ppm: ↑ abs. wt. M: + 10, 14 %, ↑ rel. wt. M/F: + 20/13, 26/31 %, ↑ incidence nephropathy **Liver:** ↑ abs. wt. (M: + **13**, 24, 41 % and F: + 28, 39, 85 %) and ↑ rel. wt. (M: + **18**, 29, 56 % and F: + 25, 53, 124 %) Hepatotoxicity:	Key study experimental study (reliable without restriction) RDT study **LOAEL:** 630 ppm (equal to **104** mg/kg bw/d in males and 142 mg/kg bw/d in females) based on necrotic liver damage	Study report 1992 (NTP, 1992; Melnick et al., 1994a)

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, ORAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
13 weeks (daily) **Mouse** (B6C3F1) 10 M/10 F per dose group Samples from all mice at termination for haematology	hypertrophy, ↑ eosinophilia, and disruption of hepatic cords, ↑ nuclear pleomorphism, multinucleated hepatocytes and necrosis ↑ enzyme activities from 1250 ppm: ALT: + n.s./28, 196/128 % (m/f) and Sorbitol-DH: n.s., + 84 % (m) **Heart:** ↑ abs. wt. (F at 2500 ppm) ↑ rel. wt. (M/F ≥ 2500/1250 ppm) minimal to marked degeneration and necrosis of cardiac myocytes from 2500 ppm		

Table 12

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, INHALATIVE EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
According to OECD TG 412, GLP **2,2'-iminodiethanol** (99.5 %) (CAS 111-42-2/EC 203-868-0) **Inhalation:** aerosol (nose/head only), no vehicle 0; 110; 210; 400 mg/m³ MMAD 3.7–4.8 µm 2 weeks (6 h/day, 5 days/week) **Rat** (Wistar) 10 M/10 F per dose group Blood samples at the end of exposure	Effects observed from 400 mg/m³: **Body weight and weight gain:** slightly decreased body weight and impaired body weight gain (77 % of controls) in M **Clinical chemistry:** slightly decreased cholesterol values (~15 – 23 % reduction) in M and F **Liver:** increased liver weights (13 %) in F No effects on blood and brain.	Supporting Study RDT study (10 exposures) experimental study (reliable without restriction) **NOAEC** (systemic toxicity): **210** mg/m³ LOAEC (systemic toxicity): 400 mg/m³ based on ↓ bw (M), ↓ cholesterol (M/F), ↑ liver wt. (F)	Study report 1993 (TL, 1993)
OECD TG 413, GLP **2,2'-iminodiethanol** (99.89 %) (CAS 111-42-2/EC 203-868-0) **Inhalation:** aerosol (nose/head only), no vehicle 0; 15; 150; 400 mg/m³ (target) 0; 15; 152; 410 mg/m³ (analytically determined) MMAD 0.6–1.9 µm 90 days (6 h/day, 5 days/week) **Rat** (Wistar) 13 M/13 F per dose group Blood samples from 10 animals daily	Significant systemic effects ≥ 150; 400 mg/m³ **Blood** (*microcytic anaemia*) at 400 mg/m³: ↓ MCV: -4/-3 % (M/F) ↓ RBC: -6.2/-8.5 % (M/F) ↓ HGB: *-10.2/-13.9 %* (M/F) **Liver:** ↑ rel. wt. (M: n.s., + 9 % and F: + 10, + 19 %) slightly increased ALP (M/F) and decreased ALT (M) **Kidney:** ↑ rel. wt. (M: + 10, 13 %, and F: + 12, + 16 %) minimal/slight tubular hyperplasia in some F and intratubular lithiasis (M) Urinalysis: M: ↑ excretion of	Key study RDT study (65 exposures) experimental study (reliable without restriction) **NOAEC** (systemic toxicity): **15** mg/m³ LOAEC (systemic toxicity): 152 mg/m³ based on ↑ kidney (M/F)/liver (f) wt., renal tubular damage, ↑ ALP (M/F), ↓ ALT (M), ↑ erosions in	Study report 1996 (TL, 1996; Gamer et al., 2008)

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, INHALATIVE EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Effects on male reproduction system reported in 7.9.7.	renal tubular epithelium cells including casts; M/F: ↑ blood in urine only at 400 mg/m³ **Glandular stomach (F):** ↑ erosions (conc.-dependent) **Local effects**: ≥ 15 mg/m³ focal squamous metaplasia of the laryngeal epithelium ≥ 150 mg/m³ ↑ laryngeal squamous hyperplasia (conc.-depend.), ↑ incidence and severity of local inflammation of larynx and trachea	glandular stomach (F) **Brain:** no histopathological effects **LOAEC** (local effects): **15** mg/m³ based on focal squamous metaplasia of ventral laryngeal epithelium at the base of the epiglottis	
OECD TG 413, GLP **2,2'-iminodiethanol** (99.89 %) (CAS 111-42-2/EC 203-868-0) **Inhalation:** aerosol (nose/head only), no vehicle 0; 1.5; 3; 8 mg/m³ MMAD 0.6–0.7 µm 90 days (6 h/day, 5 days/week) **Rat** (Wistar) 10 M/10 F per dose group (without recovery period) 10 F per dose group (with 3 month recovery period)	**Local effects:** (F: all lesions reversible after 3 month recovery) ≥ 3 mg/m³ M: 3/10 with focal squamous metaplasia of the laryngeal epithelium at the base of the epiglottis (minimal/adaptive) ≥ 8 mg/m³ M + F: 9/10 with focal squamous metaplasia of the laryngeal epithelium at the base of the epiglottis M + F: 3/10 with submucosal inflammation (adverse) M: 2/10 with squamous metaplasia at the region of ventral pouch and arytenoid cartilages	Key study RDT study (65 exposures) experimental study (reliable without restriction) NOEC (local effects): 1.5 mg/m³ **NOAEC** (local effects): **3** mg/m³ **LOAEC** (local effects): **8** mg/m³ based on squamous metaplasia in the larynx	Study report 1996 (TL, 1996; Gamer et al., 2008)

Table 13

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, DERMAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Equivalent or similar to OECD TG 411, NTP-Study: Test procedure in accordance with national standards (NTP), GLP **2,2'-iminodiethanol** (> 99 %) (CAS 111-42-2/ EC 203-868-0) **Dermal**: shaved back of each animal (unoccluded), from the mid-back to the	Significant effects ≥ 32, 63, 125, 250, 500 mg/kg bw/d **Blood (*microcytic anaemia*):** decreased MCV: M: **-1.9**, -3.8, -8.0, -10.2, 12.5 % F: -**1.8**, -3.6, -5.5, -9.4, -13.7 % decreased RBC: M: n. s. , n. s. , -3.50, -12.27, -30.44 % F: **-3.81**, -7.92, -14.50, -22.29, -35.63 % decreased HGB: M: n. s. ,-2.6, -8.4, ***-20.2, -40.9 %*** F: **-4.7**, -9.8, *-17.4,* ***-29.2, -47.6 %***	Key study RDT study experimental study (reliable without restriction) **LOAEL** (local and systemic effects): **32** mg/kg bw/d	Study report 1992 (NTP, 1992; Melnick et al., 1994b)

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, DERMAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
interscapular region Vehicle: ethanol (95 %) 0, 32, 63, 125, 250, 500 mg/kg bw/d (nominal per unit body weight) 13 weeks (once per day, 5 days/week) **Rat** (Fischer 344) 10 M/10 F per dose group	**Kidney:** ↑ abs. + rel. wt. (M/F) ↑ severity/incidence nephropathy (F) tubular mineralisation (M/F: high/all doses) tubular necrosis (F: ≥ 250 mg/kg bw/d) **Brain (medulla oblongata):** minimal demyelination ≥ 250 mg/kg bw/d M: n.s., 10/10, F: 7/10, 9/10 **Local effects**: Skin lesions: (M/F: ≥ 63/32 mg/kg bw/d) ↑ severity/incidence hyperkeratosis M/F: acanthosis (≥ 63 mg/kg bw/d) ulceration and inflammation (M/F: ≥ 250/125 mg/kg bw/d)	based on hyperkeratosis (F), ↓ MCV (M/F), ↓ RBC (F), ↓ HGB (F), nephrotoxicity (F), ↑ kidney wt. (M/F) (Note: NTP 1992 report on 2-week dermal study in rats (with limited histopathology at low and mid doses were not documented here, similar key findings)	
Equivalent or similar to OECD TG 411, NTP-Study: Test procedure in accordance with national standards (NTP), GLP **2,2'-iminodiethanol** (CAS 111-42-2/ EC 203-868-0) **Dermal**: shaved back of each animal (unoccluded), from the mid-back to the interscapular region Vehicle: ethanol (95 %) 80, 160, 320, 630, 1250 mg/kg bw/d (nominal per unit body weight) 13 weeks (once per day, 5 days/week) **Mouse** (B6C3F1) 10 M/10 F per dose group Blood samples were collected from the retroorbital sinus at the end of study	Significant effects ≥ 80, 160, 320, 630, 1250 mg/kg bw/d **Liver:** ↑ abs. wt. (M: n.s., +16, 35, 35, 48 % and F: + **23**, 28, 43, 47, 92 %) ↑ rel. wt. (M: n.s., + 17, 31, 36, 57 % and F: + **11**, 19, 33, 45, 89 %) Hepatotoxicity: hepatocellular necrosis (M) hepatocellular cytological changes: increased nuclear pleomorphism (M/F: ≥ 80/160 mg/kg bw/d) ↑ enzyme activities from 320 mg/kg bw/d: ALT: + n.s./n.s., 102/n.s., 183/47 % (M/F) and Sorbitol-DH: + **25**, 76, 91 % (M) **Kidney:** ↑ abs. wt. (M: +**10**, 10, 18, 17, 30 % and F: + **7**, 14, 11, 16, 24 %) ↑ rel. wt. (M: +**8**, 11, 15, 18, 36 % and F: n.s., n.s., n.s., +15, 23 %) minimal to mild renal tubular necrosis (M/F: ≥ 1250 mg/kg bw/d) **Heart:** ↑ abs. wt. (M/F at 1250 mg/kg bw/d) cardiac myocyte degeneration **Local effects**: Skin lesions: acanthosis (M/F) minimal to mild hyperkeratosis (M/F: ≥ 320/1250 mg/kg bw/d) ulceration and inflammation (M/F: ≥ 630 mg/kg bw/d)	Key study RDT study experimental study (reliable without restriction) **LOAEL** (local and systemic effects): **80** mg/kg bw/d based on ↑ liver wt.(F), hepatocellular necrosis (M), ↑ kidney wt. (M/F), acanthosis (M/F) (Note: NTP 1992 report on 2-week dermal study in mice (with limited histopathology at low and mid doses were not documented here, similar key findings)	Study report 1992 (NTP, 1992; Melnick et al., 1994a)
Equivalent or similar to OECD TG 451, GLP **2,2'-iminodiethanol** (> 99 %) (CAS 111-42-2/ EC 203-868-0)	Non-neoplastic significant effects: ≥ 8, 16, 32, 64 mg/kg bw/d **Liver:** decrease of incidences of basophilic foci (M/F: –/31, 5/20, 1/7, 2/– per 50 animals)	Key study 2 year study experimental study (reliable without restriction)	Study report 1999 (NTP, 1999; US DHHS, 2002)

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, DERMAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Dermal: unoccluded Vehicle: ethanol (95 %) 0, 16, 32, 64 mg/kg bw/d (M) 0, 8, 16, 32 mg/kg (F) 103 weeks (once per day, 5 days/week) **Rat** (Fischer 344/N) 50 M/50 F per dose group	**Kidney:** nephropathy (severity): 47 (minimal), 48 (mild), 48 (moderate) out of 50 females **Mammary Gland:** ↓ incidence of fibroadenoma (5 of 50 F at 32 mg/kg bw/d compared to 14 of 50 F in vehicle control) **Local effects**: Skin lesions (incidence per 50 animals): minimal hyperkeratosis (M/F: —/13, n.s./23, 5/23, 11/—) and exudate (M/F: —/7, n.s./7, n.s./7, 7/—) acanthosis (10 of 50 M at 64 mg/kg bw/d)	**LOAEL** (local and systemic effects): **8** mg/kg bw/d based on hyperkeratosis /exudate (F) and nephropathy (F)	
Equivalent or similar to OECD TG 451, GLP **2,2'-iminodiethanol** (> 99 %) (CAS 111-42-2/ EC 203-868-0) **Dermal**: unoccluded Vehicle: ethanol (95 %) 0, 40, 80, 160 mg/kg bw/d (M/F) 103 weeks (once per day, 5 days/week) **Mouse** (B6C3F1) 50 M/50 F per dose group	Non-neoplastic significant effects: ≥ 40, 80, 160 mg/kg bw/d **Liver:** ↑ incidences of hepatocyte changes: cytoplasmic (M: 17/50, 17/50, 12/50) and syncytial alteration (M/F ≥ 80 mg/kg bw/d: 38/17, 23/18 per 50 animals) **Kidney:** ↑ incidence of renal tubule hyperplasia (M at 160 mg/kg bw/d: 10 per 50 animals) **Thyroid Gland:** ↑ incidence of follicular cell hyperplasia (M/F: 22/28, 30/32, 42/39 per 50 animals compared to 18 of 50 M/F in vehicle control) **Local effects**: Skin lesions: minimal hyperkeratosis (M/F: 13/n.s., 10/8, 17/16 per 50 animals) Tumor data and attributed reduced survival see 7.9.6)	Key study 2 year study experimental study (reliable without restriction) **LOAEL** (local and systemic effects): **40** mg/kg bw/d based on hyperkeratosis (M), liver lesions (M) and lesions in thyroid gland (M/F)	Study report 1999 (NTP, 1999; US DHHS, 2002)

Repeated dose toxicity studies on DEA have been conducted in rats and mice using oral, inhalation and dermal routes of administration. Significant toxic effects of DEA were observed in 90-day repeated dose studies for all three examined application routes. DEA caused toxic effects at multiple organ sites in rats and mice after exposure via drinking water, after topical application or by inhalation. In rats target organs of DEA toxicity included the blood (microcytic anaemia), kidney, nervous system, and skin (site of application). In mice exposure to DEA caused toxic effects in the liver, kidney, heart, and skin (site of application). Data suggest that rats are somewhat more sensitive than mice to the toxic effects of DEA.

Aerosol exposure of rats to DEA for 90 days resulted in systemic effects such as anaemia, liver dysfunction and kidney lesions as well as local irritating effects on the upper respiratory tract. Squamous metaplasia in combination with inflammatory cell infiltration in the larynx or with wider extension to other larynx area than the base of the epiglottis occurring at ≥ 8 mg/m³ was considered as adverse (LOAEC). Recovery was noted at the end of the recovery period which was unusually long (3 months instead of 4 weeks recommended in the TG 413). The tracheal mucosa showed similar effects at 150 mg/m³. In contrast, the reversible minimal and focal “laryngeal squamous metaplasia” at the base of the epiglottis only in the absence of cilia and flattening of the normally cuboidal, laryngeal epithelium, which has been observed at 3 mg/m³, is regarded as a morphological correlate for slight irritation and therefore non-adverse in character (Kaufmann et al., 2009; Dungworth et al., 2001). Following 14 days of aerosol exposure, no local effects but

only systemic effects such as increased liver weights were observed. In a chronic study via the dermal route, local and systemic effects were seen at the same low dose.

The available results from animal studies show that DEA induces adverse effects following subchronic exposure. For single target organ toxicity (STOT) after repeated exposure, the existing category 2 classification according to the CLP Regulation shall be considered as a minimum classification with the kidney and haematopoietic system as the most sensitive target organs. The eMSCA considers the information on all routes of exposure as relevant for classification purposes with respect to specific target organ toxicity.

7.9.5 Mutagenicity

The registrants concluded that the substance is not mutagenic and, based on the available information, the eMSCA can support this conclusion.

While purified DEA has been shown to lack genotoxic potential, it is important to note that, like many secondary amines, it may react chemically with nitrosating compounds under favourable conditions (e.g., low pH and heat) to form a nitrosamine, in this case 2,2'-(nitrosoimino)bisethanol (NDELA). NDELA and a number of its metabolites have been shown to be mutagenic in a variety of short-term genotoxicity assays (ECETOC 1990; IARC, 2000) and, as noted below, are tumourigenic when administered to test animals.

7.9.6 Carcinogenicity

7.9.6.1 Human information

No publications were retrieved for studies that examined the risk of cancer among individuals exclusively exposed to DEA. However, ethanolamines (mainly DEA and triethanolamine (TEA)) have commonly been used as additives for metalworking fluids since the 1950s and as wetting fluids for asphalt paving. Road paving and roofing materials are complex mixtures containing many known or suspected carcinogens such as benzene, 1,3-butadiene and coal tar pitch. Numerous studies have evaluated cancer in workers exposed to metalworking fluids (so-called cutting fluids). DEA is added to soluble, semi-synthetic and synthetic fluids as a corrosion inhibitor or for pH adjustment. Metalworking fluids are complex mixtures which may vary considerably depending on the type of fluid and the additives used. These mixtures may contain many potential carcinogens and, in particular, the combined presence of nitrites (often used as additives) and DEA can lead to the formation of *N*-nitrosamines (mainly NDELA, a known carcinogen, classified as Carc. 1B). Therefore, workers who were exposed to NDELA would also have been exposed to DEA from which the nitroso derivative was formed. Numerous epidemiological studies have investigated exposure to metalworking fluids and the risk of cancer in workers who were likely exposed to DEA and other agents. In an IARC Monograph (IARC, 2000) it was reported that small increases were observed in tumours at various sites, in particular the stomach, oesophagus and larynx. In those studies, only associations with the use of soluble oils or synthetic fluids were presented and no results were given specifically in relation to exposure to DEA. Also in the numerous new studies, evaluation of the cancer risk in workers was based on exposure to metalworking fluids consisted of DEA and other agents. Excess risk of cancer was observed among workers exposed to metalworking fluids which probably contained DEA. However, these studies cannot distinguish the carcinogenic effect of DEA alone from that of the complex mixture. In consequence, occupational exposure limits and guidelines for DEA for restriction of *N*-nitrosamine generation in the manufacture and use of specific anticorrosion agents, during the handling of substances, mixtures and treated articles and in the use of cooling lubricants were recommended in some European countries, Australia and the USA. No studies were identified that evaluated human cancer associated with the use of personal care products that contain DEA (IARC, 2012).

It is probable that most of the cohorts studied included workers exposed to water-reduced metalworking fluids who were exposed to DEA by skin contact and inhalation. Due to the insufficient information on the exposure conditions to DEA and the potential for confounding factors from mixed exposure to other known or suspected carcinogens, a

robust evaluation of the carcinogenic potential of DEA based on the available epidemiological studies is very difficult.

