SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

CYCLOHEXYLAMINE

EC No 203-629-0

CAS No 108-91-8

Evaluating Member State(s): Belgium

Dated: 20 September 2017

Template Version 2.1
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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2016

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

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

DISCLAIMER

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

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

- Toxicity for reproduction
- Exposure of environment
- High aggregated tonnage

During the evaluation no other concerns were identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

NA

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	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

NA

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

NA

4.1.3. Restriction

NA

4.1.4. Other EU-wide regulatory risk management measures

NA

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

After evaluation of all available information, no concern was identified for reproductive toxicity justifying the request for further information under the substance evaluation process or regulatory action, despite the fact that the registration dossier only contained an old 6-generation study of which the eMSCA couldn't clearly identify the reliability compared to the EORGTS endpoints.

Indeed, based on the currently available information the substance has a harmonized classification as Repr. Cat. 2, H361f, and since then no new data have become available. The substance is only used in industrial settings and is also classified as Skin Corrosive 1B, H314. In addition to this, the substance has a fishy odour, so exposure to the substance at the workplace will not be unremarked and protective measures can be expected to be in place.

Based on all this information taken together in a weight of evidence approach, the eMSCA concludes that despite the questions that can be raised about the reliability of the available long term reproductive toxicity test, currently there is no concern that arises from the uses of the substance as explained above that would merit further action.

5.2. Other actions

N/A

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

N/A

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

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

- Toxicity for reproduction : Classified as Repr. Category 2, H361f, but there is limited information on the studies. Some further information would be needed to clarify the concern and to check whether the classification is appropriate.

- Exposure of environment

- High aggregated tonnage

During the evaluation also other concern[s] was/were identified. The additional concern[s] was/were:

NA

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Reprotoxicity	Concern not substantiated. No further action
Exposure of environment/high aggregated tonnage	Concern not substantiated. No further action.

7.2. Procedure

- 22 March 2016: the evaluation officially started
- 4 April 2016: the registrant was contacted and full study reports were requested.
- 18 April 2016: most full study reports were received
- 12 May 2016: the lead registrant announced initiation of transfer of the Lead role to a member of the SIEF
- 24 September 2016: the new lead registrant officially accepted this role.
- 7 October 2016: the new lead registrant was contacted to ask additional information regarding the environmental part
- 20 October 2016: the additional information was partially received and some follow-up questions were raised.
- 30 November 2016: the **new** lead registrant announces his plan to update the dossier.
- March 2017 eMSCA concludes that there is no need for a draft decision to clarify the initial reprotoxicity concern.
- End of May 2017 eMSCA considered the updated dossier concerning exposure data and took this into account in this evaluation report.

The available data were evaluated for human health and environment. After evaluation, there was no remaining concern.

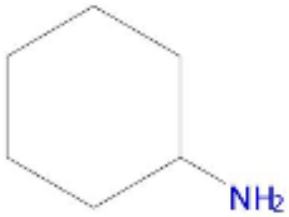
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Cyclohexylamine
EC number:	203-629-0
CAS number:	108-91-8
Index number in Annex VI of the CLP Regulation:	612-050-00-6
Molecular formula:	C6H13N
Molecular weight range:	99.1741
Synonyms:	1-aminocyclohexan Aminohexahydrobenzol CHA Cyclohexanamin Cyclohexylamin Hexahydroanilin

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

Structural formula:



The following two substances were also used in several human health tests. In aqueous medium, it can be expected that both salts will dissociate easily to result in the protonated form of cyclohexylamine and the negative ions of two strong acids (resp. HSO_4^- and CL^-). This read-across is plausible.

