Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	N,N-diethylhydroxylamine
EC Number:	223-055-4
CAS Number:	3710-84-7
Authority:	Swedish Chemicals Agency
Date:	20/03/2018

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCE

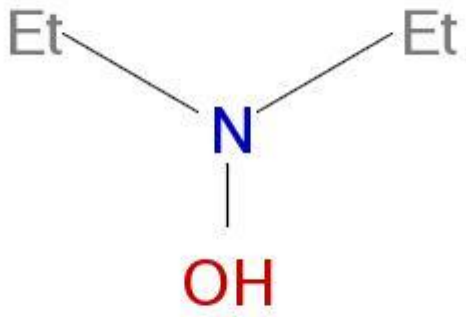
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	N,N-diethylhydroxylamine
IUPAC name (public):	N-ethyl-N-hydroxyethanamine
Index number in Annex VI of the CLP Regulation:	*NA*
Molecular formula:	C4H11NO
Molecular weight or molecular weight range:	89.136
Synonyms:	DEHA

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

Structural formula:



2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restric -tion	☐ Annex XVII[1]
Harmonised C&L	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	☐ Dangerous substances Directive Directive 67/548/EEC (NONS)	
	☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment	
	☐ In relevant Annex	
Other processes / EU legislation	☐ Other (provide further details below)	

[1] Please specify the relevant entry.

Further details	

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

NA

3.1.2 Self classification

- In the registration:

  Flam. Liq.3; H226: Flammable liquid and vapour.

  Acute Tox. 4; H312: Harmful in contact with skin.

  Acute Tox. 4; H332: Harmful if inhaled.

  STOT SE 3; H335: May cause respiratory irritation.

  Aquatic Chronic 2; H411: Toxic to aquatic life with long lasting effects.

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

  Acute Tox. 4; H302: Harmful if swallowed.

  Skin Irrit. 2; H315: Causes skin irritation.

  Eye Irrit. 2; H319: Causes serious eye irritation.

  STOT SE 2; H371: May cause damage to organs.

  Muta. 2; H341: Suspected of causing genetic defects. (1 out of 391 notifiers)

  Skin Corr. 1C; H314: Causes severe skin burns and eye damage.

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

None.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[2]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
Joint submission. Four active registrants.		

***the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11):

https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

[2] Dissemination site accessed on 11 August 2017.

4.2 Overview of uses

Table: Uses

Part 1:

☒ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☐ Consumer use	☐ Article service life	☐ Closed system

Part 2:

	Use(s)
Uses as intermediate	-
Formulation	• Formulation into mixture
Uses at industrial sites	• Colour stabilizer for chemical products (fuel, resins etc.) and for de-colourisation of phenols • Polymer processing • Use as processing aid
Uses by professional workers	• Colour stabilizer (film/photographic industry) • Use in coating
Consumer Uses	-
Article service life	-

Part 3: There is high potential for exposure of

☒ Humans	☒ Environment

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☒ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☒ C ☒ M ☐ R	☐ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[3]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☐ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☐ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[3] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

In vitro genotoxicity studies

Three key experimental studies are reported under the *in vitro* genotoxicity section of the registration dossier(s) – Ames test, chromosome aberration and gene mutation study in mammalian cells.

The key Ames test (2001) was according to the OECD 471 and GLP, with the assigned reliability score of 1. Five strains were used (TA 1535, TA 1537, TA 98, TA 100, TA 102), with and without S9-mix at 5 concentrations up to 5000 µg. Positive and negative (vehicle - distilled water) controls were included. The results were reported as negative.

The key chromosome aberration study in mammalian cells was according to the OECD 473 and GLP, with assigned reliability score of 1. Human lymphocytes were treated with and without S9-mix up to 5000 µg/ml. Positive and negative (only vehicle) controls were included. The results were reported as positive without metabolic activation and negative with metabolic activation.

The key gene mutation study in mammalian cells was according to OECD 476 and GLP, with assigned reliability score of 1. Mouse lymphoma L5178Y cells were treated with and without S9-mix up to 5000 µg/ml. Positive and negative (only vehicle) controls were included. The results were reported as positive without metabolic activation and negative with metabolic activation.

Another gene mutation study in mammalian cells was reported as a supporting study with assigned reliability score of 2. The test was performed in Chinese hamster lung fibroblasts (V79) and only without S9-mx. The results were reported as negative. An unscheduled DNA synthesis test in human lymphocytes with assigned reliability score of 3 is also reported. Furthermore, five bacterial reverse mutation assays, all with assigned reliability score of 3, performed with N,N-diethylhydroxylamine (DEHA) or the urine of animals exposed to DEHA are also reported.

In vivo genotoxicity studies

Two key experimental studies are reported under the *in vivo* genotoxicity section of the registration dossier(s) – a mammalian erythrocyte micronucleus test and an unscheduled DNA synthesis test.

The key mammalian erythrocyte micronucleus test was according to OECD 474 and GLP, with assigned reliability score of 1. Male and female ICR mice (5/sex/dose) were given DEHA by a single gavage administration of 375, 750 or 1500 mg/kg. Positive and negative (vehicle – distilled water) controls were included. Mortalities were observed in both males and females of the high dose group. The results were reported as negative.

The key unscheduled DNA synthesis test was according to the OECD 486 and GLP, with assigned reliability score of 1. Male Wistar rats (4/dose) were given DEHA by single gavage administration of 800 or 2000 mg/kg. Positive and negative (vehicle – purified water) controls were included. The results were reported as negative.

Two dominant lethal tests (one ambiguous and the other negative), one micronucleus test (negative), and one drosophila sex-linked recessive lethal test (weakly positive), all with assigned reliability score of 3 are also reported in the registration dossier(s).

Carcinogenicity studies

Two carcinogenicity studies (duration: 2 years) via inhalation route, one each in mice and rats, with assigned reliability score of 4 are reported in the registration dossier(s). In the mice study, "The incidence of all tumors, as well as subcutaneous tumors (principally fibrosarcomas), increased in exposed males with marginal significance". In the rats study, "Thyroid lesions were seen in the exposed animals after 6 months exposure, but not in animals exposed 9 months or longer. Examinations for animals exposed more than 1 year indicat[e]d no significant differences between the control and test groups, except for interstitial cell tumors of the testes which showed up in 4 of the 47 exposed males that were examined compared to 0 in the 25 control males". Another study (duration: 16 weeks) with assigned reliability score of 3 is also reported in which the effect of DEHA (via drinking water) on the incidence of tumors induced by benzo(a)pyrene in mice were studied. "Gross lesions were observed only in the lungs and squamous portion of the stomach. Treatment with DEHA produced no significant effect on the lung tumor incidence of either sex. However, a significant increase in stomach tumors was observed in the females". <u>Concerns</u> Given the positive and/or ambiguous results in the genotoxicity and carcinogenicity studies with DEHA, an in-depth evaluation of the available studies in regard to their reliability and interpretation of the results is needed.

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☐ Information ED potential	☐ Other (provide further details below)
Subject to the outcome of the evaluation of the reliability of the available genotoxicity and carcinogenicity studies in the registration dossier(s) and other relevant available information, further studies on these endpoints may need to be requested.	

5.5. Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)
If the substance fulfills the criteria given in the CLP Regulation, a harmonised C&L proposal will follow.			