7.9.6.2 Animal studies on carcinogenicity

Two 2-year carcinogenicity studies (similar to OECD TG 451) with topical application of DEA in F344/N rats and B6C3F1 mice are available as key studies (NTP, 1999; US DHHS, 2002). In a third, supporting study, a short-term test for carcinogenicity (Spalding et al, 2000), DEA was investigated in a transgenic mouse model (homozygous female Tg.AC transgenic mice). In addition, a series of mechanistic studies providing evidence of the possible mode of tumourigenesis of DEA in rodents are available (Mellert et al., 2004; TL, 2001; 2002; TL, unpublished report, 2003; Lehman-McKeeman et al., 2002; Stott et al., 2000). There were no data available for the oral or inhalation routes.

In a 2-year dermal study in rats, DEA formulated in ethanol showed no carcinogenic effects in male and female rats. However, there was clear evidence of carcinogenic activity of DEA in male and female mice based on increased incidences of benign and malignant liver neoplasms in male and female mice, multiple types of liver tumours (adenomas, carcinomas and blastomas) in male mice and increased incidences of renal tubule neoplasms (mainly adenomas, 1/50, 4/50, 6/50 and 6/50 at 0, 40, 80, and 160 mg/kg bw/d, respectively ($p = 0.05$, Poly-3 trend test)) in male mice. Carcinogenic effects in the liver were noted at all dose levels tested with significant dose-related responses for tumour induction in both sexes (≥ 40 mg/kg bw/d) indicating that a plateau effect was already seen at low or mid dose groups.

Liver tumour incidences significantly increased in male mice at 80 and 160 mg/kg bw/d (hepatocellular adenoma: 31/50, 42/50, 49/50 and 45/50 ($p < 0.001$, Poly-3 trend test); hepatocellular carcinoma: 12/50, 17/50, 33/50 and 34/50 ($p < 0.001$, Poly-3 trend test); hepatoblastoma: 0/50, 2/50, 8/50, 5/50, for the control, low-, mid- and high-dose groups, respectively). Significantly increased tumour incidences were observed in female mice in all dose groups (hepatocellular adenoma: 32/50 (control), 50/50, 48/50 and 48/50 ($p < 0.001$, Poly-3 trend test); hepatocellular carcinoma: 5/50 (control), 19/50, 38/50 and 42/50 ($p < 0.001$, Poly-3 trend test) in the control, low-, mid- and high-dose groups, respectively).

Potential mechanisms of DEA-induced carcinogenicity in the mouse discussed in the literature include its conversion to the carcinogenic nitrosamine NDELA, the induction of choline deficiency, and the displacement of ethanolamine by DEA in phospholipids, an effect which may result in a reduced endogenous production of choline. It is assumed that possible potential mechanisms of DEA carcinogenicity are not fully elucidated and the potential mechanisms of DEA-induced carcinogenesis could be more complex.

The lack of carcinogenic effects in the dermal study in rats might be explained by a lower systemic exposure to DEA due to a lower dermal absorption compared to that of mice and by the use of a lower dose range in the rat carcinogenicity study (high dose of 64 mg/kg bw/d).

Apart from that, there is a negative test outcome in the Tg.Ac transgenic mouse model which may not be predictive and is no proof that a test substance has no carcinogenic properties. This assay uses skin tumours as an endpoint, thus no data on kidney or liver were collected.

There was no evidence of genotoxicity in a battery of standard *in vitro*/*in vivo* tests. However, there is weak evidence that a genotoxic mechanism is involved in the induction of liver tumours by DEA. A genotoxic mechanism is supported by the elevated frequency of mutations in *β*-catenin *Catnb* genes in liver tumours induced by DEA.

As a secondary amine, DEA can be converted to the carcinogenic nitrosamine NDELA under favourable conditions (e.g., at low pH or heat). Nitrosamine formation *in vivo* is thought to occur as a result of a non-enzymatic reaction between an amine and nitrous acid, formed from nitrate in the acidic environment of the stomach.

NDELA is mutagenic *in vitro* and causes liver tumours (principally hepatocellular carcinomas) and benign kidney tumours (adenomas) in rats following oral administration

(drinking water) of 1-2 mg/kg bw/d (Lijinsky and Reuber, 1984; Lijinsky and Kovatch, 1985; Preussmann et al., 1982; Berger et al., 1987; ECETOC, 1990; IARC, 2000). In hamsters of both sexes, NDELA consistently induced adenocarcinomas of the nasal cavity following subcutaneous injection and at the injection site fibrosarcoma and benign tumours of the trachea (papilloma) and liver (hepatocellular adenoma) (IARC, 2000). NDELA is classified for its carcinogenic properties as Carc. 1B – H350.

No experimental data are available for the identification of potential mechanisms for the induction of kidney tumours in mice by DEA.

Overall, the evidence of carcinogenicity is shown in a single well-documented animal experiment. Tumours of the kidney and hepatoblastomas are rare spontaneous neoplasms in experimental animals. However, a few limitations of the NTP mouse study should also be considered: high incidence of benign liver tumours in the B6C3F1 mouse strain; use of mice at non-caloric restricted diet, known to be a risk factor of liver tumours; an experimental design that allowed simultaneous dermal and (by licking the application site) oral exposure; and the possible confounding influence of ethanol as vehicle. It may be speculated that ethanol evaporated within a short time, but it may also have affected the dermal absorption of DEA.

Based on evaluation of all available data, the eMSCA considers it is not possible to conclude that DEA-induced carcinogenesis is species-specific and therefore is consided as relevant for humans. This is in line with the IARC assessment concluding that there is sufficient evidence in experimental animals for the carcinogenicity of DEA. Major arguments to consider classification as a carcinogen (Category 2) are the treatment-related tumour induction in the carcinogenicity study on mice and the concern from NDELA formation taking the uncertainties and the lack of evidence for the rat (based on the used study design/dosing) into account.

7.9.7 Toxicity to reproduction

7.9.7.1 Effects on fertility

The evidence of reproductive toxicity of DEA was obtained from animal testing. Three GLP compliant rat studies are available for assessment of effects on fertility for DEA: an Extended One-Generation Reproductive Toxicity Study (EOGRTS) according to OECD TG 443 (TL, 2018a) including a preceding dose-range finding study according to a modified protocol of OECD TG 421 (TL, 2018b), a three-month nose-only inhalation study to DEA aerosols according to OECD TG 413 (TL, 1996; Gamer et al., 2008) and a sub-chronic oral treatment study via drinking water (protocol similar to OECD TG 408; (Melnick et al., 1994; NTP, 1992)).

Under the conditions of an EOGRTS including cohorts 2A, 2B (developmental neurotoxicity), and 3 (developmental immunotoxicity) in Wistar rats receiving 0, 100, 300, and 1000 ppm (0, 12.75, 37.68, 128.35 mg/kg bw/d) in drinking water (TL, 2018a), consumption of water and food as well as body weight gain were reduced in F0 females at ≥ 300 ppm during gestation and lactation. In F0 males, food consumption was lower than in controls at 1000 ppm during premating, and lower body weight gain (average 23-25 %) was seen at ≥ 300 ppm. The number of implants in F0 dams of the high dose group (1000 ppm) was decreased, accompanied by a lower litter size (and body weight gain). Gestation length was increased. No effects on fertility were observed in F0 males. Fertility effects in F1 females included prolonged/irregular oestrous cycles, and decreased primordial/growing ovarian follicles (1000 ppm). Histology revealed luteal cysts, absence of corpora lutea, diffuse ovarian atrophy, and reduced macroscopical ovarian size in F1 females. In F1 males, treatment-related effects included degeneration of testicular tubules (at 1000 ppm: 1/20 and 3/25 animals of cohorts 1A and 1B, respectively), and macrovesicular vacuolisation of the ductus deferens (in cohort 1A: 12/20 and 4/20 animals at 1000 ppm and 300 ppm, respectively). Furthermore, testicular immaturity (at 1000 ppm: 3/20 and 3/25 animals in cohort 1A and 1B, respectively) accompanied by epididymal aspermia and a decreased macroscopical size of prostate, epididymides, and seminal vesicles was observed. These findings occurred particularly in animals with lower body weight and bw gain (≤13 % at 1000 ppm) until weaning and at 1000 ppm post-weaning

(range 13-24% in males), and might therefore be secondary to body weight effects. Further findings related to fertility included pathological changes in the mammary glands of both sexes (feminisation in F1 males; increased secretions in F1 females) at the high dose.

Therefore, the NOAEL for fertility in the parental and F1 generation was 300 ppm, corresponding to 37.7 mg/kg bw/d. For general toxicity, the LOAEL was 100 ppm based on effects on blood, glandular stomach, liver, and kidney. This corresponds to 6.8 mg/kg bw/d (in F0 males).

A dose-range finding study (TL, 2018b, not cited in 7.9.4) for the above-mentioned EOGRTS, based on a modified OECD TG 421, similarly showed significant effects on female fertility. Reproductive toxicity was observed at ≥ 1000 ppm including reduced implantation sites, and decreased litter size. Post-implantation losses and resorptions were signficantly increased at ≥ 1500 ppm. Gestation and fertility indexes were significantly lower at 2000 ppm. Pup survival was significantly reduced at 1500 ppm. Therefore, the NOAEL for fertility in this study was 500 ppm corresponding to 46 mg/kg bw/d. The LOAEL for general toxicity was 500 ppm (corresponding to 46 mg/kg bw/d) based on effects on blood, liver and kidney (similar to those observed in other studies, not reported here).

The following toxic effects on fertility were observed in sub-chronic repeated dose toxicity studies with DEA in rats by the oral (Melnick et al., 1994b; NTP, 1992) and inhalation (TL, 1996; Gamer et al., 2008) routes: oral: decrease in absolute/relative weights of testis and epididymis, testicular degeneration, atrophy of the seminal vesicles and prostate glands and associated effects on spermatology from 97 mg/kg bw/d onwards corresponding to a NOAEL of 48 mg/kg bw/d (male); inhalation: diffuse testicular atrophy and minimal atrophy of the prostate at 0.4 mg/L, corresponding to a NOAEC of 0.15 mg/L. In none of the subchronic repeated dose studies, histopathological effects were observed in female reproductive organs. In summary, these data from standard repeated dose tests give reason for concern that DEA may induce toxicity to the male reproductive system. However, the effects occurred at dose levels causing other systemic effects, and the impact of toxic effects on the blood, kidney and brain, as well as their severity and biological plausibility to cause the observed reproductive effects need consideration.

A study performed by the Korean Food and Drug Administration (KFDA, 2007) investigated the reproductive and developmental toxicity of DEA in mice offspring after dermal exposure of either paternal or maternal animals. In F0 males, a significant decrease in motile sperm (≥ 20 mg/kg bw/d) accompanied by reduced sperm motility (non-significant) was detected. Male offspring from exposed fathers similarly showed a significant decrease in motile sperm (320 mg/kg bw/d). Furthermore, in F1 males at 320 mg/kg bw/d , weight of epididymis and testis was significantly lower compared to controls and this effect could not be explained by the minimal body weight effects (↓ 4 %) observed. No fertility related parameters were changed in F0 females due to DEA exposure. Offspring from exposed dams showed no significant fertility effects except for a significantly reduced absolute uterus weight in F1 females on PND 70 (320 mg/kg bw/d).

An *in vitro* study using human sperm samples revealed a significant and dose-dependent decrease in motile and viable sperm, and the percentage of morphologically normal sperm was reduced (Panchal and Verma, 2013). An oral reproductive toxicity study with DEA performed in mice by the same authors (Panchal and Verma, 2016) reported a significant and dose-dependent decrease of serum testosterone levels (significant at ≥ 110 mg/kg bw/d), testicular cholesterol as well as total lipid levels (significant at ≥ 110 mg/kg bw/d), and activity of testicular 3β- and 17β-hydroxysteroid dehydrogenase (significant at 330 mg/kg bw/d).

Further evidence of toxic effects on fertility is provided by a study investigating the neurotoxicity of DEA in mice (Craciunescu et al., 2006). Dermal exposure from GD 7-17 resulted in a dose-dependent and significant reduction of viable foetuses per litter (≥ 160 mg/kg bw/d) and a lower total number of viable foetuses (not significant). However, there was no reporting of maternal toxicity except for one dead dam in the high dose group (640 mg/kg bw/d).

In summary, DEA showed significant effects on fertility parameters in several studies. In particular, there were pronounced effects on the number of implants and on litter size in

the EOGRTS (and the preceding dose-range finder study) as well as further effects on reproductive organs in F1 animals (ovary, mammary gland). In addition to the EOGRTS, there are supporting *in vivo* and *in vitro* studies demonstrating toxic effects on male sexual organs, sperm parameters, and steroidogenesis. Some non-specific toxicity (see 7.9.4) occurred at similar or lower doses than those causing reproductive toxicity in several studies. Nonetheless, the effects of DEA on fertility have to be considered as a specific intrinsic property of the substance which is related to its interference with choline uptake and metabolism.

The absence of effects on implantation and litter size in several OECD TG 414 studies with DEA (TL, 1993; NTP, 1999; Price et al., 2005; Marty et al., 1999; Neeper-Bradley, 1992a and 1992b) is in agreement with studies on the related substance ethanolamine and other alcohol amines. For ethanolamine, Moore et al. (2018) demonstrated that premating exposure is necessary to impair implantation success which can be ameliorated by choline supplementation. Furthermore, the authors hypothesised that reduced synthesis of platelet-activating factor (PAF) and/or formation of a functionally impaired PAF analogue is the predominant mode of action underlying the anti-fertility effects of alcohol amines (Moore et al., 2018). In fact, in the EOGRTS (TL, 2018a), DEA treatment reduced plasma and tissue choline, and plasma PAF levels were decreased in F0 females. Thus, the adverse effects of DEA on fertility are considered as a specific intrinsic property of the substance and not just secondary to other non-specific toxic effects.

Therefore, DEA-related effects on fertility shall be considered for classification.

7.9.7.2 Developmental toxicity

Several guideline and non-guideline studies with different routes of exposure are available investigating developmental effects of DEA. Prenatal developmental toxicity studies according to OECD TG 414 via inhalation (TL, 1993) or dermal exposure (Marty et al., 1999; Neeper-Bradley, 1992) in rats showed maternal toxicity (in particular on body weight, kidney, blood, liver). Developmental effects were restricted to an increase of skeletal variations in fetuses (TL, 1993; Marty et al., 1999; Neeper-Bradley, 1992). Similarly, in rabbits, a dermal study according to OECD TG 414 revealed maternal toxicity (food consumption, body weight, kidney) but no developmental toxicity was evident (Marty et al., 1999; Neeper-Bradley, 1992). Furthermore, an oral non-guideline screening study in rats (NTP, 1999; Price et al., 2005) investigated post-natal developmental toxicity after applying DEA from GD 6-19. This study reported an increase in post-implantation losses, early post-natal mortality, and reduced pup body weight and weight gain. However, strong maternal toxicity was observed in high-dose (300 mg/kg bw/d) dams which had to be terminated early. At lower dose levels, maternal toxicity consisted of lower body weight and weight gain in comparison to controls, and increased kidney weight. The NOAEL for both maternal and developmental toxicity was similar (50 mg/kg bw/d).

The key study for evaluating developmental toxicity is an oral EOGRTS (OECD TG 443) in rats including the DNT and DIT cohorts (TL, 2018a). In many cases, DEA affected similar toxicological endpoints in parental animals and offspring (body weight, blood, kidney, liver). However, compared to parental animals, effects on several blood parameters occurred already at lower doses in the F1 generation (e.g. on RBC; HGB, HCT). Developmental immunotoxicity was evident from analysis of spleenic lymphocyte subpopulations which revealed effects on T-helper cells and cytotoxic T-cells in F1 females at the high dose (1000 ppm). Furthermore, some effects on fertility parameters in the F1 generation could not be observed in parental animals and therefore are of developmental aetiology. These include effects on differential ovarian follicle count, oestrus cycle, histology of male and female sexual organs, as well as effects on the mammary glands. Regarding changes in plasma T4, the increases observed in F1 females were not observed in maternal animals.

Developmental neurotoxicity was evident in F1 males and females: High-stepping gait and piloerection were observed in all F1 cohorts at several time-points (not observed in F0 animals). Neurobehavioural testing revealed lower maximum amplitudes in the auditory startle response test and no habituation to the test environment occurred. Histologically, degeneration of nerve fibers in the spinal cord and medulla oblongata were observed in

cohort 2B animals on PND 77. Although similar effects have been documented in adult rats in a former repeated dose toxicity study (Melnick et al., 1994; NTP, 1992), no histological changes could be observed in the F0 generation of the present EOGRTS, indicating higher sensitivity of F1 animals. Furthermore, eosinophilic cysts were observed in the pars distalis of the pituitary (anterior pituitary), occurring exclusively in F1 animals in cohort 2A and 2B (in cohort 2A even at the lowest dose (100 ppm) tested). Although the functional relevance of these cysts remains unknown, their appearance in the master gland of the endocrine system, the affected part of which regulates several processes through synthesis and secretion of releasing hormones relevant for growth, reproduction, lactation, thyroid stimulation and others, is of concern and has to be considered adverse.

Additional non-guideline studies provide evidence for developmental neurotoxicity of DEA. The reproductive and developmental toxicity study performed by KFDA (KFDA, 2007) reported on significant effects in behavioural testing after dermal DEA exposure of either paternal or maternal animals. Furthermore, a series of *in vitro* and *in vivo* studies in mice demonstrated effects of DEA on prenatal neurogenesis (Craciunescu et al., 2009; Craciunescu et al., 2006; Niculescu et al., 2007).

In conclusion, exposure to DEA leads to several developmental effects in offspring related to fertility, immunotoxicity, and neurotoxicity. The finding of eosinophilc cysts in the pituitary and changes in T4 levels in F1 animals in the EOGRTS are of similar concern. Although DEA treatment affects physiology at multiple levels in maternal animals as well as in offspring, the above-mentioned findings in F1 animals are unlikely to occur as side-effects of general toxicity (blood, kidney, liver, body weight). Given the disturbance of choline uptake and homeostasis by DEA and the importance of choline and choline-metabolites in cell function and signal transduction, the adverse developmental effects of DEA are considered as a specific intrisic property of the substance.

Therefore, DEA-related effects on development shall be considered for classification.

7.9.8 Hazard assessment of physico-chemical properties

Not assessed in the course of this evaluation.

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

7.9.9.1 Overview of typical dose descriptors for all endpoints

DNEL and DMEL derivation followed the procedure laid out in the REACH Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose (concentration)–response for human health (Version 2.1), (ECHA-2010-G-19-EN). According to this guideline, a DNEL for the leading health effect needs to be derived for every relevant human population and all relevant routes, durations and frequencies of exposure.

The dose descriptors are gathered from the available and relevant experimental animal studies. Out of this database together with information published in reviews by international bodies, suitable studies and typical dose descriptors for derivation of DNEL values are selected. The table below summarises the studies which were used for derivation of the critical DNELs.