SUBSTANCE IDENTITY	
Public name:	Cyclohexylamine sulfate
EC number:	-
CAS number:	27817-50-1
Index number in Annex VI of the CLP Regulation:	-

Molecular formula:	C6H15NO4S
Molecular weight range:	197.2526
Synonyms:	

SUBSTANCE IDENTITY	
Public name:	Cyclohexylammonium chloride
EC number:	225-661-4
CAS number:	4998-76-9
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C6H14ClN
Molecular weight range:	135.64
Synonyms:	Cyclohexanamine hydrochloride cyclohexanaminium chloride Cyclohexylamine Hydrochloride

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid with a strong, fishy, amine-like odor
Vapour pressure	**Number of data from peer-reviewed handbooks:** 1.028 kPa at 25° (estimated by calculation, purity unknown) 1.4 kPa at 20°C (experimental result, purity unknown) 1.283 kPa at 25°C (estimated by calculation, purity unknown) 1.261 kPA at 25°C (experimental result, purity unknown) **1.43kPa at 20°C (experimental result, purity unknown), used for CSR** 1.340 at 25°C (estimated by calculation, purity unknown) Epi Suite v.4.11 estimation: 1.346 kPa at 25°C
Water solubility	**Number of data from peer-reviewed handbooks**: - 1000 g/L at 20°C (estimated by calculation, study report)

	- **Completely miscible with water at 20°C, pH not specified (experimental result, study report, purity >98%), used for CSR** - Miscible (experimental results, purity unknown) Epi Suite v.4.11. estimation: 61040 mg/L at 25°C (from LogKow) (WSKOW v1.42)
Partition coefficient n-octanol/water (Log Kow)	**Key study** (experimental result, according to OECD TG 117 HPLC method): - **log Pow 3,7 at 25°C (purity unknown), used for CSR** **Number of data from peer-reviewed handbooks**: - log Pow 1.49 at 25°C, pH not specified (experimental result, purity unknown) - Log Pow: 1,49, pH and temp. not reported (experimental result, purity unknown) log Pow 1.4, pH and temp. not specified (experimental result, purity unknown) - log Pow 1.63 (estimated by calculation, study report, calculation by KOWWIN v1.67) - log Pow 1.49, pH=13, temp. not reported (estimated by calculation, purity unknown) Epi Suite v. 4.11 estimation: log Pow = 1.63 (KOWIN v1.68)
Flammability	Flammable
Flash point	**Number of data from peer-reviewed handbooks**: - 26.5°, pressure not reported (experimental result, purity unknown) **- 28°C at 101.325 kPa in closed cup (experimental result, purity unknown), used for CSR (flammable liquid)**
Explosive properties	Justified data waiving based on the chemical structure of the substance: lack of a chemical moiety suggesting potential for explosivity (Column 2 of Annex VII of REACH Regulation).
Oxidising properties	Justified data waiving based on chemical structure of the substance: lack of a chemical moiety suggesting oxidising potential. (Column 2 of Annex VII of REACH Regulation).
Granulometry	Justified data waiving with accordance to Column 2 of Annex VII, REACH Regulation.
Stability in organic solvents and identity of relevant degradation products	**Peer-reviewed handbook data:** The substance is unstable, as it is capable to react with ketones (like acetone) or aldehydes (like formaldehyde) (experimental result, purity unknown).

Dissociation constant	**Number of data from peer-reviewed handbooks:** pKa: 10.7, temp. not reported (experimental result, purity unknown) pKa:10.66 temp.: 24°C (experimental result, purity unknown) pKa: 10.67, temp. not reported (experimental result, purity unknown) pKa:10.64 at 25°C (experimental result, purity unknown) **pKa:10.68, temp.: 25°C (experimental result, purity unknown)**

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

This aggregated tonnage includes also the tonnages for the intermediate uses. Non-intemediate tonnage is in the range of 100-1000 t/a.

7.5.2. Overview of uses

Table 7

USES	Use(s)
Uses as intermediate	NA
Formulation	Use for formulation of preparations : industrial (PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 15)
Uses at industrial sites	Use as laboratory chemical, as intermediate in chemical synthesis, as corrosion inhibitor, use of formulations containing the substance as cutting oil and as water treatment chemical (PROC 1, 2, 3, 4, 8a, 8b, 9, 15, 17, 18, 21, 24)
Uses by professional workers	Use of formulations containing the substance as water treatment and as cutting oil, use as laboratory chemical (PROC 1, 2, 3, 8b, 9, 17, 18, 20, 21, 24)
Consumer Uses	NA
Article service life	NA

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 No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
612-050-00-6	Cyclohexylamine	203-629-0	108-91-8	Flam. Liq. 3 Acute Tox. 4* Acute Tox. 4* Skin Corr. 1B Repr. 2	H226 H302 H312 H314 H361f		

7.6.2. Self-classification

- In the registration(s) (as verified on 9th Augustus 2016)*:*

Acute Tox. 3; H301

Acute Tox. 3; H 311

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (as verified on 9th Augustus 2016):

Skin Irrit. 2; H315

Eye Damage 1; H318

STOT SE 3 (central nervous system); H336

Aquatic chronic 3; H412

Met. Corr. 1; H290

Flam. Liq. 2; H225

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Photo-degradation in air

The photo-degradation in air was estimated using AOP Program v1.91 of EPi-suite software. According to the calculations a half-life of 6.95h for the neutral form and 11.2h for the protonated form can be expected (Registration dossier: study report 2006).

A calculation with the atmospheric Oxidation Program v 1.83 led to a half-life of 4.6h.

Although the half-life seems to be in the order of hours, photo-transformation in air is not expected to be a major degradation route in view of the relatively low vapour pressure and Henry value of the substance.

7.7.1.2. Hydrolysis

Hydrolysis is considered not relevant since the substance is readily biodegradable.

The eMSCA supports this conclusion.

7.7.1.3. Biodegradation in water

In a test according to EU method C.4-E (Closed bottle test) (Registration dossier: study report, 1976), 75% degradation was seen after 10 days and 92% within 20 days. It can therefore be concluded that the substance is readily biodegradable.

The eMSCA agrees with this conclusion.

7.7.2. Environmental distribution

In an adsorption/desorption study according to OECD Guideline 121 (Registration dossier: study report 2010), a Log Koc value of 3.4 was determined at 25°C and at a pH of 6.7.

Based on model calculations (Mackay level I, v.2.11) performed by the registrant, the neutral form of the substance will mainly partition to water (95.16%). Only smaller amounts of the substance are expected to partition to air (4.37%) , soil (0.23%) and sediment (0.24%). For the protonated form, the calculated distribution was 100% distribution to water.

Based on the dissociation constant of around 10.68 (Registration dossier: study report 1965), the substance will under environmental relevant conditions (pH 4 to 9)), be present solely in the protonated form.

The eMSCA performed a MacKay level III fugacity estimation (Episuite 4.1), with a water solubilty of 1000 g/l, a vapour pressure of 10.5 mmg Hg and a log Kow of 3.7. In this estimation 66.1% partitioned to soil and 33.2% to water. Smaller amounts partitioned to air (0.6%) and sediment (0.1%).

The Mackay level I fugacity model does not take transformation (eg. Photolysis, biodegradation) and active transport into account (closed system in equilibrium). The level III model however does and seems to be a more realistic estimation of the environmental fate of the substance (open system in steady state).

Based on the available data, the eMSCA concludes that the substance will mainly partition to soil and water.

7.7.3. Bioaccumulation

The registrant reported a measured log Kow value of 3.7 (pH of 6.8) via HPLC method (Registration dossier: study report, 2010). In a supporting study (KOWWIN estimation) a value of 1.63 for the neutral form and -1.55 for the protonated form are reported.

The eMSCA concludes that cyclohexylamine shows some potential to bioaccumulate (based on the measured Log Kow of 3.7). No definite bioaccumulation study is available. Since there is no PBT/vPvB concern, no further testing is required.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Short term

In a 14 day prolonged fish toxicity study (Registration dossier: review article or handbook 1997) with *Oryzias Latipes* (OECD 204) an LC50 of 19 mg/L in unbuffered media was found. The pH in the unbuffered medium significantly increased reaching a pH of 9.5. In a buffered medium no fatalities were recorded up to a concentration of 100 mg/L.

It is stated in OECD guideline 204 that the pH of the media should preferably be between 6.0 and 8.5. If the pH in the unbuffered media increases above 8.5, it can be assumed that the adverse effects seen are mainly due to the increase in pH. These high pH values however don't reflect relevant enviromental conditions.

In a 96h acute fish toxicity study (Registration dossier: review article or handbook 1997) (OECD 203) with Oryzias latipes an LC50 of 33 mg/L was established in an unbuffered medium. Again in a buffered medium no mortalities were seen at the highest concentration of the substance of 100mg/L.