Table 14

OVERVIEW OF DOSE DESCRIPTORS PER ENDPOINT AS RESULT OF HAZARD ASSESSMENT			
Endpoint of concern	**Type of effects**	**Critical studies**	**Quantitative dose descriptors**
Acute toxicity - inhalation	5/8 animals died following exposure	Acute screening studies (aerosol) (Foster, 1971;	LC_{50} (rat) = 6.4 mg/L/105 min

OVERVIEW OF DOSE DESCRIPTORS PER ENDPOINT AS RESULT OF HAZARD ASSESSMENT			
Endpoint of concern	**Type of effects**	**Critical studies**	**Quantitative dose descriptors**
	Signs of toxicity: lethargy, irregular respiration, affected blood pressure Gross pathology: congestion in lung, liver, spleen; discolouration in kidney and thymus	Hartung et al., 1970)	2/4 rats died 80-90 min post exposure LC_{75} (rat) = 6.4 mg/L/80 min 3/4 rats died 2-4 hrs post exposure
Repeated dose toxicity: sub-acute - inhalation	Signs of toxicity: Impaired body weight gain, decreased cholesterol values (M/F) increased liver weights (F)	Short-term repeated dose toxicity, inhalation (nose-only, aerosol), Wistar rat, (OECD TG 412; TL, 1993)	$NOAEC_{systemic}$: **210 mg/m³** **(0.21 mg/L)** Target organs: - Clinical chemistry - Liver
Repeated dose toxicity: sub-chronic - oral	Dose-related adverse effects: Microcytic anemia, renal tubular degeneration, liver cell hypertrophy and increased AST/ALP Sensitive parameters ≥ 100 ppm M/F (6.8/12.3 mg/kg bw/d) Blood: Decreased MCV (F0, M) Kidney: Increased absolute (F0, F) and relative weight (F0, M/F) Liver: Increased absolute (F0, F) and relative weight (F0, M) Glandular stomach: increased oedema with inflammatory cell infiltrates (F0, F)	EOGRTS (OECD TG 443) including DNT and DIT, oral (drinking water), Wistar rat (TL, 2018a)	LOAEL (RDT): **6.8 mg/kg bw/d** (calculated intake of F0 males as most sensitive sex for systemic effects) Target organs: - Blood - Kidney - Liver - Glandular stomach (local)
Repeated dose toxicity: sub-chronic - inhalation	Larynx: focal squamous metaplasia of the larynx epithelium; submucosal inflammation (8 mg/m³) Kidney: tubular hyperplasia; occasional intratubular lithiasis (≥ 150 mg/m³) Liver: increased weight; increased ALP; no histopathological findings (≥ 150 mg/m³) Glandular stomach: erosions (≥ 150 mg/m³, F)	Sub-chronic, inhalation (nose-only, aerosol), Wistar rat, (OECD TG 413; TL, 1996; Gamer et al., 2008)	$NOAEC_{local}$: **3 mg/m³** **(0.003 mg/L)** $NOAEC_{systemic}$: **15 mg/m³** **(0.015 mg/L)** Target organs: - Larynx (local) - Kidney - Liver
Repeated dose toxicity: chronic - dermal	Non-neoplastic findings: Hyperkeratosis; exudate; ≥ 8 mg/kg bw/d (F) Kidney: nephropathy ≥ 8 mg/kg bw/d (F) Liver: decrease of basophilic foci ≥ 8/16 mg/kg bw/day (F/M)	Chronic (2 years), dermal (unoccluded), F344 rat (similar to OECD TG 451; NTP, 1999)	$LOAEL_{local, systemic}$: **8**/16 (f/m) **mg/kg bw/d** Target organs: - Skin (local) - Kidney - Liver
Reproductive toxicity fertility impairment	Fertility effects in F0 and F1 animals at 1000 ppm (128.4 mg/kg bw/day):	EOGRTS (OECD TG 443) including DNT and DIT, oral	NOAEL (fertility): **37.7 mg/kg bw/d** (calculated mean intake over all cohorts and

OVERVIEW OF DOSE DESCRIPTORS PER ENDPOINT AS RESULT OF HAZARD ASSESSMENT			
Endpoint of concern	**Type of effects**	**Critical studies**	**Quantitative dose descriptors**
- oral	Increased gestation length; lower number of implants and litter size (F0) Prolonged/irregular oestrous cycle, ovary atrophy, luteal cysts, absence of corpora lutea (F1) Decreased primordial and growing follicles (F1) Mammary gland effects (F1, feminisation (M), diffuse hyperplasia (M), increased secretion(F))	(drinking water), Wistar rat (TL, 2018)	study periods at 300 ppm) Effects on: Gestation, Implants (F0) Estrous cycle (F1), ovary (F1); DOFC (F1); mammary gland (F1)
Reproductive toxicity developmental toxicity - oral	Dose-related adverse effects in pups: Lower viability index, lower body weight gain, neurotoxicity (nerve tissue degeneration) and neuronal dysfunction (decreased startle response, gait abnormality), microcytic anaemia, decreased T-cell counts in spleen, centrilobular/peripheral hypertrophy and fatty change/increased AST/ALP activity in liver Sensitive parameters (developmental effects in F1) at ≥ 100 ppm: Blood: Decreased MCH (M); RBC, HGB, HCT, MONOA, MONO, BASO (F); increased Ca (M) Kidney: Increased absolute and relative weight (M/F) Liver: Increased absolute (F) and relative weight (M/F) Decreased choline levels (M/F) in plasma (PND 90) and liver (PND 22/90) Pituitary: Eosinophilic cysts in pars distalis (M/F) Thyroid hormones: sign. increased T4 at PND4 (F); non-sign., dose-dependent increases at PND 22/92 (M/F)	EOGRTS (OECD TG 443) including DNT and DIT, oral (drinking water), Wistar rat (TL, 2018)	LOAEL (development): **12.25 mg/kg bw/d** (calculated mean intake of Cohorts 1A, 1B, 2A based on effects in males and females) Effects in F1 on: - Blood - Choline level - Kidney - Liver - Pituitary - Thyroid hormones

7.9.9.2 Derivation of the critical DNELs for the general population

For the general population, long-term DNEL values for the dermal, inhalation and oral route of exposure were derived by the eMSCA. Further, DNEL values were derived for short-term exposure to DEA for the inhalation route. The derivation of DNEL values for the general population in Table 15 is based on the data from the studies with experimental animals collected in Table 14.

Table 15

CALCULATION OF THE CRITICAL DNELS FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DNEL Calculation with Justification/Remarks**
Inhalation Acute, Systemic	**Most appropriate starting point is the $LC_{50\ \{75\}}$ = 6.4 mg/L/105 {80} minutes (1476 ppm) achieved in acute screening studies in Sprague-Dawley rats (Foster, 1971; Hartung et al., 1970)** Modification of the relevant dose descriptor by time extrapolation: $C^3 * t = [LC_{50}\ (15\ min)]^3 * 15\ min = [LC_{50}\ (105\ \{80\}\ min)]^3 * 105\ \{80\}\ min$ modified Haber's law: $C^n * t$ = const.; n = 3 (from longer to shorter duration) $LC_{50}\ (15\ min) = \sqrt[3]{[(6.4\ mg/L)^3 * 105\ \{80\}\ min/15\ min]} = 12.2\ \{11.2\}\ mg/L$ Starting point: LC_{50} (15 min): **12200** {**11200**} mg/m³ Discussion of application of AF to get the DNEL: AF for severe effects (LC_{50}): **100** (default) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is an LC_{50}) Quality of database: **1** Total AF: **100 * 2.5 * 10 * 1 * 1 = 2500** **$DNEL_{acute\text{-}systemic\ effects\text{-}inhal}$: 12200** {**11200**} mg/m³/**2500** = **4.9** {**4.5**} **mg/m³**
Inhalation Short-Term, Systemic	**Most appropriate starting point is the NOAEC of 210 mg/m³ for systemic effects (signs of toxicity on liver and clinical chemistry) achieved in a sub-acute (14 days) repeated dose inhalation toxicity study in Wistar rats (protocol according to OECD TG 412; 6 h/d, 5 d/wk; TL, 1993)** Modification of the relevant dose descriptor: Corrected inhalatory $NOAEC_{human}$ = inhalatory $NOAEC_{rat}$ * (6/24) * (5/7) = 210 mg/m³ * 0.25 * 5/7 = 37.5 mg/m³ Correction of exposure duration in study (6 h/d, 5 d/wk) to default general population exposure (24 h/d, 7 d/wk). Starting point: $NOAEC_{systemic\ effects}$: **37.5** mg/m³ Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (NOAEC is based on a sub-acute study) AF for interspecies extrapolation: **1** (NOAEC is compared directly) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEC) Quality of database: **1** Total AF: **1 *1 * 2.5 * 10 * 1 * 1 = 25** **$DNEL_{sub\text{-}acute\text{-}systemic\ effects\text{-}inhal}$:** 37.5 mg/m³/**25** = **1.5 mg/m³**
Dermal Short-Term, Systemic	**Most appropriate starting point is the NOAEC of 210 mg/m³ for systemic effects (signs of toxicity on liver and clinical chemistry) achieved in a sub-acute (14 days) repeated dose inhalation toxicity study in Wistar rats (protocol according to OECD TG 412; 6 h/d, 5 d/wk; TL, 1993)** Modification of the relevant dose descriptor by route-to-route extrapolation: Corrected dermal NOAEL = corrected inhalatory NOAEC * 1.15 m³/kg/d * ($ABS_{inhalation,rat}/ABS_{dermal,human}$) = 37.5 mg/m³ (cf. row above) * 1.15 m³/kg/d * (100 %/50 %) = 86.25 mg/kg/d Modification factor for differences between routes: $ABS_{inhal,rat}/ABS_{demal,human}$ = 2. Starting point: $NOAEL_{systemic\ effects}$: **86.3** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (NOAEL is based on a sub-acute study) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEL)

CALCULATION OF THE CRITICAL DNELS FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DNEL Calculation with Justification / Remarks**
	Quality of database: **1** Total AF: **1 * 4 * 2.5 * 10 * 1 * 1 = 100** **$DNEL_{sub\text{-}acute\text{-}systemic\ effects\text{-}dermal}$: 86** mg/kg bw/d/**100** = **0.9 mg/kg bw/d**
Oral Long-Term, Systemic	**Most appropriate starting point is the LOAEL of 6.8 mg/kg bw/d (100 ppm) for systemic effects (toxic effects on blood and kidney) achieved in an EOGRTS in F0 male Wistar rats (OECD TG 443; TL, 2018)** Modification of the relevant dose descriptor: Oral $LOAEL_{human}$ = Oral $LOAEL_{rat}$ * ($ABS_{oral,rat}$/$ABS_{oral,human}$) There is no need for a modification factor: $ABS_{oral,rat}$/$ABS_{oral,human}$ = 1. POD: $LOAEL_{systemic\ effects}$: **6.8** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (LOAEL is based on **EOGRTS**) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEL to NOAEL) Quality of database: **1** Total AF: **2 * 4 * 2.5 * 10 * 3 * 1 = 600** **$DNEL_{long\text{-}term\text{-}systemic\ effects\text{-}oral}$: 6.8** mg/kg bw/d/**600** = **0.0113 mg/kg bw/d**
Inhalation Long-Term, Systemic	**Most appropriate starting point is the NOAEC of 15 mg/m³ for systemic effects (toxic effects on liver and kidney) achieved in a sub-chronic (3 months) repeated dose inhalation toxicity study in Wistar rats (protocol similar to OECD TG 413; 6 h/d, 5 d/wk; TL, 2002)** Modification of the relevant dose descriptor: Corrected inhalatory $NOAEC_{human}$ = inhalatory $NOAEC_{rat}$ * (6/24) * (5/7) = 15 mg/m³ * 0.25 * 5/7 = 2.7 mg/m³ Correction of exposure duration in study (6 h/d, 5 d/wk) to default general population exposure (24 h/d, 7 d/wk). Starting point: $NOAEC_{systemic\ effects}$: **2.7** mg/m³ Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (NOAEC is based on a sub-chronic study) AF for interspecies extrapolation: **1** (NOAEC is compared directly) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEC) Quality of database: **1** Total AF: **2 * 1 * 2.5 * 10 * 1 * 1 = 50** **$DNEL_{long\text{-}term\text{-}systemic\ effects\text{-}inhal}$: 2.7** mg/m³/**50** = **0.05 mg/m³**
Inhalation Long-Term, Local	**Most appropriate starting point is the NOAEC of 3 mg/m³ for local effects (local upper respiratory tract effects on larynx) achieved in a sub-chronic (3 months) repeated dose inhalation toxicity study in Wistar rats (protocol similar to OECD TG 413; 6 h/d, 5 d/wk; TL, 2002)** Modification of the relevant dose descriptor: Daily inhalatory $NOAEC_{rat}$ = daily inhalatory $NOAEC_{rat}$ * (5/7) = 3 mg/m³ * 5/7 = 2.1 mg/m³ Determination of daily concentration (7 d/wk) per rat during the exposure period from exposure duration in study (5 d/wk), no time scaling as local effects on the respiratory tract are mainly driven by the exposure concentration. Starting point: $NOAEC_{local\ effects}$: **2.1** mg/m³ Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (NOAEC is based on a sub-chronic study)

CALCULATION OF THE CRITICAL DNELS FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DNEL Calculation with Justification / Remarks**
	AF for interspecies extrapolation: **1** (no scaling for local effects) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEC) Quality of database: **1** Total AF: **2 *1 * 2.5 * 10 * 1 * 1 = 50** **$DNEL_{long\text{-}term\text{-}local\ effects\text{-}inhal}$: 2.1** mg/m³/**50** = **0.04 mg/m³**
Dermal Long-Term, Systemic	**Most appropriate starting point is the LOAEL of 8 mg/kg bw/d for systemic effects (nephropathy) achieved in a two year dermal study in female F344/N rats (similar to OECD TG 451; 5 d/wk, 103 d; NTP, 1999; US DHHS, 2002)** Modification of the relevant dose descriptor: Corrected dermal $LOAEL_{human}$ = dermal $LOAEL_{rat}$ * (5/7) = 8 mg/kg bw/d * 5/7 = 5.7 mg/kg bw/d Determination of daily dose (7 d/wk) per rat during the exposure period from exposure duration in study (5 d/wk). There is no need for a modification factor: $ABS_{dermal,rat}/ABS_{dermal,human}$ = 1. POD: $LOAEL_{systemic\ effects}$: **5.7** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (LOAEL is based on chronic study, 103 d) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEL to NOAEL) Quality of database: **1** Total AF: **1 *4 * 2.5 * 10 * 3 * 1 = 300** **$DNEL_{long\text{-}term\text{-}systemic\ effects\text{-}dermal}$: 5.7** mg/kg bw/d/**300** = **0.02 mg/kg bw/d**
Dermal Long-Term, Local	**Most appropriate starting point is the LOAEL of 8 mg/kg bw/d for local effects on the skin (acanthosis and hyperkeratosis) achieved in a two year dermal study in female F344/N rats (similar to OECD TG 451; 5 d/wk, 103 d; NTP, 1999; US DHHS, 2002)** Modification of the relevant dose descriptor: Corrected dermal $LOAEL_{human}$ = dermal $LOAEL_{rat}$ * (5/7) = 8 mg/kg bw/d * 5/7 = 5.7 mg/kg bw/d Determination of daily dose (7 d/wk) per rat during the exposure period from exposure duration in study (5 d/wk). POD: $LOAEL_{local\ effects}$: **5.7** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (LOAEL is based on chronic study, 103 d) AF for interspecies extrapolation: **1** (no scaling for local effects) For remaining uncertainties: **1** (direct chemical reactivity) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEL to NOAEL) Quality of database: **1** Total AF: **1 *1 * 1 * 10 * 3 * 1 = 30** **$DNEL_{long\text{-}term\text{-}local\ effects\text{-}dermal}$: 5.7** mg/kg bw/d/**30** = **0.2 mg/kg bw/d**
Oral Long-Term, Fertility	**Most appropriate starting point is the NOAEL of 37.7 mg/kg bw/d (300 ppm) for fertility effects (effects on gestation length, number of implants, estrus cycle, ovary, mammary gland) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)** Modification of the relevant dose descriptor: Oral $NOAEL_{human}$ = Oral $NOAEL_{rat}$ * ($ABS_{oral,rat}/ABS_{oral,human}$) There is no need for a modification factor: $ABS_{oral,rat}/ABS_{oral,human}$ = 1.