Other supporting acute fish tests were presented by the registrant(s) providing LC50 values >54 mg/L. These tests were not considered because of insufficient test duration and/or other methodological deficiencies.

The eMSCA accepts that the LC50 value of 19 mg/L presents a worst case value.

Long term:

No data available.

7.8.1.2. Aquatic invertebrates

Short term:

In an OECD 202 (Daphnia acute immobilisation) test (registration dossier : review article or handbook 1997) a 48h EC50 of 36.3 mg/L was determined. The medium in the test was not adjusted for pH increases. It is possible that the effects seen are based on the pH increases rather than on the toxicity of the substance itself and therefore, this result can be considered as worst case.

Long term

In a OECD 211 (Daphnia magna reproduction) test (Registration dossier : review article or handbook 1997) a 21d NOEC of 1.6 mg/L was determined, based on effects on reproduction. The pH of the test medium remained within the range of 6 to 9 as the test method prescribes, except for the highest concentration tested (30,3 mg/l). This tested concentration slightly exceeded the pH range of the test with a pH of 9.1. This sample was excluded from the evaluation because 60% of the parental daphnia died after the test duration of 21 days.

The eMSCA accepts the established NOEC of 1.6 mg/L as being a worst case value.

7.8.1.3. Algae and aquatic plants

The effects on aquatic plants and algae were tested according to OECD 201 (Registration dossier : review article or handbook 1997): Alga, growth inhibition test. The 72h EC50 was 29.3 mg/L based on growth rate. The 72h NOEC was 10.3 mg/L. The test medium was not

adjusted for pH and the pH values increased with increasing substance concentration. It is possible that the effects seen are caused by the increase in pH rather than the toxicity of the substance itself.

The eMSCA accepts that the established NOEC of 10.3 mg/L presenst a worst case value.

7.8.1.4. Sediment organisms

No data available. The equilibrium partitioning method (EPM) is applied for PNEC derivation (see section 7.8.4).

7.8.2. Terrestrial compartment

No data available. The equilibrium partitioning method (EPM) is applied for PNEC derivation (see section 7.8.4).

7.8.3. Microbiological activity in sewage treatment systems

Several non-guideline tests based on single species of microorganisms are included in the registration dossier. Generally, tests for the assessment of toxicity to microorganisms in sewage treatment plants are performed using inocula with multiple species of microorganisms. Therefore only those tests with multiple species were considered.

In an activated sludge ISO 8192 test (Registration dossier: study report 1990) for inhibition of oxygen consumption by activated sludge, a 3h EC50 of 2152 mg/L and a 3h EC10 of 326 mg/L were determined.

7.8.4. PNEC derivation and other hazard conclusions

Table 9

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC Aqua (freshwater) 0.016 mg/L	Assessment factor: 100 Based on the NOEC for Daphnia of 1.6 mg/L. An assessment factor of 100 was used because 2 long term results from species representing different trophic levels are available, but not fro the most sensitive species (fish).
Marine water	PNEC Aqua (marine) 0.0016 mg/L	Assessment factor: 1000 Based on NOEC for fresh water
Intermittent releases to water	PNEC Aqua (intermitted release) 0.19 mg/L	Assessment factor: 100 Based on the most sensitive species fish EC50 of 19 mg/L
Sediments (freshwater)	PNEC sediment (freshwater): 4.1 mg/kg sediment dw	Equilibrium partitioning (TGD EU, 2003). A Koc of 2512, and PNEC aqua of 0.016 mg/L
Sediments (marine water)	PNEC sediment (marine): 0.41 mg/kg sediment ww	Equilibrium partitioning (TGD EU, 2003). A Koc of 2512,

		Henrys Law constant of 0.42 Pa m3/mole and PNEC aqua of 0.0016 mg/L
Sewage treatment plant	PNEC STP: 21.5 mg/L	Assessment factor 100 Based on EC50 of 2153 mg/L
Soil	PNEC soil: 0.805 mg/kg dw	Equilibrium partitioning (TGD EU, 2003) using a Koc of 2512, Henrys Law constant of 0.42 Pa m3/mole and PNEC aqua of 0.016 mg/L

7.8.5. Conclusions for classification and labelling

The chronic aquatic toxicity results are above 1 mg/L, the substance is readily biodegradable and has a log Kow below 4.