CALCULATION OF THE CRITICAL DNELS FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DNEL Calculation with Justification / Remarks**
	POD: $NOAEL_{fertility}$: **37.7** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (NOAEL is based on **EOGRTS**) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEL) Quality of database: **1** Total AF: **2 *4 * 2.5 * 10 * 1 * 1 = 200** **$DNEL_{long\text{-}term\text{-}fertility\ effects\text{-}oral}$: 37.7** mg/kg bw/d/**200** = **0.19 mg/kg bw/d**
Inhalation Long-Term, Fertility	**Most appropriate starting point is the NOAEL of 37.7 mg/kg bw/d (300 ppm) for fertility effects (effects on gestation length, number of implants, estrus cycle, ovary, mammary gland) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)** Modification of the relevant dose descriptor by route-to-route extrapolation: Corrected inhalatory $NOAEC_{human}$ = Oral $NOAEL_{rat}$/1.15 m³/kg/d * ($ABS_{oral,rat}/ABS_{inhal,human}$) = 37.7 mg/kg bw/d/1.15 m³/kg/d * (50 %/100 %) = 16.4 mg/m³ Default modification factor: $ABS_{oral,rat}/ABS_{inhal,human}$ = ½. Starting point: $NOAEC_{fertility}$: **16.4** mg/m³ Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (NOAEL is based on **EOGRTS**) AF for interspecies extrapolation: **1** (NOAEC is compared directly) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEL) Quality of database: **1** Total AF: **2 *1 * 2.5 * 10 * 1 * 1 = 50** **$DNEL_{long\text{-}term\text{-}fertility\ effects\text{-}inhal}$: 16.4** mg/m³/**50** = **0.33 mg/m³**
Dermal Long-Term, Fertility	**Most appropriate starting point is the NOAEL of 37.7 mg/kg bw/d (300 ppm) for fertility effects (effects on gestation length, number of implants, estrus cycle, ovary, mammary gland) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)** Modification of the relevant dose descriptor by route-to-route extrapolation: Dermal $NOAEL_{rat}$ = Oral $NOAEL_{rat}$ * ($ABS_{oral,rat}/ABS_{dermal,rat}$) * ($ABS_{dermal,rat}/ABS_{dermal,human}$) There is no need for a modification factor: $ABS_{oral,rat}/ABS_{dermal,rat}$ = $ABS_{dermal,rat}/ABS_{dermal,human}$ = 1. POD: $NOAEL_{fertility}$: **37.7** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **2** (NOAEL is based on **EOGRTS**) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **1** (No AF applied because POD is a NOAEL) Quality of database: **1** Total AF: **2 *4 * 2.5 * 10 * 1 * 1 = 200** **$DNEL_{long\text{-}term\text{-}fertility\ effects\text{-}dermal}$: 37.7** mg/kg bw/d/**200** = **0.19 mg/kg bw/d**
Oral Long-Term, Develop-ment	**Most appropriate starting point is the LOAEL of 12.25 mg/kg bw/d (100 ppm) for developmental effects (effects on blood, liver, kidney, pituitary, thyroid hormones) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)**

CALCULATION OF THE CRITICAL DNELS FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DNEL Calculation with Justification / Remarks**
	Modification of the relevant dose descriptor: Oral $LOAEL_{human}$ = Oral $LOAEL_{rat}$ * ($ABS_{oral,rat}/ABS_{oral,human}$) There is no need for a modification factor: $ABS_{oral,rat}/ABS_{oral,human}$ = 1. POD: $LOAEL_{development}$: **12.25** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (sensitive window covered by **EOGRTS**) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEL to NOAEL) Quality of database: **1** Total AF: **1 *4 * 2.5 * 10 * 3 * 1 = 300** **$DNEL_{long\text{-}term\text{-}developmental\ effects\text{-}oral}$: 12.25** mg/kg bw/d/**300** = **0.04 mg/kg bw/d**
Inhalation Long-Term, Develop-ment	**Most appropriate starting point is the LOAEL of 12.25 mg/kg bw/d (100 ppm) for developmental effects (effects on blood, liver, kidney, pituitary, thyroid hormones) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)** Modification of the relevant dose descriptor by route-to-route extrapolation: Corrected inhalatory $LOAEC_{human}$ = Oral $LOAEL_{rat}$/1.15 m³/kg/d * ($ABS_{oral,rat}/ABS_{inhal,human}$) = 12.25 mg/kg bw/d/1.15 m³/kg/d * (50 %/100 %) = 5.3 mg/m³ Default modification factor: $ABS_{oral,rat}/ABS_{inhal,human}$ = ½. Starting point: $LOAEC_{development}$: **5.3** mg/m³ Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (sensitive window covered by **EOGRTS**) AF for interspecies extrapolation: **1** (NOAEC is compared directly) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEC to NOAEC) Quality of database: **1** Total AF: **1 *1 * 2.5 * 10 * 3 * 1 = 75** **$DNEL_{long\text{-}term\text{-}developmental\ effects\text{-}inhal}$: 5.3** mg/m³/**75** = **0.07 mg/m³**
Dermal Long-Term, Develop-ment	**Most appropriate starting point is the LOAEL of 12.25 mg/kg bw/d (100 ppm) for developmental effects (effects on blood, liver, kidney, pituitary, thyroid hormones) achieved in an EOGRTS in Wistar rats (OECD TG 443; TL, 2018a)** Modification of the relevant dose descriptor by route-to-route extrapolation: Corrected dermal $LOAEL_{human}$ = Oral $LOAEL_{rat}$ * ($ABS_{oral,rat}/ABS_{dermal,human}$) There is no need for a modification factor: $ABS_{oral,rat}/ABS_{dermal,human}$ = 1. Starting point: $LOAEL_{development}$: **12.25** mg/kg bw/d Discussion of application of AF to get the DNEL: AF for difference in duration of exposure: **1** (sensitive window covered by **EOGRTS**) AF for interspecies extrapolation: **4** (default; for allometric scaling, rat) For remaining uncertainties: **2.5** (default; other interspecies differences) Intraspecies differences: **10** (default; for general population) Dose response: **3** (extrapolation from LOAEC to NOAEC) Quality of database: **1** Total AF: **1 *4 * 2.5 * 10 * 3 * 1 = 300** **$DNEL_{long\text{-}term\text{-}developmental\ effects\text{-}dermal}$: 12.25** mg/kg bw/d/**300** = **0.04 mg/kg bw/d**

7.9.9.3 Derivation of the critical DMEL for the general population

7.9.9.3.1 T25 as basis of DMEL derivation

Based on the assumption that a genotoxic mechanism may also be involved in the induction of liver tumours by DEA (through the induction of NDELA) and the acknowledgement that the potential mechanisms of chemical carcinogenesis are certainly more complex, it is generally accepted and applied in the characterisation of the potential risk caused by genotoxic carcinogens that a threshold for tumorigenic activity cannot be set. As no thresholds for carcinogenicity can be set, no DNEL values but rather only DMEL values can be derived.

The purpose of this evaluation is to provide an estimation of an exposure level for oral, inhalation and dermal route of exposure of nitrosamines with minimal or negligible additional health risk. This level of acquiring disease should not exceed the risk level of the general background incidence in the population.

The REACH Guidance Document (R.8) states that extra cancer risk levels of 10^{-5} and 10^{-6} could be seen as indicative of tolerable risks levels when setting derived minimal effect levels (DMELs) for workers and the general population, respectively. In summary, the cancer risk decision points used for lifetime exposure of the general population are generally in the range of 10^{-6}.

According to the REACH Guidance document (REACH, Chapter R.8) the T25 should be used as the default dose descriptor unless the dose-response curve is clearly sub- or supra-linear. This was not indicated for NDELA.

7.9.9.3.2 Calculation of risk estimates using the dose-descriptor T25

The risk level determination is based on a calculation of T25 from experimental data on the genotoxic carcinogen NDELA as the dose descriptor (Dybing et al. 1997) followed by linear extrapolation to the 10^{-6} risk level.

Seven oral studies are available for 2,2'-(nitrosoimino)bisethanol (NDELA): Lijinsky et al. (1984b), Lijinsky and Kovatch (1985), Zerban et al. (1988), Hecht et al. (1989), Berger et al. (1987), Berger et al. (1990), and Preussman et al. (1982). The study of Preussman et al. (1982) was used for T25 calculation as all other studies have their limitations in study design or reporting.

Preussmann et al (1982) administered NDELA orally via drinking water (5 mL per rat) to a total of n = 340 Sprague-Dawley rats (approximately 100 days old, 2-4 animals per cage) at the necessary concentration to obtain a daily dose of 1.5, 6, 25, 100 and 400 mg/kg bw/d for 88, 72, 72, 36, 36 and 36 animals, respectively. Treatment was repeated 5 times/week; on weekends, tap water was given for 2 days *ad libitum*. Untreated controls received tap water only. All animals were allowed to die naturally or were killed when moribund. NDELA treatment at the five dose levels resulted in a significant number of animals with benign and malignant liver tumours (predominantly hepatocellular carcinomas and adenomas but also mesenchymal haemangioendotheliomas, cholangiofibromas and cholangiocarcinomas). Neoplasms in the nasal cavity (comprising squamous cell carcinomas and neuroepitheliomas) were also observed. Liver tumours occurred with median latencies of 938, 840, 632, 465, 357 days in the five dose groups at the incidences of 7/72, 43/72, 33/36, 32/36 and 31/36, respectively. In the control group none (0/88) were found. Tumours at organ sites other than the liver were not considered treatment-related. The liver tumour data were suitable for the T25 approach. The lowest dose level with significantly increased incidence of liver tumours was used for calculation. This dose was 6.0 mg/kg bw/d.

7.9.9.3.3 Calculation of T25 for developing hepatocellular carcinomas and adenomas in rats

Adjustment of background tumour incidences is needed (Dybing et al., 1997): 6.0 mg/kg bw/d NDELA via drinking water; 5 d/wk; median survival time: 809 days (724-835 days, 95 % confidence limit, ≈ 116 weeks): Control: 0/88; 6.0 mg/kg bw/d: 43/72; net% = 60 %.

Daily dose per rat during the exposure period: the daily dose given the observed tumour incidence over lifetime will be derived by correcting the applied dose as follows: daily dose = (5/7) * 6.0 mg/kg bw/d = 4.28 mg/kg bw/d.

At 4.28 mg/kg bw/d, 60 % of the animals developed liver tumours.

The chronic dose giving tumours in 25 % of the animals at a specific tissue site (T25) for NDELA is calculated from 4.28 mg/kg bw/d at which 60 % of the animals developed liver tumours: (25/60)* 4.28 mg/kg bw/d = **1.78 mg/kg bw/d**.

The relevant dose descriptor: The T25 value for the species rat, exposure oral, for lifetime derived from the study Preussmann et al. (1982) is 1.78 mg/kg bw/d.

7.9.9.3.4. DMEL values of NDELA for the general population

For derivation of a DMEL for the non-threshold carcinogen NDELA the **"linearised" approach** is applied.

Table 16

CALCULATION OF DMEL VALUES (BASED ON T25) OF NDELA FOR THE GENERAL POPULATION	
Route and type of effect	**Critical study for Corrected dose descriptor (e.g. NOAEL, NOAEC) and DMEL Calculation with Justification / Remarks**
DMEL, oral	**Relevant Dose descriptor: T25 (rat, oral) = 1.78 mg/kg bw/d** Modification of the relevant dose descriptor: For the scenario for the general population (oral exposure) there is no need for a modification factor: 1 **PoD: Corrected T25 of 1.78 mg/kg bw/d** Discussion of application of AF to get the DMEL: AF for interspecies extrapolation: **4** for allometric scaling AF for intraspecies extrapolation: not applied AF for remaining uncertainties: **1** (default) Total AF: **4 * 1 = 4** Extrapolation (high to low dose): **250 000 (linearity, 1:1 000 000)** Calculation of DMEL: 1.78 mg/kg bw/d/(4 * 250 000) = 0.00178 µg/kg bw/d = 1.78 ng/kg bw/d DMEL values (based on T25) associated with a lifetime cancer risk of low concern were obtained: Linearised approach, **10^{-6} risk level (1:1 000 000): 1.78 ng/kg bw/d**
DMEL, inhalation	**Relevant Dose descriptor: T25 (rat, oral) = 1.78 mg/kg bw/d** Modification of the relevant dose descriptor: Route-specific bioavailability: 50% oral absorption; 100% absorption by inhalation: **50/100** Adjustment of route of exposure (from rat oral in mg/kg bw/d to rat inhalation (0.8 L/min/kg, 24h)): **1/1.15 m^3/kg bw** Daily exposure of 24 hours (7 days a week) for 75 years = equivalent to the lifetime exposure in experimental animal studies of 2 years in rats: **1** Calculation of modified dose descriptor: T25 of 1.78 mg/kg bw/d multiplied by 50/100 * 1/1.15 * 1 = 0.77 mg/m^3 **PoD: Corrected T25 of 0.77 mg/m^3** Discussion of application of AF to get the DMEL:

	AF for interspecies extrapolation: **1** for allometric scaling AF for intraspecies extrapolation: not applied AF for remaining uncertainties: **1** Total AF: **1** Extrapolation (high to low dose): **250 000 (linearity, 1:1 000 000)** Calculation of DMEL: 0.77 mg/m^3/(1 * 250 000) = 0.000003086 mg/m^3 = 0.00308 µg/m^3 = 3.08 ng/m^3 DMEL values (based on T25) associated with a lifetime cancer risk of low concern were obtained: **Linearised approach, 10^{-6} risk level (1:1 000 000): 3.08 ng/m^3**
DMEL dermal	**Relevant Dose descriptor: T25 (rat, oral) = 1.78 mg/kg bw/d** Modification of the relevant dose descriptor: For the scenario for the general population (dermal exposure) there is no need for a modification factor: **1** Corrected dermal T25 = oral T25 * (ABSoral-rat/ABSdermal-human = 1) **PoD: Corrected T25 of 1.78 mg/kg bw/d** Discussion of application of AF to get the DMEL: AF for interspecies extrapolation: **4** for allometric scaling AF for intraspecies extrapolation: not applied AF for remaining uncertainties: **1** (default) AF for differences in duration: **1** (default) Total AF: **4 * 1 * 1 = 4** Extrapolation (high to low dose): **250,000 (linearity, 1:1 000 000)** Calculation of DMEL: 1.78 mg/kg bw/d/(4 * 250,000) = 0.00178 µg/kg bw/d = 1.78 ng/kg bw/d DMEL values (based on T25) associated with a lifetime cancer risk of very low concern were obtained: **Linearised approach, 10^{-6} risk level (1:1 000 000): 1.78 ng/kg bw/d**

7.9.9.4 Derivation of the critical DNELs/DMELs for workers

The routes of exposure to DEA for workers are inhalation and dermal contact with exposure to the eyes being a possibility as well. While inhalation exposure to DEA vapour is unlikely due to its very low vapour pressure, inhalation exposure may occur in processes where aerosols are formed.

In view of the exposure routes for workers, long-term DNEL values have been derived for workers for the inhalation and dermal routes of exposure.

In the one-year evaluation process of DEA a long-term DNEL$_{systemic}$ of 0.3 mg/m^3 and a long-term DNEL$_{local}$ of 0.06 mg/m^3 were derived by the German CA from 90-day inhalation toxicity studies in Wistar rats, (TL, 1996; 2002, Gamer et al., 2008). In 2016, a German occupational limit value (Arbeitsplatzgrenzwert, AGW) for systemic and local effects of DEA was derived by the German national committee for hazardous substances (Ausschuss für Gefahrstoffe, AGS). Thus, in theory for the risk assessment of DEA the AGW of 0.5 mg/m^3 could be used. However, one result at the end of the one-year substance evaluation process was the request of an EOGRTS to assess DEA in terms of reproductive toxicity. In the meantime, this EOGRTS (oral OECD TG 443 with rat) was performed (TL 2018a). The evaluation of this data by the eMSCA shows that the derived inhalation DNEL for developmental toxicity of 0.4 mg/m^3 is lower than the derived AGW for systemic and local effects after inhalation exposure. Thus, this DNEL$_{developmental}$ of 0.4 mg/m^3 was used for the inhalation risk assessment.

For dermal risk assessment, a long-term DNEL for local and systemic effects was derived from a 2-year dermal study with rats (protocol similar to OECD TG 451), (NTP, 1999; US DHHS, 2002).

The inhalation and dermal DNELs for systemic, local, fertility and developmental effects are listed below. Detailed overviews concerning the single steps for the derivation of the DNELs are given in the following tables.

Table 17

CRITICAL DNELS/DMELS FOR WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s)**	**DNEL/ DMEL**	**Justification/ Remarks**
Long-term inhalation systemic effects	The critical systemic effects appear to be liver and kidney effects	Sub-chronic inhalation study,rat OECD TG 413 (TL, 1996; Gamer et al., 2008)	$NOAEC_{worker}$ 7.54 mg/m^3	$DNEL_{worker}$ 0.3 mg/m^3	
Long-term inhalation local effects	The critical local effect appear to be a focal squamous metaplasia of the laryngeal epithelium with inflammatory cell reaction	Sub-chronic inhalation study,rat OECD TG 413 (TL, 2002; Gamer et al., 2008)	$NOAEC_{worker}$ 1.5 mg/m^3	$DNEL_{worker}$ 0.15 mg/m^3	In contrast to the derivation of this DNEL in 2013 the AF for remaining differences are omitted
Long-term inhalation fertility effects	Dose-related adverse effects appear to be increased gestation length, lower number of implants, prolonged/irregular oestrus cycle, ovary atrophy, luteal cysts, decreased primordial and growing follicles, mammary gland effects	EOGRTS, oral, rat OECD TG 443 (TL, 2018)	$NOAEC_{worker}$ 46.53 mg/m^3	$DNEL_{worker}$ 1.86 mg/m^3	
Long-term inhalation developmental effects	Dose-related adverse effects in pups appear to be: Lower viability index, lower body weight gain, neurotoxicity (nerves tissue degeneration) neuronal dysfunction (decreased startle response, gait abnormality), pituitary cysts, microcytic anaemia, decreased T-cell counts in spleen, centrilobular/peripher-al hypertrophy and fatty change/increased AST/ALP activity in	EOGRTS, oral, rat OECD TG 443 (TL, 2018)	$LOAEC_{worker}$ 15.12 mg/m^3	$DNEL_{worker}$ 0.4 mg/m^3	

CRITICAL DNELS/DMELS FOR WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s)**	**DNEL/ DMEL**	**Justification/ Remarks**
	liver, increased (T4) thyroid hormones				
Long-term dermal systemic/local effects	The critical systemic effects appear to be kidney and liver toxicity and anaemia.	2 years, dermal, rat OECD TG 451 (NTP, 1999)	systemic $LOAEL_{worker}$ 8 mg/kg bw/d	$DNEL_{worker}$ 0.05 mg/kg bw/d	
Long-term dermal local effects	The critical local effects appear to be acanthosis and hyperkeratosis of the skin.	2 years, dermal, rat OECD TG 451 (NTP, 1999)	local $LOAEL_{worker}$ 8 mg/kg bw/d	$DNEL_{worker}$ 0.53 mg/kg bw/d	
Long-term dermal fertility effects	Dose-related adverse effects appear to be increased gestation length, lower number of implants, prolonged/irregular oestrus cycle, ovary atrophy, luteal cysts, decreased primordial and growing follicles, mammary gland effects	EOGRTS, oral, rat OECD TG 443 (TL, 2018)	$NOAEL_{worker}$ 52.78 mg/kg bw/d	$DNEL_{worker}$ 0.5 mg/kg bw/d	
Long-term dermal developmental effects	Dose-related adverse effects in pups appear to be: Lower viability index, lower body weight gain, neurotoxicity (nerves tissue degeneration) neuronal dysfunction (decreased startle response, gait abnormality), pituitary cysts, microcytic anaemia, decreased T-cell counts in spleen, centrilobular/peripheral hypertrophy and fatty change/increased AST/ALP activity in liver, increased (T4) thyroid hormones	EOGRTS, oral, rat OECD TG 443 (TL, 2018)	$LOAEL_{worker}$ 17.15 mg/kg bw/d	$DNEL_{worker}$ 0.11 mg/kg bw/d	

Table 18

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, INHALATION, LONG-TERM, SYSTEMIC) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	NOAEC 15 mg/m^3	The NOAEC based on the sub-chronic inhalation study in rats is 15 mg/m^3. The critical systemic effects appear to be liver and kidney effects

Modification of the starting point	hours/day (*6/8) 6.7 m^3 light act. – 10 m^3 worker *0.67	differences occupational exposure and lifetime exposure rat differences in activity
Modified dose descriptor	$NOAEC_{worker}$ 7.54 mg/m^3	
AF for interspecies differences	1	NOAEC is compared directly
AF for remaining differences	2.5	default assessment factor for remaining differences
AF for intraspecies differences	5	default factor for workers, no substance-specific information is available
AF for differences in exposure duration	2	the key study is a 90-day study
AF related to dose response relationship	1	
DNEL, systemic effects	7.54 mg/m^3 / (1 x 2.5 x 5 x 2 x 1) = **0.3 mg/m^3**	