Therefore, the eMSCA concludes that based on the available information there is no classification needed for environmental hazards.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Table 10 : Summary of toxicokinetic informations

Method	Results	Rel.	Reference
In vitro Rabbit liver microsomes Test substance (CAS number) : 108-91-8	Major metabolic route : deamination (in presence of NADPH and oxygen by liver microsomes) Cyclohexylamine is also metabolized to N-hydroxylated cyclohexylamine		Kurebayashi H. *et al.* (1979)
In vivo Human Doses : 2.5, 5, 10 mg/kg bw Oral Test material (CAS number): 108-91-8	Absorption : almost complete enteral absorption Excretion : 86-95% of the doses were excreted in urine during 48h as unchanged compound Half life in plasma : 3.5-4.8h	2	Eichelbaum M. *et al.* (1974)
In vivo Rat (4/group) Exposure : once, IV Test material (CAS number): 108-91-8	Distribution : penetrates membrane barriers 92% distributed in tissue : GI tract>liver>lungs>tail wash>testes>brain>spleen>muscle>heart >kidney. And 8% bound to plasma proteins 49% of the dose detected in carcass	2	Air prods & Chem Inc (1987)
In vivo Rats (Wistar), rabbits (New Zealand White), guinea pigs (Duncan-Hartley) (oral and Ip) : 50, 500 mg/kg bw Human (oral) : 25,	Absorption : total recovery : 92-94% (rat), 94% (rabbit), 98-100% (guinea pig), 95% (man) Excretion : mainly in urine and largely unchanged (4-5% metabolites for rat and guinea pig, 1-2% for man vs 30% for rabbit) Metabolism : in rat 5 major metabolites	2	Renwick A.G. And Williams R.T. (1972)

200 mg/person Test substance (CAS number): 4998-76-9	(cyclohexanol, trans-3-, cis-4-, trans-4-4 and cis-3-aminocyclohexanol) In rabbit 8 metabolites (cyclohexanol, trans-cyclohexan-1,2-diol, cyclohexanone, cyclohexylhydroxylamine, trans-3-, cis-3-, trans-4- and cis-4-aminocyclohexanol) In guinea pig 6 minor metabolites (cyclohexanol, trans-cyclohexane-1,2-diol, trans-3-, cis-3-, trans-4- and cis-4-aminocyclohexanol) In man 2 metabolites (cyclohexanol and trans-cyclohexane-1,2-diol)		
In vivo IV to 2 pregnant monkeys Doses : 50 µCi Exposure : 180min Test material (CAS number): 4998-76-9	Distribution : levels of radioactivity in dams and foetuses relatively identical (then freely diffuse the primate placenta)	2	Pitkin R.M. *et al.* (1969)
In vivo Male Mouse (3/group) (IP, SC and oral) Doses (once) : ip : 35 mg/kg bw, oral : 35, 200 and 500 mg/kg bw and sc : 35 mg/kg bw Test substance (CAS number): 4998-76-9	Metabolite : 95-96% unchanged cyclohexylamine, 1-2% 3-aminocyclohexanol or 4-aminocyclohexanol Excretion : 90% in urine within 24h	2	Roberts A. and Renwick A.G. (1985)
In vivo Rabbit (1/sex/dose) Doses : 170 mg/kg bw (once) Feed Test substance (CAS number): 108-91-8	Metabolites : 45% of dose unconjugated cyclohexylamine, 0.2% as N-Hydroxycyclohexylamine in conjugated form Excretion : 68% in urine within 60h	/	Ellio T.H. *et al.* (1968)
In vivo Rat (Wistar and DA) (IP and oral) Doses : male wistar rats : iP : 35 mg/kg bw, oral : 35, 200 and 500 mg/kg bw Female wistar rat : oral : 35 mg/kg bw Male CD rat : oral 200 mg/kg bw Test material (CAS number): 4998-76-9	Excretion : about 80% in urine within 24h (mainly unchanged)	/	Roberts A. and Renwick A.G. (1985)
In vivo 1 Dog (oral and SC) Doses : 80 or 120 mg/kg bw Exposure : 7d Test material (CAS number): 4998-76-9	The organisme catabolise the substance completely (no catabolic products detected in urine)	/	Bernhard K. (1937)

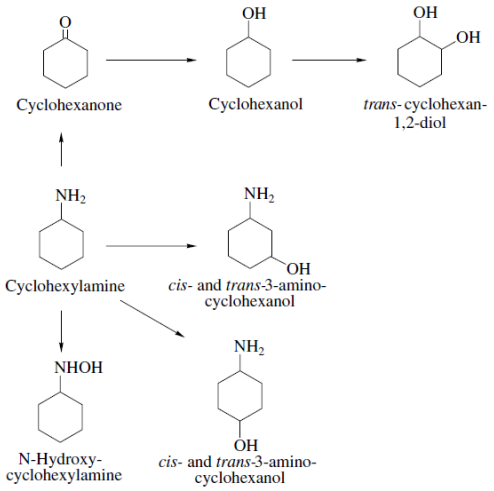
Absorption: Cyclohexylamine is rapidly and completely absorbed in man and animals when it is orally administrated and peak blood or plasma level occurred between 1 and 2 hours. The half life ranged from 3 to 5 hours.

Distribution: In rats the highest concentrations were observed in lungs, spleen, liver, adrenal glands, heart, gastrointestinal tract and kidneys.

Cyclohexylamine diffuses across the placental barrier.

Metabolism : See Figure 1. Metabolism of Cyclohexylamine (Bopp B.A. *et al.* 1986)

Figure 1. Metabolism of Cyclohexylamine (Bopp B.A. *et al.* 1986)



Elimination: approximately 90% of the administered dose of cyclohexylamine is eliminated in the urine.

Difference between species: Cyclohexylamine is absorbed and eliminated more rapidly by mice than by rats.

The eMSCA agrees that cyclohexylamine has no bioaccumulation potential.

7.9.2. Acute toxicity and Corrosion/Irritation

7.9.2.1. Acute toxicity

Oral route :

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

Method	Results	Rel.	Reference
Standard acute method In male rat (Wistar) 15/group By gavage : 25, 50, 100, 250, 300, 350, 500, 600, 750, 1000 mg/kg bw (no control group) No GLP Test material (CAS number) : 108-91-8	Mortality : 0, 0, 0, 0, 2, 4, 9, 13, 15, 15/15 respectively at 25, 50, 100, 250, 300, 350, 500, 600, 750, 1000 mg/kg bw LD50 : 432 mg/kg bw	2	Registration dossier (study report 1968)

Standard acute method In rat (NIA) By gavage : 1-4% aequous solutions (no control group) No GLP Test material (CAS number) : 108-91-8	Mortality : no data available LD50 : 350 ml/kg bw (ca 300 mg/kg bw)	2 in the registration dossier eMSCA supports a reliability of 3 (no data available in the registration dossier)	Registration dossier (study report 1970)
Standard acute method In male rat (Wistar) 15/dose By gavage : 250, 500, 1000, 1500, 2000 and 2500 mg/kg bw (no control group) No information about GLP compliance Test material (CAS number) : 4998-76-9	Mortality : 0, 0, 1, 7, 10, 13/15 respectively at 250, 500, 1000, 1500, 2000, 2500 mg/kg bw LD50 : 1660 mg/kg bw	2	Registration dossier (study report 1968)
In rat Test material (CAS number) : 108-91-8	LD50 : 348 mg/kg bw No more information available	No reliability indicated in the registration dossier eMSCA supports a reliability of 3 (no data available)	Bopp B.A. *et al.* (1986)
Standard acute method In rat (Sprague-Dawley) 5/dose By gavage : 316, 398, 501, 631, 794 mg/kg bw Test material (CAS number) : 108-91-8	Mortality : 0, 1, 1, 3, 5/5 respectively at 316, 398, 501, 631, 794 mg/kg bw LD50 : 590 mg/kg bw	4	Randall D.J. and Bannister R.M. (1990)
Standard acute method In rat (Sprague Dawley) (5/group) By gavage : 7.94, 10.0, 12.6, 15.8 mg/kg bw Test material (CAS number) : 108-91-8	Mortality : 0/5, 2/5, 2/5, 4/5 LD50 : ca 11 mg/kg bw/d	4	Randall D.J. and Bannister R.M. (1990)
Standard acute method In rat (Wistar and Wistar-Imamichi) 10/sex/dose/strain By gavage (no control group) No information available about dose levels Test material (CAS number) : 108-91-8	No information available about mortality LD50 (Wistar males) : 278 mg/kg bw LD50 (Wistar females) : 237 mg/kg bw LD50 (Wistar-Imamichi females non pregnant) : 157 mg/kg bw LD50 (Wistar Imamichi females pregnant) : 180 mg/kg bw	4	Tanaka S. *et al.* (1973)
In mouse Test material (CAS number) : 108-91-8	LD50 : 710 mg/kg bw No more information available	4	Takahashi A. (1976)