Table 19

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, INHALATION, LONG-TERM, LOCAL) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	NOAEC 3 mg/m^3	The NOAEC based on the sub chronic inhalation study with rat is 3 mg/m^3. At this dose 3/10 males developed a focal squamous metaplasia of the laryngeal epithelium without any inflammatory cell reaction, which was completely reversible in the recovery period. Such a finding of 'larynx squamous metaplasia' was evaluated and discussed on 1st international ESTP expert workshop and was assessed as 'non-adverse'.
Modification of the starting point	hours/day (*6/8) 6.7 m^3 light act. – 10 m^3 worker *0.67	differences occupational exposure and lifetime exposure rat differences in activity
Modified dose-descriptor	$NOAEC_{worker}$ 1.5 mg/m^3	
AF for interspecies differences	1	AF for allometric scaling (no scaling for local effects)
AF for remaining differences	1	local effect
AF for intraspecies differences	5	default factor for workers, no substance-specific information is available
AF for differences in exposure duration	2	the key study is a 90 day study
AF related to dose response relationship	1	
DNEL, local effects	1.5 mg/m^3 / (1 x 1 x 5 x 2 x 1) = **0.15 mg/m^3**	

Table 20

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, INHALATION, LONG-TERM, DEVELOPMENTAL) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	LOAEL 12.25 mg/kg bw/d	the NOAEL value from an EOGRTS study in Wistar rats (OECD TG 443; TL, 2018) The respective LOAEL for development based on effects on blood, liver, kidney, pituitary, thyroid hormones.
Modification of the starting point	days/week (*7/5) resp. Vol. rat: /0.38 m^3/kgbw/8h 6.7 m^3 light Act. - 10m^3 worker *0.67 oral-inhalation default *0.5	differences occupational expo and lifetime expo rat differences in activity route-to-route extrapolation
Modified dose-descriptor	$LOAEC_{worker}$ 15.12 mg/m^3	
AF for interspecies differences	1	NOAEC is compared directly
AF for remaining differences	2.5	default assessment factor for workers, no substance-specific information is available
AF for intraspecies differences	5	default factor for workers, no substance-specific information is available
AF for differences in exposure duration	1	Sensitive window is covered by EOGRTS
AF related to dose response relationship	3	extrapolation from LOAEL to NOAEL
DNEL, developmental effects	15.12 mg/m^3 / (1 x 2.5 x 5 x 1 x 3) = **0.4 mg/m^3**	

Table 20

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, DERMAL, LONG-TERM, SYSTEMIC) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	LOAEL 8 mg/kg bw/d	The overall LOAEL based on the sub-chronic and chronic dermal studies with rats and mice is 8 mg/kg bw/d. The critical systemic effects appear to be kidney and liver toxicity and anaemia. Beside anaemia, nephropathy was observed at the lowest tested dose in the 13-week dermal toxicity study (32 mg/kg bw/d in rats). After 13 weeks, kidney effects are not attributed to aging effects. Therefore, the observation of nephropathy in female rats at the lowest tested dermal dose of 8 mg/kg bw/d in the 2-year study is also considered adverse.
Modification of the starting point		not necessary
AF for interspecies differences	4	AF for allometric scaling, rat
AF for remaining differences	2.5	default AF for remaining differences

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, DERMAL, LONG-TERM, SYSTEMIC) FOR DEA		
Description	**Value**	**Remark**
AF for intraspecies differences	5	The default factor for workers was applied because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	The key study is a 2-year study.
AF related to dose response relationship	3	extrapolation from LOAEL to NOAEL
Qualitiy of database	1	
DNEL, dermal, systemic effects	8 mg/kg bw/d / (4 x 2.5 x 5 x 1 x 3 x 1) = **0.05 mg/kg bw/d**	

Table 21

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, DERMAL, LONG-TERM, LOCAL) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	LOAEL 8 mg/kg bw/d	The overall LOAEL based on the sub-chronic and chronic dermal studies with rats and mice is 8 mg/kg bw/d. The critical local effects appear to be acanthosis and hyperkeratosis of the skin. Lesions of the treated skin were dose-related increased in incidence and severity.
Modification of the starting point		not necessary
AF for interspecies differences	1	not necessary for local effects
AF for remaining differences	1	direct chemical reactivity
AF for intraspecies differences	5	The default factor for workers was applied because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	The key study is a 2-year study
AF related to dose response relationship	3	extrapolation from LOAEL to NOAEL
Qualitiy of database	1	
DNEL, dermal, local effects	8 mg/kg bw/d / (1 x 1 x 5 x 1 x 3 x 1) = **0.53 mg/kg bw/d**	

Table 22

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, DERMAL, LONG-TERM, DEVELOPMENTAL) FOR DEA		
Description	**Value**	**Remark**
Relevant dose descriptor	LOAEL 12.25 mg/kg bw/d	The NOAEL value is from an **EOGRTS** study in **Wistar** rats (OECD TG 443; **TL, 2018**) The respective LOAEL is for development based on effects on blood, liver, kidney, pituitary, thyroid hormones.

Modification of the starting point	days/week (*7/5) oral-dermal default *1	differences between occupational exposure and lifetime exposure of rats route-to-route extrapolation
Modified dose-descriptor	$LOAEL_{worker}$ 17.15 mg/kg/d	
AF for interspecies differences	4	AF for allometric scaling, rat
AF for remaining differences	2.5	default; for other interspecies differences
AF for intraspecies differences	5	The default factor for workers was applied because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	sensitive window is covered by **EOGRTS**
AF related to dose response relationship	3	extrapolation from LOAEL to NOAEL
Qualitiy of database	1	
DNEL, dermal, developmental effects	17.15 mg/kg bw/d / (4 x 2.5 x 5 x 1 x 3 x 1) = **0.11 mg/kg bw/d**	

In addition to the DNELs for DEA, DMELs for the reaction product NDELA which is a known genotoxic carcinogen were derived. This means that no thresholds for carcinogenicity can be set and no DNELs but only DMELs can be derived. For this purpose, the oral 2-year cancer study (Preussman et al., 1982) was used.

The routes of exposure to NDELA for workers are also by inhalation and dermal contact, exposure to the eyes is possible as well. The table below shows an overview of the inhalation and dermal DMELs for NDELA. For derivation of a DMEL for the non-threshold carcinogen NDELA, the 'linearised' approach is applied following the procedure as laid out in the REACH Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose–response for human health (Version 2.1), (ECHA-2010-G-19-EN). A detailed overview concerning the single steps for the DMEL derivation of the two DMELs for inhalation and dermal exposure of NDELA is given in the table below.

Table 23

CRITICAL DNELS/DMELS FOR NDELA				
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptors (e.g. NOAEL, NOAEC)**	**DNEL/DMEL**
Long-term inhalation carcinogenicity	Significantly increased incidence of liver tumours, at the lowest dose level 6 mg/kg bw/d	2-year cancer study, oral, rat	$T25_{worker}$ 3.22 mg/m³	$DMEL_{worker}$ 0.13 µg/m³ (1:100 000, linear)
Long-term dermal carcinogenicity	Significantly increased incidence of liver tumours, at the lowest dose level 6 mg/kg bw/d	2-year cancer study, oral, rat	$T25_{worker}$ 5.08 mg/kg bw/d	$DMEL_{worker}$ 0.051 µg/kg bw/d (1:100 000, linear)

Table 24

DETAILED OVERVIEW OF THE DERIVATION OF THE DMEL (WORKER, INHALATION) FOR NDELA		
Description	**Value**	**Remark**
Relevant dose descriptor	T25 rat, oral, lifetime 1.79 mg/kg bw/d	The T25 is based on the 2-year oral study with rats (Preussman et al., 1982). In this study, groups of 50 Sprague-Dawley rats/sex/group were orally treated with NDELA via drinking water. The daily dose was 0, 1.5, 6, 25, 100 and 400 mg/kg bw/d. Treatment was repeated 5 times/week. Treatment at the five dose levels resulted in a significant number of animals with benign and malignant liver tumours (predominantly hepatocellular carcinomas and adenomas but also mesenchymal hemangioendothelioms, cholangio-fibromas and cholangiocarcinoms. Neoplasms in the nasal cavity (comprising squamous cell carcinomas and neuroepitheliomas) were also observed. Liver tumours occurred with median latencies of 938, 840, 632, 465, 357 days in the five dose groups at the incidences of 7/72, 43/72, 33/26, 32/36 and 31/36 respectively. In the control group, none (0/88) was found. Tumours at organ sites other than liver were considered as non-treatment related. The liver tumour data were suitable for the T25 approach. Tumour incidence was saturated at or near 100% in the three highest doses. The lowest dose level with significantly increased incidence of liver tumours was used for calculation. This dose was 6.0 mg/kg bw/d.
Modification of the starting point	50 % oral/ 100 % inhalation rat oral mg/kg bw/d/ rat inhalation 0.384 m^3/d/8h (6.7 m^3/10 m^3) Days/week 7/5 Weeks/year 52/48 Years/live 75/40	Route specific bioavailability Translation oral dose to inhalation dose activity difference Differences between occupational exposure and lifetime exposure of rats
Modified dose-descriptor	3.22 mg/m^3	
AF for interspecies differences	1	
AF for remaining differences	Not applied	
Nature of the carcinogenic process	Not applied	
Point of comparison	Not applied	
High to low extrapolation	25 000 in case of 10^{-5} risk	
$DMEL_{inhalation}$ (based on T25) Associated with a lifetime cancer risk of very low concern	0.13 µg/m^3 (1:100 000, linear)	

Table 25

DETAILED OVERVIEW OF THE DERIVATION OF THE DMEL (WORKER, DERMAL) FOR NDELA		
Description	**Value**	**Remark**
Relevant dose descriptor	T25 rat, oral, lifetime 1.79 mg/kg bw/d	The T25 is based on the 2-year oral study with rats (Preussman et al., 1982). Study description see above.
Modification of the starting point	50 % oral/ 50 % dermal rat oral mg/kg bw/d/ rat inhalation 0.384 m^3/d/8h Days/week 7/5 Weeks/year 52/48 Years/live 75/40	Route-specific bioavailability Translation oral dose to inhalation dose Differences between occupational exposure and lifetime exposure of rats
Modified dose-descriptor	5.08 mg/kg bw/d	
AF for interspecies differences	4	
AF for remaining differences	Not applied	
Nature of the carcinogenic process	Not applied	
Point of comparison	Not applied	
High to low extrapolation	25 000 in case of 10^{-5} risk	
$DMEL_{dermal}$ (based on T25) Associated with a lifetime cancer risk of very low concern	51 ng/kg bw/d (1:100 000, linear)	

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

DEA is acutely toxic (LD_{50} of 1600 mg/kg bw) meeting the criteria for classification as Acute Tox. 4 (300 < ATE ≤ 2000 mg/kg bw) – H302 (Harmful if swallowed) according to CLP Regulation (EC) No. 1272/2008.

DEA shows acute inhalation toxicity. LC_{50} values presented for inhalation of DEA in rats of 6.4 mg/L were based on tests with 80 and 105 minutes exposure. For a 4-hour exposure by inhalation, an LC_{50} value of DEA can be derived by time extrapolation using the modified Haber's law: $C^n \cdot t$ = const. For extrapolation from shorter to longer durations, n is set to 1, resulting in a time-scaled LC_{50} (4 h) = 6.4 mg/L · (105 min/240 min) = 2.8 mg/L. However, no mortality occurred in rats after exposure of 3.35 mg/L (768 ppm) for up to 4 hours. Therefore, it is assumed that the LC_{50} value of DEA for a 4-hour exposure by inhalation lies above 3.35 mg/L. As a follow-up to this substance evaluation, the question whether DEA needs to be classified for acute inhalation toxicity based on the cut-off value for Acute Tox. 4 – H332 (1.0 < ATE ≤ 5.0 mg/L) according to CLP needs further discussion.

DEA meets the criteria for classification for skin irritation as Skin Irrit. 2 – H315: Causes skin irritation and for serious eye damage/eye irritation as Eye Damage 1 - H318: Causes serious eye damage (CLP Regulation).

Data available for skin sensitisation are conclusive, but not sufficient for classification according to the CLP Regulation.

For specific target organ toxicity arising from repeated exposure, the following significant toxic effects observed in rats in drinking water studies (90-day and EOGRTS) are relevant for classification of DEA for the oral route:

Female/male rats: haematological changes (anaemia), (serious effects according to 3.9.2.5.2 CLP Guidance): ≥ 57/73 mg/kg bw/d

Female/male rats: nephrotoxicity: ≥ 14/22 mg/kg bw/d

Toxic effects on the blood and kidney were seen to occur within the guidance value range of 10 < C ≤ 100 mg/kg bw/d for classification in STOT RE 2 - H373 (CLP Regulation). Therefore, the legal classification of DEA for the oral route of exposure was confirmed.

The following significant systemic toxic effects were observed in rats exposed nose-only to DEA aerosols for 6 h/d, on 5d/wk for three months:

Female/male rats: nephrotoxicity: 0.15 mg/L

Toxic effects on the kidneys were seen to occur within the guidance value range for mists of 0.02 < C ≤ 0.2 mg/L, 6 h/d for classification in STOT RE 2 - H373 (CLP Regulation), therefore, classification of DEA for the inhalation route of exposure will be applicable.

The following significant systemic toxic effects observed in rats in a 90-day study with topical application once per day, 5 days/week are relevant for STOT RE classification of DEA for the dermal route:

Female/male: nephrotoxicity: ≥ 32/250 mg/kg bw/d

Toxic effects on the kidneys were seen to occur within the guidance value range of 20 < C ≤ 200 mg/kg bw/d for classification in STOT RE 2 - H373 (CLP Regulation), therefore, the dermal route of exposure is considered relevant. Additional adverse effects (anaemia and demyelination of the brain) were observed at 250 mg/kg bw/d, indicating that the dermal route cannot be excluded.

Available data for germ cell mutagenicity of DEA are conclusive, but not sufficient for classification according to CLP.

Under the conditions of a two-year dermal study, there was clear evidence of a carcinogenic potential of DEA in male and female mice based on increased incidences of liver neoplasms in male and female mice, multiplicity of liver tumours in the mouse and increased incidences of renal tubule neoplasms in male mice.

In the view of the eMSCA, therefore, the evaluation of the existing data on DEA on carcinogenicity has shown the availability of sufficient information on carcinogenicity that indicates that classification as Carc. 2 is required.

DEA showed significant effects on fertility parameters in several studies. In particular, there were pronounced effects on the number of implants and the litter size in the EOGRTS (and the preceding dose-range finder study) as well as further effects on reproductive organs in F1 animals (ovary, mammary gland). In addition to the EOGRTS, there are supporting *in vivo* and *in vitro* studies demonstrating toxic effects on male sexual organs, sperm parameters, and steroidogenesis.

Exposure to DEA leads to several developmental effects in offspring related to fertility, immunotoxicity, and neurotoxicity. The finding of eosinophilic cysts in the pituitary and changes in T4 levels in F1 animals in the EOGRTS are of similar concern.

Consequently, the eMSCA considers classification of DEA as a reproductive toxicant (Repr. 1B) necessary. A detailed assessment of the data on the reproductive toxicity of DEA will be included in the CLH proposal.

The eMSCA considers the following classification and labelling for DEA as necessary based on the available information.

Table 26

CLASSIFICATION AND LABELLING FOR DEA ACCORDING TO THE ASSESSMENT OF THE EVALUATING MEMBER STATE	
Classification	
Hazard Class and Category Codes	**Hazard statement codes**
Acute Tox. 4 STOT RE 2 Skin Irrit. 2 Eye Dam. 1 Carc. 2 Repro. 1B	H302 H373 H315 H318 H351 H360

7.10 Assessment of endocrine disrupting (ED) properties

Not assessed in the course of this evaluation.

7.11 PBT and VPVB assessment

Not assessed in the course of this evaluation.

7.12 Exposure assessment

7.12.1 Human health

7.12.1.1 Workers

7.12.1.1.1 Overview of uses and exposure scenarios

DEA is used in a wide variety of industrial and professional applications. According to the registration dossiers provided, DEA is used as an intermediate in chemical synthesis, as a laboratory chemical and in the formulation of DEA-containing products. It is also used in textile, paper and leather processing, in industrial gas treatment, in detergents and cleaners, as an additive in plastic, concrete, cement, wood protection formulations, fuel and as an anti-corrosion agent in metalworking fluids. There are no uses advised against.

7.12.1.1.2 Scope and type of exposure

According to the lead registrant, the use of DEA can lead to inhalation and dermal exposure, exposure to the eyes is possible as well. Exposure to the eyes can occur in two ways: directly (splashes, aerosols, dust) or indirectly via hand-eye contact. The likelihood/frequency of hand-eye contact is considered to be low for all contributing scenarios due to the fact that the likelihood of actual hand exposure is at most low and workers have been trained to prevent exposure. The exposure assessment carried out during the substance evaluation is based on the information of the registrants provided in the aggregated CSR.

7.12.1.1.3 Monitoring data

The registration contains internal information regarding occupational exposure of workers at production plants. Precautions are taken at the production plant: DEA is handled in technically closed processes at all plants and operations. Short-term tasks showing in general a potential for exposure are limited to sampling, analytical work, filter changes or filling operations. The results of the 53 measurements indicate a rather low level of inhalation exposure. Further measured data on workplace exposure (inhalation, dermal) to DEA were not provided in the registration.

In addition, DEA can be converted to NDELA by reaction with nitrosating agents such as nitrogen oxides. Since nitrogen oxides are ubiquitous in the environment and their occurrence at the workplace in particular is frequently unavoidable (exhaust fumes from internal combustion engines, etc.), the formation of NDELA must be expected in all places where DEA is used. The registrant(s) did not address the formation of NDELA, nor did they provide measurement data on NDELA exposure at workplaces in the registration.

7.12.1.1.4 Modelled data

Workplace exposure to DEA was estimated in the registration using the tier 1 models ECETOC TRA V2.0 with modifications (inhalation, dermal) and RISKOFDERM V2.2 (dermal). The higher tier model ART V1.0 (75th percentile, inhalation) has been used for tasks where aerosol formation may become more relevant, e.g. for spraying processes and loading activities with substantial splashing. A comparison of the modelled exposure with the DNELs derived by the eMSCA showed risk characterisation ratios > 1 for a number of exposure situations indicating some deficiencies.

Following initial assessment of the available information, information requests were formulated to address the deficiencies in occupational exposure assessment identified by the eMSCA, e.g. the missing assessment of the risk of NDELA formation, specification and information on duration of use of personal protective equipment as well as missing justification for modifications.

7.12.1.1.5 Updated registration

The chemical safety assessments for both DEA and its transformation product NDELA were amended by the registrant(s) according to the information requirements of the substance evaluation decision. The examination of the eMSCA is as follows:

Worker Request 1:

Measured values for inhalation exposure during manufacture of DEA have been provided, demonstrating that inhalation exposure to NDELA leads to acceptable risks. However, no measurements from downstream uses have been included. Neither for manufacture nor for the uses of DEA measurements or biomonitoring data for dermal exposure to NDELA were submitted. Instead, concentrations of NDELA in DEA were used to estimate the dermal exposure during manufacture and the inhalation and dermal exposure during downstream uses via EasyTRA leading to RCRs < 1. However, it is not clear to the eMSCA which products were evaluated for the determination of the NDELA concentrations. The registrant did not document the corresponding parameters that are known to influence the formation of NDELA (e.g. process temperature, pH value, age of the used mixture etc.) in preparations (e.g. metalworking fluids) as required in the decision. The eMSCA considers that these parameters should be taken into account and documented in further updates of the chemical safety assessment by the registrants and also communicated along the supply chain.

Worker request 2:

The registrant has used established higher tier models for dermal contact (RiskofDerm) and inhalation (Advanced REACh Tool) to estimate exposure to DEA for the exposure situations in question. The corresponding exposure estimates appear plausible as standard input parameters for exposure determinants and exposure mitigation measures (respiratory protection, gloves, LEV) are used. However, for a number of exposure situations the risk characterisation ratios are still significantly above 1, if the DNEL derived by the eMSCA is used.

Worker request 3

The registrant points out that rotating parts are generally used in closed machines. Therefore, there is no risk of gloves being entangled. The eMSCA takes note of this. The higher tier assessment carried out appears plausible. However, for some of the exposure situations the risk characterisation ratios are still significantly above 1 if the DNEL derived by the eMSCA is used.

Worker request 4

The registrant has complied with this request and has submitted appropriate and consistent information on personal protective equipment regarding the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios. The registrant also used the default efficiencies of gloves as specified in the corresponding models.

7.12.1.2 Consumers

7.12.1.2.1 Registered consumer uses

In the initial substance evaluation year, 2012, DEA was registered for the following uses:

- Use of concrete and cement (Consumer),
- Use of fuel (Consumer),
- Use of DEA in detergents and cleaners (Consumer),
- Use of DEA in wood protection formulations (Consumer) and
- Service life of DEA when used as processing aid for paper, textile and leather.

Due to deficiencies of the evaluated information on consumer exposure in the CSRs, ECHA required revised exposure scenarios and exposure calculations for the registered consumer uses of DEA, additional information on consumer exposure to NDELA for these uses and information on consumer exposure to DEA and NDELA in certain consumer articles. Exposure information was to be provided until 25 May 2015. After evaluation of the registrations at this time, the eMSCA conducted a meeting with the lead registrant on 14 October 2015.[5]

On 20 May 2016, the lead registrant informed the eMSCA about their registration update of 25 May 2016. They confirmed that the decision´s information requirements regarding exposure and risks of NDELA and DEA in consumer mixtures were no longer considered because no consumer uses of DEA were identified in a detailed review performed recently. The registrants also removed the use of DEA as a processing agent in the production of plastic and rubber from the updated dossier, but maintained uses of DEA in the production of textile, leather and paper. Therefore the information requirements regarding consumer exposure to DEA and NDELA in paper, leather and textile articles remained valid. In response to these requirements, the lead registrant forwarded to the eMSCA an exposure assessment for DEA and NDELA from consumer uses of paper, leather and textiles.

Subsequently, most of the other registrants updated their registration dossiers and removed their consumer uses. Nevertheless, on 8 June 2020, the following consumer uses were still found in the information from registration dossiers for DEA on ECHA´s dissemination website:

- Use of DEA in wood protection formulations (PC8),
- Use of DEA in concrete and cement (PC 0),
- Use of fuel (PC 13),

[5] The lead registrant was asked why many uses, including all consumer uses, had disappeared from his registration. It was explained that in the early phase of REACH, many downstream users had communicated uses and use descriptors that were not found plausible and had to be verified by internet searches. After receiving the draft decision, the SIEF members were asked on their uses by means of a questionnaire. After that, the DEA consortium (i.e. the lead registrant and five other registrants) sent a letter to their downstream users informing them that consumer uses were not supported any more. The eMSCA inquired whether residual DEA could still be contained in consumer products as a result of incomplete reactions of DEA. The lead registrant answered that he was not able to respond to this due to lack of data. Regarding consumer use of DEA in cement, the lead registrant clarified that due to the low maximum DEA concentration in consumer cement products no relevant exposure was expected. The lead registrant accepted to provide the outstanding exposure scenarios and exposure estimations for DEA and NDELA in consumer articles made from paper, leather and textiles.

- Use of DEA in detergents and cleaners, with contributing scenarios for washing and cleaning products (PC 35) and for cosmetics, personal care products (PC 39).

In addition, DEA has been registered as a constituent of other registered substances with consumer uses such as triethanolamine (CAS 102-71-6) or fatty acid diethanolamides.

7.12.1.2.2 Information from product registers

In order to identify possible consumer uses of DEA not described in the Chemical Safety Reports, a broad internet search was performed in the year 2012.[6] In addition, the product registers from Sweden, Denmark and Switzerland were queried for information on DEA in registered products. Most of the consumer preparations containing DEA and registered in Denmark or Sweden were cleaning agents or paints. Summarising information from a literature/internet search and from product registers, the following additional consumer products were identified in 2012: paints, lubricants and greases, photochemicals, surface treating agents, special cleaners (stain removers, car care).

In June 2019, the "SPIN - Substances in Products in Nordic Countries" database was searched (http://spin2000.net/). The SPIN exposure toolbox contained data on DEA in registered products from Denmark (latest data 2017), Norway (latest data 2017) and Sweden (latest data 2015). In all three countries, one or several product uses indicated highly probable consumer exposure (Use index 5), one or several uses indicated a highly probable use in article production (Article index 3) and the range of uses was very wide (Range of use index 5) with > 100 applications. The products with the highest tonnages were intermediates, process regulators, construction materials, corrosion inhibitors and solvents, which together amounted to more than 1 000 tonnes in 2017, while cleaning/ washing agents amounted to less than 20 tonnes. Norway and Sweden explicitly indicated products for consumer use in 2017, but the respective consumer product categories were not communicated. No clear time trend could be detected between 2000 and 2017 regarding the total amounts used or the amounts used in washing and cleaning products.

In addition, a query was performed in the German Product Register (GIFAS database) regarding mixtures that contain DEA and were submitted between 2011 (i.e. before the substance evaluation had started) and 2017. The results are shown in Table 28.

Table 27

MIXTURES CONTAINING DEA IN THE GERMAN PRODUCT REGISTER: SUBMISSION NUMBERS FOR THE YEARS 2011 TO 2017

Year	Industrial or Professional Use	No Information	Consumer Use	Consumer or Professional Use	Unknown	All Uses
2011	171	26	28	9		234
2012	1 892	26	21	25		1 964
2013	1 020	8	28	11	5	1 072
2014	1 305	3	2	22		1 332
2015	343	7	12	20		382
2016	966		41	37		1 044
2017	224	7	51	46		328

[6] The search included Hazardous Substances Data Bank (HSDB), RÖMPP Online, GESTIS-Stoffdatenbank, National Toxicology Programme, Substances in Products in Nordic Countries (SPIN), Rapid Exchange of Information System (RAPEX), OECD-SIDS Initial Assessment Reports, WHO-Concise International Chemical Assessment Documents (CICAD), WHO-International Programme on Chemical Safety (IPCS), IARC Monographs, Centers for Disease Control and Prevention (CDC), ATSDR – Toxicological Profiles, Danish Environmental Protection Agency, Swedish Chemicals Agency, Environment Canada, National Institute for Public Health and the Environment (RIVM), Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA), Scorecard.

All Years	**5 921**	**77**	**183**	**170**	**5**	**6 356**
%	**93.2**	**1.2**	**2.8**	**2.7**	**0.1**	**100**

Only 2.8 % of the registered products containing DEA were assigned to consumer use and only 2.7 % to consumer or professional use. There was no indication of changes in the numbers of registered consumer products over time.

7.12.1.2.3 Conclusion on consumer uses

In summary, despite the fact that most registrants removed their consumer uses from the registration dossiers for DEA, there are still indications of continuing consumer uses:

- There are still registration dossiers that support consumer uses.
- The Swedish, Norwegian and German product registers still list consumer products containing DEA. No time trend (i.e. decline) can be deduced from the registrations in these registers.
- Several registrations for other substances that contain DEA as an impurity or constituent include consumer uses.

On the other side, it did not become clear, how relevant these consumer uses are in terms of quantity and numbers of preparations on the market. At least the low percentage of submissions for consumer use in the German Product Register could indicate that the market share of consumer products with DEA is comparatively low.

Also, it did not become clear which categories of consumer products and articles are the most relevant. In this situation, the eMSCA decided to focus its conclusions on the product and article categories that were covered by the exposure scenarios for DEA in 2012 and to supplement them with product categories that were registered for consumer uses of “Amides, C8-18 (even numbered) and C18-unsatd., N, N-bis(hydroxyethyl)” (CAS 68155-07-7), in a registration dossier that lists DEA as an impurity.

Regarding wood protection products (PC8), the eMSCA decided not to evaluate them in the scope of this substance evaluation, as they are regulated by the Biocidal Products Regulation (EU) No 528/201. Nevertheless, evaluations for DEA in coatings and paints (PC 9a) could be applicable for wood protection products in the present case.

Risks from DEA in finger paints (PC 9c) were not evaluated because they are addressed in the European Standard EN 71-12 ("Safety of toys - Part 12: N-Nitrosamines and N-nitrosatable substances"). According to this standard, the migration of N-nitrosatable substances from finger paints shall not exceed 1 mg/kg of toy material, calculated as sum of all detected N-nitrosamines after nitrosation. The resulting list of consumer product and article categories that are focussed on in the present substance evaluation is as follows:

- PC3 - Air care products,
- PC9a - Coatings, paints, thinners, removers,
- PC9b - Fillers, putties, plasters, modelling clay (for concrete and cement),
- PC13 - Fuels,
- PC31- Polishes and wax blends
- PC35 - Washing and cleaning products
- AC5 - Fabrics, textiles and apparel
- AC6 - Leather articles
- AC8 - Paper articles

The eMSCA considers that as a first step a harmonised classification and labelling of DEA according to the hazard classes listed above will improve the safe use of DEA and DEA-containing substances and mixtures by consumers.

According to Entry 30 of Annex VII of the REACH Regulation, a classification of DEA as Repr. 1B would result in a restriction of the concentration of DEA in mixtures for the general

public to the specific concentration limit according to Annex VI of Regulation (EC) No 1272/2008 or to the generic concentration limit according to Annex I of Regulation (EC) No 1272/2008. Below, the eMSCA evaluates whether this measure would be sufficient to address the consumer risks from DEA.

7.12.1.2.4 Scope and type of exposure

Use of DEA can lead to consumer exposure by inhalation, dermal contact and ingestion. In addition, DEA can be converted to NDELA by reaction with nitrosating agents such as nitrogen oxides, in particular upon microbial contamination. Since nitrogen oxides are ubiquitous in the environment, the formation of NDELA should be considered in all places where DEA is used.

In the case of textile, leather and paper articles, exposure is considered to be long-term and/or repeated. Therefore long-term exposure has been calculated for the dermal, the inhalation and the oral route where relevant.

In the case of mixtures, long-term exposure for these routes has been calculated, too, if relevant. Subacute exposure has been calculated for several mixtures with use frequencies below 15 times per year.

In addition, DEA is classified as Acute Tox. 4 for the oral route. Acute hazards have been identified for the inhalation route in this evaluation and short-term DNELs have been derived. Therefore a 15-minute peak exposure has also been calculated for the inhalation route where relevant.

DEA is also classified as irritating to skin (Skin Irrit. 2) and severely damaging the eyes. However, as the consumer risk assessment has been limited to mixtures with DEA concentrations up to 0.3 %, these effects are less relevant for this assessment.

7.12.1.2.5 Monitoring data

Monitoring data on the occurrence of DEA and NDELA in cosmetic products, NDELA in tattoo colours, finger paints and rubber balloons are included in a confidential annex.

<u>DEA and NDELA in leather and paper</u>

In May 2016 the lead registrant forwarded to the eMSCA an exposure assessment for DEA and NDELA from consumer uses of paper, leather and textiles that was partly based on monitoring data. More information on these data and on the resulting exposure assessments can be found in the Confidential Annex.

<u>DEA in textiles</u>

As the data base for DEA and NDELA in textiles was considered very weak, the eMSCA initiated a consultation with an industry association which initiated a study on DEA concentrations in treated textiles performed by a member company. The resulting data were provided to the eMSCA.

Free DEA was determined in samples of different textile materials taken during and after processing. Two mixtures containing DEA were applied: a processing aid that is rinsed off the material and a fabric softener (for industrial use) that is intended to remain on the textile.

The processing aid with 25 % DEA was used in a washing process that was followed by rinsing. DEA contents in textile samples after this process were between 50 and 70 ppm for wool, and between 10 and 20 ppm for polyester and cotton. Higher values were found if, as an improbable worst case simulation, washing was performed without rinsing. The processing step is followed by dyeing or bleaching with subsequent rinsing, and dyeing and rinsing were chosen for the analyses. After dyeing, DEA was below the limit of detection of 10 ppm for the three tested textile materials.

The fabric softener with < 0.5 % DEA was applied to the textiles with two different industrial procedures, the exhaust process and the padder application. After both processes DEA was determined in different fibre types (cotton, polyester and a mixed fabric made

from cotton and polyester), and the concentrations were at or below the limit of quantification.

The table below summarises the measured concentrations of DEA in treated textiles provided during this project.

Table 28

CONCENTRATIONS OF DEA IN TREATED TEXTILES (DATA PROVIDED BY IND ASSOCIATION)	
Process Scenario	**Concentration in textile (ppm)**
PROCESSING AID	
Wool RC: wash, rinse, dye	12*
Wool: wash, rinse	73*
Wool WC: wash	567*
Polyester RC: wash, rinse, dye	< LOQ*
Polyester: wash, rinse	24*
Polyester WC: wash	39*
Cotton RC: wash, rinse	19*
Cotton WC: wash	451*
Cotton WC: wash, higher DEA content in processing aid	1760**
FABRIC SOFTENER	
Cotton exhaust process RC 3 % stock solution	< LOQ***
Cotton exhaust process WC 5 % stock solution	< LOQ***
Cotton foulard application RC 40 g/L stock solution	< LOQ***
Cotton foulard application WC 60 g/L stock solution	14***
Polyester exhaust process RC 3 % stock solution	< LOQ***
Polyester exhaust process WC 5 % stock solution	< LOQ***
Polyester foulard application RC, 40 g/L stock solution	< LOQ***
Polyester foulard applicationWC 60 g/L stock solution	< LOQ***
Cotton/Polyester exhaust process RC 3 % stock solution	< LOQ***
Cotton/Polyester exhaust process WC 5 % stock solution	< LOQ***
Cotton/Polyester foulard application RC 40 g/L stock solution	11***
Cotton/Polyester foulard application WC 60 g/L stock solution	15***

RC= Real Case, WC = Worst Case, LOQ is 10 ppm.
* Highest value of double determinations for two textile samples in each process scenario
**Highest value of double determination with especially high DEA content in solution to simulate misuse
***Average value of double determination

7.12.1.2.6 Exposure to DEA in consumer mixtures

The evaluation in 2012 was based on the exposure scenarios and exposure assessments from the lead CSR. The deficiencies found in its exposure scenarios and exposure estimations were summarised in the decision that was sent to the registrants by ECHA in 2014, requiring information on consumer exposure from mixtures.

After receiving this decision, most, but not all, of the registrants removed uses of DEA in consumer mixtures from their registrations.

With this ambiguous information regarding DEA content in consumer mixtures, the eMSCA now tried to clarify the consequences of a possible classification of DEA as Repr. 1B. According to Entry 30 of Annex VII of the REACH Regulation, the concentration of DEA in mixtures for the general public would be restricted to the specific concentration limit according to Annex VI of Regulation (EC) No 1272/2008 or to the generic concentration limit according to Annex I of Regulation (EC) No 1272/2008. As the generic concentration limit is 0.3 % in this case, the eMSCA decided to perform exposure assessments with this concentration for all product categories identified as relevant for this evaluation (see above).

The calculations were performed in June and July 2019. Body weight for an adult was assumed as 60 kg, molecular weight of DEA as 105 g/mol, vapour pressure of DEA as 0.00855 Pa. As no specific use conditions were known, the product subcategories, exposure scenarios, relevant routes of exposure, exposure models and exposure parameters were directly taken from the ConsExpo Fact sheets as preinstalled in the ConsExpo Web version 1.0.6 (https://www.rivm.nl/en/consexpo), if possible. This was the case for PC9a - Coatings, paints, thinners, removers, PC31- Polishes and wax blends and PC35 - Washing and cleaning products.

A specific approach was chosen, if ConsExpo was not applicable or if the calculation could be refined by using specific data. This was the case for the following product categories:

PC3 - Air care products

The calculations were perfomed using several parameters from the Cleaning Products Factsheet preinstalled in the ConsExpo Web version 1.0.6 and from the Specific Consumer Exposure Determinants (SCEDs) published by the International Association for Soaps, Detergents and Maintenance Products (AISE, 2017). For solid and liquid air care products (in AISE: Air Care products – Non aerosol), dermal exposure was calculated by assuming instant application to 2 fingertips = 5 cm^2, a layer thickness of 0.01 cm and a density of 1 g/cm^3. Dermal exposure (E) was calculated as

E = 0.01 cm x 5 cm^2 x 1 g/cm^3 x 0.003 / 60 kg

Inhalation exposure for solid and liquid air care products was calculated assuming: discharge rate $2.9*10^{-5}$ g product/s , room volume 20 m^3, ventilation rate 0.6/h.

Dermal exposure to air care spray products was calculated using several assumptions for cleaning spray products from ConsExpo: generation rate 1.2 g product/s (for trigger sprays), release duration doubles spray duration, contact rate 46 mg/min (for bathroom cleaner spray) use frequency 2/day (AISE, 2017).

PC9b - Cement

For indoor use of concrete and cement products, an exposure scenario was constructed based on the existing Scenario for Wall plaster in the Do-it-yourself-products Factsheet preinstalled in the ConsExpo Web version 1.0.6. Only dermal exposure was assessed using the Constant rate model for direct contact. Relevant exposure parameters were: Use frequency 0.2/year, Exposed area 1 900 cm^2, Contact rate 50 mg/min and Release duration 120 minutes.

PC13 – Fuels

Measured data from the study by Galea et al (2014) were used for the calculation of dermal exposure when filling a diesel tank. In this study, 10 volunteers completed two exposure situations to simulate filling a vehicle fuel tank. Dermal exposure to the hands and forearms was monitored using a wipe sampling method, and the measured mass in mg was converted to mg/cm^2 using an average surface area of forearm and hand, 0.099 m^2 for males and 0.0895 m^2 for females. Dermal exposure to the hands and forearms ranged from < 0.25 $\mu g/cm^2$ to 96.21 $\mu g/cm^2$. As seven out of ten volunteers were males, the eMSCA used the average surface area for males from the study report to recalculate the maximum measured amount of fuel on skin. Using 0.3 % as DEA concentration, the exposure (E) was calculated as

E = 0.096 mg/cm^2 x 990 cm^2 x 0.003 / 60 kg

The table below shows the results of the exposure assessments performed by the eMSCA for consumer mixtures with an assumed concentration of 0.3 % DEA.