Standard acute method In female mouse (Swiss) 10/dose By gavage : 5.0, 6.0, 6.5, 7.5, 10.0 ml/kg bw No GLP Test material (CAS number) : 108-91-8	Mortality : 1, 2, 4, 6 and 8/10 LD50 : 7.3 ml/kg bw	4	Registration dossier (study report 1987)
In rat (Wistar) (5males/group) By gavage (no information about dose levels) Test substance (CAS number) : 108-91-8	No information available about mortality LD50 : 610 mg/kg bw	4	Smyth H.F. *et al.* (1969)
Standard acute method In female mouse (Swiss Webster) 10/group By gavage : trial 1 : 1000, 1500, 2000, 2500 mg/kg bw (no control group) Trial 2 : 250, 350, 500, 750, 850, 1000, 1250 mg/kg bw (no control group) Test material (CAS number) : 27817-50-1	Mortality : trial 1 : 0, 4, 6 and 7/10 Trial 2 : 0, 3, 3, 5, 6, 8 and 9/10 LD50 (trial 1) : 1850 mg/kg bw LD50 (trial 2) : 680 mg/kg bw	4	Registration dossier (study report 1987)
In female mouse (Swiss Webster) 10/dose By gavage : trial 1 : 400, 500, 600, 750, 850, 1250 mg/kg bw Trial 2 : 1000, 2000, 2500, 2750, 3500 mg/kg bw No GLP Test material (CAS number) : 4998-76-9	Mortality : trial 1 : 0, 3, 6, 8, 9, 9 and 10/10 Trial 2 : 0, 1, 2, 7 and 10/10 LD50 (trial 1) : 530 mg/kg bw LD50 (trial 2) : 2750 mg/kg bw	4	Registration dossier (study report 1987)

Three studies of reliability 2 in the registration dossier, performed in rats, showed a LD_{50} of 300 mg/kg bw (Registration dossier: study report 1970), of 432 mg/kg bw (Registration dossier : study report 1968) for the studies performed with cyclohexylamine and of 1660 mg/kg bw (Registration dossier: study report 1968) for the study performed with cyclohexylammonium chloride.

eMSCA comment : the eMSCA does not agree with the reliability of 2 for the study which has a LD50 of 300 mg/kg bw (Registration dossier: study report, 1970). The only information available is the LD50. The eMSCA supports a reliability of 3.

Other studies with minimal description of methods and results (reliability 4) were presented. The calculated LD50 in the study using cyclohexylamine were between 11 and 610 mg/kg bw in rats and a LD50 of 710 mg/kg bw and of 7.3 ml/kg in mice.

Cyclohexylamine has a harmonised classification as **Acute toxicity Category 4* H302 Harmful if swallowed.**

The registrant concludes that the substance is acutely toxic via the oral route and classified, in the registration dossier, the substance as **Acute toxicity Category 3 H301 Toxic if swallowed**.

Based on the available information, the eMSCA concludes that there is no need to request further information under this substance evaluation.