Table 29

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC3 - Air care products	solid & liquid	0.026	0.026	0.0025			1/day	480	See text	AISE SCEDs and Cleaning product Fact Sheet in ConsExpo
PC3 - Air care products	aerosol spray (non-volatile)			0.0013			2/day	15	See text	AISE SCEDs and Cleaning product Fact Sheet in ConsExpo
PC9a - Paints	high solid paint	0.0032	0.005	0.18	n.a.		1/year	132	ConsExpo Web, version 1.0.6, 13-02-2019	Paint Products fact sheet in ConsExpo Web
PC9a - Paints	solvent rich paint	1.80E-03	2.70E-03	0.18	n.a.		10/year	132	ConsExpo Web, version 1.0.6, 13-02-2019	Paint Products fact sheet in ConsExpo Web
PC9a - Paints	waterborne wall paint	8.00E-04	0.0011	0.18	n.a.		2/year	132	ConsExpo Web, version 1.0.6, 13-02-2019	Paint Products fact sheet in ConsExpo Web
PC9a - Paints	waterborne paint	2.70E-04	4.10E-04	0.18	n.a.		1/year	132	ConsExpo Web, version 1.0.6, 13-02-2019	Paint Products fact sheet in ConsExpo Web
PC9a - Paints	spray can	4.4	4.4	0.075	n.a.		2/year	20	ConsExpo Web, version 1.0.6, 13-02-2019	Paint Products fact sheet in ConsExpo Web
PC9b - Cement	application	n.a.	n.a.	0.3	9.50E-03		0.2/year		ConsExpo Web, version 1.0.6, 13-02-2019	Do-it-yourself product fact sheet in ConsExpo Web

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC13 - Fuels	filling a Diesel tank	n.a.	n.a.	0.00475	0.096		52/year	1	E= D*A*C/BW	dermal load D and exposed area A: (Galea, et al 2014), use frequency and exposure duration: CONCAWE (2014)
PC31 - Polishes	floor-polish-liquid-application	1.00E-04	1.90E-04	0.028	0.0073		52/year	90	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC31 - Polishes	floor-polish-spray (non-volatile)	0.1	0.31	0.0025	6.90E-05		52/year	90	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC31 - Polishes	furniture-polish-spray	0.47	3.6	0.0092	2.50E-04		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC31 - Polishes	furniture-polish-liquid	n.a.	n.a.	0.028	0.0075		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC31 - Polishes	shoe-polish-cream	9.00E-05	1.30E-04	0.065	0.017		12/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC31 - Polishes	shoe-polish-spray	0.023	0.17	0.14	0.019		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-powder (mixing/loading)	1.90E-05	1.90E-05	3.50E-05	9.30E-06		365/year	0.25	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-powder hanging	1.20E-07	1.30E-07	3.5E-04	2.30E-05		365/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC35 - Washing/Cleaning Products	machine-washing-powder postapplication	n.a.	n.a.	0.003	1.10E-05		365/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-liquid-hanging	1.20E-07	1.30E-07	3.5E-04	2.30E-05		365/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-liquid-mixing loading (cap)	7.50E-08	7.50E-08	0.027	0.03		365/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-liquid-mixing loading (direct)	7.50E-08	7.50E-08	5E-04	1.30E-04		365/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	machine-washing-liquid-postapplication	n.a.	n.a.	0.003	1.10E-05		365/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-powder application	1.90E-08	1.90E-08	0.0097	2.60E-04		52/year	10	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-powder hanging cloth	1.40E-06	1.50E-06	0.004	2.60E-04		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-powder mixing/loading	1.90E-05	1.90E-05	3.5E-05	9.30E-06		52/year	0.25	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-liquid application	5.50E-10	5.50E-10	0.0097	2.60E-04		52/year	10	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-liquid hanging	1.40E-06	1.50E-06	0.004	2.60E-04		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC35 - Washing/Cleaning Products	hand-washing-liquid mixing-loading-pouring with cap	7.50E-08	7.50E-08	0.026	0.03		52/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-liquid mixing loading - direct pouring	7.50E-08	7.50E-08	5E-04	1.30E-04		52/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	hand-washing-liquid postapplication	n.a.	n.a.	0.035	1.20E-04		365/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	all-purpose cleaner - liquid - mixing/loading	1.80E-08	1.80E-08	5E-04	1.30E-04		197/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	all-purpose cleaner - liquid -application	2.00E-06	2.30E-06	0.014	3.90E-04		197/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	all-purpose cleaner - liquid - rubbing off	n.a.	n.a.	0.12	0.0024		197/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	all-purpose cleaner - spray -rinsing	n.a.	n.a.	0.016	4.10E-03		365/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	all-purpose cleaner - spray-non-volatile	8.90E-03	0.019	0.0011	2.90E-05		365/year	60	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	bathroom cleaner liquid application	9.50E-07	1.40E-06	0.015	4.10E-04		156/year	25	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	bathroom cleaner liquid mixing loading	3.00E-08	3.00E-08	0.0005	1.30E-04		156/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC35 - Washing/Cleaning Products	bathroom cleaner spray application	0.033	0.04	0.0061	1.70E-04		120/year	24	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	bathroom cleaner spray rinsing	n.a.	n.a.	0.031	8.30E-03		120/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	toilet cleaner acid application	4.00E-06	4.00E-06	0.019	2.60E-03		156/year	7	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	toilet cleaner bleach application	4.00E-06	4.00E-06	0.019	0.0026		156/year	7	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing machine liquid mixing loading	5.00E-08	5.00E-08	5.00E-04	1.30E-04		365/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing machine liquid rinse aid mixing loading	3.00E-08	3.00E-08	5.00E-04	1.30E-04		35/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing machine liquid rinse aid post application	n.a.	n.a.	n.a.	n.a.	1.10E-04	35/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing machine powder mixing loading	7.50E-06	7.50E-06	3.50E-05	9.30E-06		365/year	0.25	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing manual application	2.70E-09	4.00E-09	0.0018	4.20E-05		426/year	45	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	dish washing manual post application	n.a.	n.a.	n.a.	n.a.	2.10E-05	365/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo

EXPOSURE ESTIMATES FOR CONSUMER MIXTURES ASSUMING A CONCENTRATION OF 0.3 % DEA										
Product Category	**Scenario**	**Inhalation Mean event concen-tration (mg/m³)**	**15 min Peak concen-tration (mg/m³)**	**Dermal external dose on day of exposure (mg/kg bw/d)**	**Dermal load (mg/cm²)**	**Ingested dose on day of exposure Oral (mg/kg bw/d)**	**Use Fre-quency**	**Exposure duration (min)**	**Exposure Model**	**Parameters**
PC35 - Washing/Cleaning Products	floor liquid cleaning mixing loading	3.00E-08	3.00E-08	5.00E-04	1.30E-04		161/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	floor liquid cleaner application	2.40E-06	2.70E-06	0.018	4.90E-04		161/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	floor liquid cleaner postapplication	n.a.	n.a.	0.002	4.00E-05		161/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	glass cleaning - spray cleaning	n.a.	n.a.	0.038	0.03		66/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	glass cleaning spray spraying	0.0023	0.0079	0.0014	3.80E-05		66/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	liquid-carper-cleaning-manual application	8.80E-06	1.00E-05	0.075	0.002		52/year	240	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	liquid-carper-cleaning-manual mixing loading	2.50E-08	2.50E-08	5.00E-04	1.30E-04		52/year	0.75	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	liquid-carper-cleaning postapplication	n.a.	n.a.	0.09	0.0018		52/year		ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	metal-cleaning-naphta-application	4.00E-05	6.30E-05	0.065	0.017		6/year	60	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo
PC35 - Washing/Cleaning Products	metal-cleaning-water application	2.20E-05	3.40E-05	0.055	0.015		6/year	60	ConsExpo Web, version 1.0.6, 13-02-2019	Cleaning and washing Fact Sheet in Consexpo

Body weight = 60 kg except toddle

7.12.1.2.7 Exposure to DEA in consumer articles made from textile, leather and paper

In response to the information requirements by ECHA, the lead registrant provided exposure calculations for DEA and NDELA in consumer articles made from textile, leather and paper. More details on these assessments are included in the confidential annex.

Based on the measured concentrations for DEA in treated textiles (C in ppm) presented in Table 29, the eMSCA performed exposure calculations using the so called BfR model (Krätke and Platzek, 2004). Table 31 shows the results of these calculations.

Details on the process scenarios for the measured concentrations in textiles are given in the section on monitoring data. Assumptions made for the exposure calculations are: migrated fraction of a hydrophilic substance: 2%, textile mass per unit area: 100 g/m², area of exposed skin: 1 m^2, body weight 60 kg, correction factor for chronic exposure: 0.1. Using the necessary unit correction factors, chronic exposure to DEA (E) in mg/kg bw/day was calculated as:

$E = C \times 10^{-6} \times 0.02 \times 100 \times 1 \times 1000 \times 0.1 / 60$ mg/kg bw/day

As the calculations were performed for an adult person, an additional calculation was performed for a 10 kg toddler whose whole body surface of 0.6 m² would be covered by a textile. The dermal exposure calculated for adults is lower by a factor of 3.6, and based on an ECETOCTRA 3.1 calculation, for children an oral exposure between 0.00001 mg/kg bw (real case) and 0.0176 mg/kg bw (worst case misuse simulation) would have to be added.

Table 30

CHRONIC DERMAL EXPOSURE ESTIMATES FOR DEA IN TREATED TEXTILES (SOURCE: OWN REPRESENTATION BASED ON CONCENTRATION DATA GIVEN BY INDUSTRY ASSOCIATION)		
Process Scenario	**Concen-tration in textile (ppm)**	**Chronic external dermal exposure, adult (mg/kG bw/d)**
Processing Aid		
Wool RC: wash, rinse, dye	12	4.00E-05
Wool: wash, rinse	73	2.43E-04
Wool WC: wash	567	1.89E-03
Polyester RC: wash, rinse, dye	< 10	< 3.33E-05
Polyester: wash, rinse	24	8.00E-05
Polyester WC: wash	39	1.30E-04
Cotton RC: wash, rinse	19	6.33E-05
Cotton WC: wash	451	1.50E-03
Cotton WC: wash, higher DEA content in processing aid	1760	5.87E-03
Textile Softener		
Cotton exhaust process RC 3 % stock solution	< 10	< 3.33E-05
Cotton exhaust process WC 5 % stock solution	< 10	< 3.33E-05
Cotton foulard application RC 40 g/l stock solution	< 10	< 3.33E-05
Cotton foulard application WC 60 g/l stock solution	14	4.67E-05
Polyester exhaust process RC 3 % stock solution	< 10	< 3.33E-05

Polyester exhaust process WC 5 % stock solution	< 10	< 3.33E-05
Polyester foulard application RC 40 g/l stock solution	< 10	< 3.33E-05
Polyester foulard application WC 60 g/l stock solution	< 10	< 3.33E-05
Cotton/Polyester exhaust process RC 3 % stock solution	< 10	< 3.33E-05
Cotton/Polyester exhaust process WC 5 % stock solution	< 10	< 3.33E-05
Cotton/Polyester foulard application RC 40 g/l stock solution	11	3.67E-05
Cotton/Polyester foulard application WC 60 g/l stock solution	15	5.00E-05

RC= Real Case
WC= Worst Case

7.12.1.2.8 Exposure to NDELA from consumer mixtures and articles

No further information could be gathered on the NDELA content in mixtures for consumer use. Therefore, consumer exposure deriving from degradation of DEA to NDELA in consumer mixtures remains unknown.
In response to the information requirements by ECHA, the lead registrant provided exposure calculations for DEA and NDELA in consumer articles made from textile, leather and paper. More details on these assessments can be found in the confidential annex.

7.12.1.2.9 Uncertainty analysis

Subsequently, main sources of uncertainty regarding the consumer exposure assessment are qualitatively discussed.

Regarding exposure to DEA from consumer mixtures it should be noted that for the calculations of the eMSCA the concentration of DEA in mixtures was set to 0.3 % (Generic Concentration Limit for Repr. 1A/B) in order to conclude on the effectiveness of a possible classification of DEA as a risk management measure. It is not applicable for consumer mixtures with a higher (or lower) DEA concentration. The assessment may underestimate (or overestimate) the consumer exposure for products on the market which are not in agreement with the applied exposure scenarios for the substance or for substances that contain DEA as an impurity.

An important source of uncertainties regarding exposure to DEA from consumer mixtures are model uncertainties. For estimating dermal exposure, it was assumed that none of the product that gets into contact with the skin is removed by washing or wiping off. This assumption might substantially overestimate the actual exposure for some applications. For the inhalation route, both, the evapouration model as well as the non-volatile spray model (after spraying) of ConsExpo assumes that the concentration within the room is homogeneous. However, a concentration gradient from the applied substance is to be expected. Given that for typical applications, the person is rather close to the applied area, concentrations of DEA the person is exposed to are probably larger than the average concentration in the room. Therefore, the assumption of homogeneous room concentration underestimates the real exposure via inhalation.

Most of the calculations for exposure to mixtures refer to standard scenarios of ConsExpo with default values. While these scenarios describe typical situations, other uses are also possible and can lead to lower or higher exposure. For example, parameters for the use of all-purpose cleaner spray have been derived assuming an application in the kitchen; however it could also be used in any other room. For the parameter values given in the Fact Sheets of ConsExpo that exhibit variability, the 75th (or 25th) percentile was chosen (estimated) to specify the situation for high-end users. It should be noted that, if data were available, the model aimed to describe the circumstances in the Netherlands and is therefore not necessarily representative of the European situation.

For assessing dermal exposure while refueling a car, the dermal load was set to be the maximum value reported in a study conducted by Galea et al. (2014). Given that in this

study only two sample runs for in total 10 participants were recorded, it should be noted that it cannot be inferred that larger values are insignificant for consumer exposure.

Regarding the exposure estimations for DEA in consumer articles performed with information provided by the lead registrant in response to the decision, the MS CA understood that it was the intention of the lead registrant to provide measured data from worst case situations. However, as no information was given on the methods for sampling and analysis and on the representativeness of the technical processes and samples, the eMSCA is not able to conclude on whether this is the case.

For exposure assessments for NDELA in consumer articles data is even more scarce: NDELA concentrations in the materials were deduced from the concentrations in processing aids or colours containing DEA together with information on the percentage of DEA from products that was retained in or on the materials. This was based on the assumption that the occurrence of reaction of the residues of DEA to NDELA during service life was negligible, and that a similar percentage of NDELA would remain as residue in the materials after rinsing, as in the case of DEA. Both assumptions are debatable and the uncertainty of the measured retention factors for DEA ads to the uncertainty of the very few measured NDELA data. Therefore the eMSCA concludes that the exposure estimates for NDELA are highly uncertain.

In the case of textiles, the eMSCA did not agree with the main assumption of the registrant that the processes for leather and for textiles are comparable, and therefore searched for a more reliable approach for the exposure estimation. No alternative approach was found for NDELA in textiles, but the exposure assessment for DEA in textiles was based on data provided by an industry association. It should be noted that for treated textiles, the worst case concentrations in this data set and the assessments based on them correspond to rather experimental situations that do not represent the normal processes and highly overestimate exposure.

7.12.2 Environment

Not assessed in the course of this evaluation

7.13 Risk characterisation

7.13.1 Workers

Dermal exposure is compared to the **long-term** (LT) **$DNEL_{dermal}$, systemic of 0.05 mg/kg bw/d.** The DNEL is calculated on the overall LOAEL of 8 mg/kg bw/d based on the sub- and chronic dermal studies with rat and mice. The critical systemic effects appear to be anaemia, kidney and liver toxicity. Beside anaemia, nephropathy was observed at the lowest tested dose in the 13-week dermal toxicity study (32 mg/kg bw/d in rats). Additional lesions of the treated skin showed a dose-related increase in incidence and severity. After 13-weeks, kidney effects are not contributed to aging effects. Therefore, the observation of a dose-related increase in severity of nephropathy in female rats at the lowest tested dermal dose of 8 mg/kg bw/d in the 2-year study is also considered adverse. The substance is classified for skin irritation. Furthermore, after repeated dermal exposure local (irritation) dermal effects were reported from this dose upwards.

Therefore, the overall dermal LOAEL derived from female rats of the two years study for systemic and local toxicity was 8 mg/kg bw/d.

In 2016 a German Occupational Limit Value (AGW) for systemic and local effects of DEA was derived by the national committee for hazardous substances (AGS). Thus in theory for the risk assessment of DEA the AGW of 0.5 mg/m^3 could be used. However, one result at the end of the one-year evaluation process was the request of an EOGRTS to assess DEA in terms of reproductive toxicity. In the meantime this EOGRTS (oral OECD TG 443 in rats) was performed (TL, 2018a). The evaluation of this data by the eMSCA shows that the derived inhalation DNEL for developmental toxicity of 0.4 mg/m^3 is lower than the derived AGW for systemic and local effects after inhalation exposure. Thus, this $DNEL_{developmental}$ of 0.4 mg/m^3 is used for inhalation risk assessment. **Inhalation exposure** is compared to

the long-term **$DNEL_{inhalation}$, developmental effects of 0.4 mg/m³**. The $DNEL_{inhalation, systemic}$ is based on the NOAEC of 15 mg/m³ from a sub-chronic inhalation study in rats. The critical systemic effects appear to be liver and kidney effects. The $DNEL_{inhalation}$, developmental effects bases on a LOAEL of 12.25 mg/kg bw/d from an oral EORGTS in rats. The critical effects appear to be increased body weight and cysts in the pituitary.

The RCR for the combined exposure values are determined through the summation of the RCRs resulting from the comparison of the exposure values for inhalation and dermal exposure with the corresponding DNEL.

The table below shows an overview of the exposure scenarios and PROCs specified for DEA which have an RCR above 1 for one single exposure route (inhalation, dermal) and the combined exposure.

Long-term dermal and inhalation exposure estimates were provided by the registrants.

Table 31

OVERVIEW OF THE EXPOSURE SCENARIOS AND PROCS WHICH ARE IN CONCERN BY THE USE OF DEA			
Exposure Scenario	**Risk dermal route**	**Risk inhalation route**	**Overall Risk**
Exposure Scenario 1 – Manufacturing of DEA	5 PROCs RCR 1.4 – 2.1		**5 PROCs RCR 1.5 – 2.2**
Exposure Scenario 2 – Formulation of products (industrial)	6 PROCs RCR 1.4 – 2.1		**6 PROCs RCR 2 – 2.5**
Exposure Scenario 3 – Formulation of products (professional)	6 PROCs RCR 1.4 – 2.1		**6 PROCs RCR 1.6 – 2.2**
Exposure Scenario 4 – Use of DEA as an intermediate	4 PROCs RCR 1.4 – 2.1	2 PROCs RCR 1.1	**5 PROCs RCR 1.8 – 2.5**
Exposure Scenario 5 – Use in construction chemicals	4 PROCs RCR 1.4 – 2.0		**4 PROCs RCR 1.5 – 2.1**
Exposure Scenario 6 – Use in construction chemicals (e.g. cement and concrete) (professional)	5 PROCs RCR 1.4 – 2.0		**5 PROCs RCR 1.4 – 2.2**
Exposure Scenario 7 – Gas treatment with DEA	2 PROCs RCR 1.4 – 2.1	1 PROC RCR 1.1	**3 PROCs RCR 1.5 – 2.2**
Exposure Scenario 8 – Use of DEA in metal working-fluids (Industrial)	2 PROCs RCR 1.4		**2 PROCs RCR 1.4**
Exposure Scenario 9 – Use of DEA in metal working-fluids (Professional)	2 PROCs RCR 1.4		**2 PROCs RCR 1.4**
Exposure Scenario 10 – Use as additive in PU-systems (Industrial)	8 PROCs RCR 1.4 – 2.0		**8 PROCs RCR 1.7 – 2.2**
Exposure Scenario 11 – Use as additive in PU-systems (Professional)	6 PROCs RCR 1.4 – 2.0		**6 PROCs RCR 1.7 – 2.2**
Exposure Scenario 12 - Use as additive or processing aid in leather, textile or paper	8 PROCs RCR 1.0 – 2.1		**8 PROCs RCR 1.1 – 2.1**
Exposure Scenario 13 – Use of DEA as processing aid in paper, textile and leather	8 PROCs RCR 1.0 – 2.2		**8 PROCs RCR 1.1 – 2.3**
Scenario 16: Formulation and processing (specific registrant's production site I)	5 PROCs RCR 1.4 – 2.1	1 PROC RCR 1.1	**6 PROCs RCR 1.5 – 2.2**
Scenario 17: Manufacturing of the substance (specific registrant's production site II)	5 PROCs RCR 1.4 – 2.1	1 PROC RCR 1.1	**6 PROCs RCR 1.4 – 2.2**

As can be seen in the table above, 15 of the exposure scenarios for DEA show combined RCRs above 1.The highest RCR results from scenario 2 with a value of 2.5. Only in scenarios 14 and 15 the RCRs are below 1. In most cases the high RCRs result from a high burden from the dermal exposure route. Four scenarios are of concern because inhalation exposure exceeds the $DNEL_{inhalation}$ in 1 oder 2 PROCs.

This indicates that for industrial and professional uses, especially a reduction of dermal exposure should be achieved based on available information. The eMSCA considers that this issue should be addressed in a first step by the harmonised classification and labelling of DEA according to the hazard classes listed above to enable the safe use of DEA in occupational settings. Since the inhalation exposure exceeds the DNEL -Inhalation in a

number of scenarios, the setting of an EU-wide occupational exposure limit should be envisaged as well.

7.13.2 Consumers

7.13.2.1 Risk characterisation for consumer exposure to DEA

A risk characterisation for long-term exposure is performed for all exposures to consumer articles and for exposures to selected consumer mixtures with a hypothetical DEA concentration of 0.3% and use frequencies of more than 15 times per year. The exposure estimates are compared to the lowest long-term DNEL for the general population and the respective route from Table 15, section 7.9.9.2:

The **dermal dose on the day of exposure** is compared to the **$DNEL_{LT\text{-}systemic\ effects\text{-}dermal}$ of 0.02 mg/kg bw/d.** This DNEL is also protective of local, fertility and developmental effects from long-term dermal exposure.

The **oral exposure** is compared to the **$DNEL_{LT\text{-}systemic\ effects\text{-}oral}$ of 0.0113 mg/kg bw/d.** This DNEL is also protective of fertility and developmental effects from long-term oral exposure.

The **mean event concentration** in air is compared to the **$DNEL_{LT\text{-}local\ effects\text{-}inhalation}$ of 0.04 mg/m³.** This DNEL is also protective of systemic, fertility and developmental effects from long-term exposure by inhalation. In order to account for the fact that the exposure duration is shorter than 24 hours, a refinement factor is applied to the raw RCR for inhalation. This factor applies Haber´s Law to the respective exposure duration and is taken from the ECHA Guidance R.15 for Consumer Exposure Assessment (ECHA 2016).

RCRs for the combined exposure values are determined through the summation of the RCRs for inhalation (adapted for exposure duration), dermal and oral exposure.

For consumer mixtures with use frequencies of less than 15 times per year, exposure is considered infrequent for the purpose of this evaluation, and a risk characterisation for subacute effects is performed (see ECHA 2016):

The **dermal dose on the day of exposure** is compared to the

$DNEL_{sub\text{-}acute\text{-}systemic\ effects\text{-}dermal}$ of 0.9 mg/kg bw/d and the **mean event concentration in air is compared to the $DNEL_{sub\text{-}acute\text{-}systemic\ effects\text{-}inhal}$ of 1.5 mg/m³**.

The refinement factor to account for exposure duration is also applied for subacute exposure and the RCR for combined exposure values is calculated as written above.

In addition, as DEA is classified as Acute Tox. 4 for the oral route and acute hazards have been identified for the inhalation route, risks from short-term exposure by inhalation are characterised for consumer mixtures where applicable, and the **15-minutes peak exposure by inhalation** is compared to the **$DNEL_{acute\text{-}systemic\ effects\text{-}inhalation}$ of** 4.5 - **4.9 mg/m³.**

7.13.2.2 Risk Characterisation for DEA in consumer mixtures

In order to clarify whether a concentration limit of 0.3% would be sufficient to control consumer risks from exposure to mixtures containing DEA, the exposure estimates from Table 30 are compared to the DNELs as described above. Additionally, for all mixtures with RCRs above 1, the concentrations are estimated where the combined RCR would yield 1 (safe concentration).[7]

[7] This is carried out by using the following relationships:

- Dermal exposure determined by ConsExpo depends linearily on substance concentration
- Inhalative exposure via spray determined by ConsExpo depends linearily on substance concentration

The resulting RCRs for long-term effects of mixtures with use frequencies of 15 per year and above are compiled in Table 33. For mixtures with use frequencies of less than 15 times per year, the risk characterisation is performed for subacute effects and the resulting RCRs are compiled in Table 34. In addition, risks from short-term exposure by inhalation are characterised where applicable. The resulting RCRs are all < 1 (not shown).

While most products have RCRs < 1, RCRs above 1 (for long-term or for subacute effects) are found for several spray products (aircare aerosol spray, furniture polish spray, shoe polish spray, bathroom and glass cleaning spray, paint spray can). Other products with RCRs > 1 are several kinds of polishes, machine and handwashing liquids and carpet cleaners. The highest RCR (9.57) corresponds to aircare aerosol spray, and the corresponding safe concentration would be 0.03 %.

Using the above assumptions, health risks from DEA in consumer mixtures would currently not be fully controlled by a concentration limit of 0.3% that may result from a harmonised classification and labelling of DEA as Repr. 1B and corresponding inclusion in the existing Annex XVII entry 30 restricting the supply of reprotoxic substances in mixtures or as constituents for supply to the general public. While most registrants discontinued consumer uses of DEA, there are still registration dossiers that support them and consumer uses of other substances that contain DEA as an impurity. Therefore, these health risks cannot be excluded at present.

- Inhalative exposure via evapouration determined by ConsExpo depends generally nonlinearily on substance concentration, however the resulting inhalative RCR is minor compared to the dermal RCR caused by the same use

As the result, a linear relationship between the combined RCR and substance concentration can be assumed. Given that the combined RCRs were calculated for a concentration of 0.3%, dividing this concentration by the overall RCR leads to the safe concentration.

Table 32

RISK CHARACTERISATION RATIOS FOR LONG-TERM EFFECTS FROM USE OF CONSUMER MIXTURES CONTAINING 0.3 % DEA								
Product Category	**Scenario**	**Exposure duration Refinement Factor**	**RCR long-term inhalation raw**	**RCR long-term inhalation adjusted for exposure duration**	**RCR long-term dermal**	**RCR long-term oral**	**RCR long-term combined**	**Safe Concen-tration in % if < 0.3 %**
PC3 - Air care products	solid & liquid	1.5	6.50E-01	4.33E-01	1.25E-01		**0.56**	
	aerosol spray (non-volatile)	1.5	1.43E+01	9.50E+00	6.50E-02		**9.57**	**0.03**
PC13 - Fuels	filling a diesel tank	4.5			2.38E-01		**0.24**	
PC31 - Polishes	floor-polish-liquid-application	2	2.50E-03	1.25E-03	1.40E+00		**1.40**	**0.21**
	floor-polish-spray (non-volatile)	2	2.50E+00	1.25E+00	1.25E-01		**1.38**	**0.21**
	furniture-polish-spray	1.5	1.18E+01	7.83E+00	4.60E-01		**8.29**	**0.03**
	furniture-polish-liquid	1.5			1.40E+00		**1.40**	**0.21**
	shoe-polish-spray	1.5	5.75E-01	3.83E-01	7.00E+00		**7.38**	**0.04**
PC35 - Washing/ Cleaning Products	machine-washing-powder (mixing/loading)	4.5	4.75E-04	1.06E-04	1.75E-03		**0.00**	
	machine-washing-powder hanging	1.5	3.00E-06	2.00E-06	1.75E-02		**0.02**	
	machine-washing-powder postapplication				1.50E-01		**0.15**	
	machine-washing-liquid-hanging	1.5	3.00E-06	2.00E-06	1.75E-02		**0.02**	
	machine-washing-liquid-mixing loading (cap)	4.5	1.88E-06	4.17E-07	1.35E+00		**1.35**	**0.22**
	machine-washing-liquid-mixing loading (direct)	4.5	1.88E-06	4.17E-07	2.50E-02		**0.03**	
	machine-washing-liquid-postapplication				1.50E-01		**0.15**	
	hand-washing-powder application	4.5	4.75E-07	1.06E-07	4.85E-01		**0.49**	
	hand-washing-powder hanging cloth	1.5	3.50E-05	2.33E-05	2.00E-01		**0.20**	
	hand-washing-powder mixing/loading	4.5	4.75E-04	1.06E-04	1.75E-03		**0.00**	
	hand-washing-liquid application	4.5	1.38E-08	3.06E-09	4.85E-01		**0.49**	
	hand-washing-liquid hanging	1.5	3,50E-05	2.33E-05	2.00E-01		**0.20**	
	hand-washing-liquid mixing-loading - pouring with cap	4.5	1,88E-06	4.17E-07	1.30E+00		**1.30**	**0.23**
	hand-washing-liquid mixing loading - direct pouring	4.5	1.88E-06	4.17E-07	2.50E-02		**0.03**	
	hand-washing-liquid postapplication				1.75E+00		**1.75**	**0.17**
	all-purpose cleaner - liquid -mixing/loading	4.5	4.50E-07	1.00E-07	2.50E-02		**0.03**	

RISK CHARACTERISATION RATIOS FOR LONG-TERM EFFECTS FROM USE OF CONSUMER MIXTURES CONTAINING 0.3 % DEA								
Product Category	**Scenario**	**Exposure duration Refinement Factor**	**RCR long-term inhalation raw**	**RCR long-term inhalation adjusted for exposure duration**	**RCR long-term dermal**	**RCR long-term oral**	**RCR long-term combined**	**Safe Concen-tration in % if < 0.3 %**
	all-purpose cleaner - liquid –application	1.5	5.00E-05	3.33E-05	7.00E-01		**0.70**	
	all-purpose cleaner - liquid - rubbing off				7.50E-02		**0.08**	
	all-purpose cleaner - spray - rinsing				8.00E-01		**0.80**	
	all-purpose cleaner - spray-non-volatile	3	2.23E-01	7.42E-02	5.50E-02		**0.13**	
	bathroom cleaner liquid application	3	2,38E-05	7.92E-06	7.50E-01		**0.75**	
	bathroom cleaner liquid mixing loading	4.5	7.50E-07	1.67E-07	2.50E-02		**0.03**	
	bathroom cleaner spray application	3	8.25E-01	2.75E-01	3.05E-01		**0.58**	
	bathroom cleaner spray rinsing				1.55E+00		**1.55**	**0.19**
	toilet cleaner acid application	4.5	1.00E-04	2.22E-05	9.50E-01		**0.95**	
	toilet cleaner bleach application	4.5	1,00E-04	2.22E-05	9.50E-01		**0.95**	
	dish washing machine liquid mixing loading	4.5	1.25E-06	2.78E-07	2.50E-02		**0.03**	
	dish washing machine liquid rinse aid mixing loading	4.5	7,50E-07	1.67E-07	2.50E-02		**0.03**	
	dish washing machine liquid rinse aid post application					9.73E-03	**0.01**	
	dish washing machine powder mixing loading	4.5	1,88E-04	4.17E-05	1.75E-03		**0.00**	
	dish washing manual application	3	6,75E-08	2.25E-08	9.00E-02		**0.09**	
	dish washing manual post application					1.86E-03	**0.00**	
	floor liquid cleaning mixing loading	4.5	7.50E-07	1.67E-07	2.50E-02		**0.03**	
	floor liquid cleaner application	1.5	6,00E-05	4.00E-05	9.00E-01		**0.90**	
	floor liquid cleaner postapplication				1.20E-02		**0.01**	
	glass cleaning - spray cleaning	1.5			1.90E+00		**1.90**	**0.15**
	glass cleaning spray spraying	1.5	5.75E-02	3.83E-02	7.00E-02		**0.11**	
	liquid-carpet-cleaning-manual application	1.5	2.20E-04	1.47E-04	3.75E+00		**3.75**	**0.08**
	liquid-carpet-cleaning-manual mixing loading	4.5	6.25E-07	1.39E-07	2.50E-02		**0.03**	
	liquid-carpet-cleaning postapplication				2.80E-01		**0.28**	

Table 33

RISK CHARACTERISATION RATIOS FOR SUBACUTE EFFECTS FROM INFREQUENT USE OF CONSUMER MIXTURES CONTAINING 0.3 % DEA					
Product Category	**Scenario**	**RCR sub-acute systemic effects inhalation**	**RCR sub-acute systemic effects dermal**	**RCR sub-acute systemic effects combined**	**Safe Concen-tration in %, if < 0.3 %**
PC9a – Paints	high solid paint	2.1E-03	0.20	0.20	
	solvent rich paint	1.2E-03	0.20	0.20	
	waterborne wall paint	5.3E-04	0.20	0.20	
	waterborne paint	1.8E-04	0.20	0.20	
	spray can	2.9E+00	0.08	3.02	0.10
PC9b - Cement	application		0.33	0.33	
PC31 - Polishes	shoe-polish-cream	6.0E-05	0.07	0.07	
PC35 - Washing/ Cleaning Products	metal-cleaning-naphta-application	2.7E-05	0.07	0.07	
	metal-cleaning-water application	1.5E-05	0.06	0.06	

7.13.2.3 Risk Characterisation for DEA in consumer articles made from textile, leather and paper

The exposure estimates based on information provided by the lead registrant on DEA in consumer articles made from leather and paper are compared to the long-term DNELs for the general population as described above. All combined RCRs are < 1. More details on these assessments are included in a confidential annex to the substance evaluation report.

The exposure estimates for dermal exposure to textiles based on measured data from an Industry Association presented in Table 31 are compared to the **$DNEL_{LT\text{-}systemic\ effects\text{-}dermal}$ of 0.02 mg/kg bw/d** as described above. All RCRs are < 1 (not shown).

No indication on unacceptable health risks from consumer exposure to DEA in consumer textiles, leather or paper articles has been found.

7.13.2.4 Risk characterisation for consumer exposure to NDELA

No information could be gathered on the NDELA contents in mixtures for consumer use.

In response to the information requirements by ECHA, the lead registrant provided information for NDELA in consumer articles made from textile, leather and paper. Based on this information, the eMSCA performed exposure estimations and risk characterisations where the **dermal exposure estimate** is compared to the **$DMEL_{dermal}$ of 1.78E-6 mg/kg bw/d,** the **oral exposure exstimate** is compared to the **$DMEL_{oral}$ of 1.78E-6 mg/kg bw/d** and the **inhalation exposure estimate** was compared to the **$DMEL_{inhalation}$ of 3.08E-6 mg/m³.** This results in RCRs below 1 for most product subcategories preinstalled in ECETOCTRA 3.1. Only for diapers a slightly elevated RCR is calculated (see confidential annex) corresponding to a lifetime cancer risk of 1: 10^6. However, there is high uncertainty in the database for the exposure calculation (see there), and the assessment does not account for the fact that diapers are only used for few years in lifetime. More details can be found in the confidential annex.

Consumer risks derived from degradation of DEA to NDELA in consumer mixtures remain unknown.

Considering the uncertainty of the exposure database, no clear indication of unacceptable health risks from consumer exposure to NDELA in consumer textiles, leather or paper articles has been found.

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7.15 Abbreviations

ABS	Absorption
AC	Article Category
AF	Assessment Factor
AGW	Arbeitsplatzgrenzwert (Occupational Limit Value)
AISE	International Association for Soaps, Detergents and Maintenance Products
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ART	Advanced REACH Tool
AST	Aspartate Transaminase
ASTM	American Society for Testing and Materials
ATE	Acute Toxicity Estimate
BASO	Basophils
bw	body weight
CLH	Harmonised Classification and Labelling
CLP	Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures
CMR	Carcinogenic, Mutagenic or Reprotoxic
CoRAP	Community Rolling Action Plan
Crl:WI(Han)	Wistar Han IGS (Interational Genetic Standard) Rats
CSR	Chemical Safety Report
DEA	2,2'-iminodiethanol (CAS 111-42-2/EC 203-868-0)
DHHS	Department of Health and Human Services
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
eMSCA	evaluating Member State Competent Authority
EOGRT(S)	Extended One-Generation Reproductive Toxicity (Study) (OECD TG 443)
ESTP	European Society of Toxicologic Pathology
GD	Gestation Day
GIFAS	Giftinformations- und Archivierungssystem (Poison Information and Archiving System)
GLP	Good Laboratory Practice
HCT	Hematocrit
HGB	Hemoglobin
IARC	International Agency for Research on Cancer
KFDA	Korean Food & Drug Administration
LC	Lethal Concentration
LD	Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
LOQ	Limit of Quantification
MCH	Mean Cellular Hemoglobin
MCV	Mean Corpuscular Volume
MMAD	Mass Median Aerodynamic Diameter
MONO(A)	Monocytes (absolute)
NDELA	2,2'-(nitrosoimino)bisethanol (CAS 1116-54-7/EC 214-237-4)
NOAEC	No Observed Adverse Effect Concentration

NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PAF	Platelet Activating Factor
PC	Product Category
PND	Postnatal Day
POD	Point of Departure
PROC	Process Category
PU	Polyurethane
RBC	Red Blood Cells
RCR	Risk Characterization Ratio
RDT	Repeated Dose Toxicity
REACH	Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals
SCED	Specific Consumer Exposure Determinant
SPIN	Substances in Preparations in Nordic Countries
STOT (RE)	Single Target Organ Toxicity (Repeated Exposure)
SVHC	Substance of Very High Concern
TEA	Triethanolamine
TG	Test Guideline
TL	Testing Laboratory