Inhalation route :

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

Method	Results	Rel.	Reference
Standard acute method in rats (10/sex/doses) Doses : 555, 1500 mg/m³ Exposure : 1h Test material (CAS number) : 108-91-8	LC50 : >15 mg/l air No mortality	4	Registration dossier (study report 1966)
Standard acute method in mouse (20), rabbit (3), guinea pig (5) Doses : 555, 1500 mg/m³ Exposure : 1h Test material (CAS number) : 108-91-8	LC50 : >15 mg/l air No mortality	4	Registration dossier (study report 1966)
In rats Doses : up to 11500 mg/m³ Test material (CAS number) : 108-91-8	LC50 : 7500 mg/m³ air	4	Lomonova G.V. (1963)
Standard acute method in rats (20 males/group) Doses : 363 mg/m³ (exposure 1h) 360, 837, 900 mg/m³ (exposure 4h) Exposure : 1h and 4h Test material (CAS number) : 108-91-8	LC50 : >0.363 mg/l air after 1h of exposure LC50 : >900 mg/m³ after 4h of exposure (5mortality at 900 mg : 2/20)	4	Registration dossier (study report 1966)
Standard acute method in rats (10/sex/doses) Doses : 96, 108, 700 mg/m³ Exposure : 4h Test material (CAS number) : 108-91-8	LC50 : >700 mg/m³ 700 mg/m³ : 1 rat died	4	Registration dossier (study report 1966)
Standard acute method in rats Dose : a satisfied vapour atmosphere Exposure : 10min, 30min	Mortality : 0/12 after 10min of exposure and 3/6 after 30min of exposure	4	Registration dossier (study report 1970)

Test material (CAS number) : 108-91-8			
Study in rats and mice Doses : 60mg/l resp 60000 mg/m³ Exposure : 1h Test material (CAS number) : 108-91-8	LC50 : >6000 mg/m³ No mortality	4	Registration dossier (study report 1966)
Standard acute method in rats (6/group) Doses : no information Exposure : 4h Test material (CAS number) : 108-91-8	No mortality at 4ppm All rats died at 8 ppm	4	Smyth H.F. *et al.* (1969)
Study in mouse Doses : 4, 15, 49, 355 ppm Exposure : 50min Test material (CAS number) : 108-91-8	RD50% : 27ppm	4	Nielsen G.D. and Yamagiwa M. (1989)
Study in mice Doses : up to 4300 mg/m³ Exposure : unspecified Test material (CAS number) 108-91-8	LC50 : 1070 mg/m³	4	Lomonova G.V. (1963)
Study in rats Doses : unspecified Exposure : 2h Test material (CAS number) : 108-91-8	50% mortality after 2h	4	Smyth H.F. *et al.* (1969)
No information Test material (CAS number) : 108-91-8	Lethal dose in rabbits, guinea pigs and rats : 4900 mg/m³ air	4	Watrous R.M. and Schulz H.N. (1950)
Study in mouse, rabbit, guinea pig Doses : 98, 108, 700 mg/m³ Exposure : 4h Test material (CAS number) : 108-91-8	LC50 : >700 mg/m³ Mortality 108 mg/m³ 1/10mice and 700mg/m³ 4/5guinea pigs and 1/20mice	4	Registration dossier (study report 1966)
In rat Test material (CAS number) : 108-91-8	LC50 : 1000 (no information about unit)	No reliability indicated in the registration dossier. eMSCA supports a rel. of 4(no information available)	Izmerov *et al.* (1982)

Only studies with minimal description of methods and results (reliability 4) were presented and summarized in a weight of evidence approach.

No effects were seen in these inhalation studies, that would merit the need for further testing.

Dermal route :

Table 13 : Summary table of animal studies on acute dermal toxicity

Method	Results	Rel.	Reference
Standard acute method In male rabbit (New Zealand white) 4/dose (no more information avalaible) Occlusive No GLP Test material (CAS number) : 108-91-8	LD50 : 275 mg/kg bw	4	Smyth H.F. *et al.* (1969)
Standard acute method In rabbit (New Zealand white) 1/dose Doses : 398, 631, 1000 and 1560 mg/kg bw Test material (CAS number) : 108-91-8	Approx. LD50 : >631 - < 1000 mg/kg bw/d	4	Randall D.J. and Bannister R.M. (1990)

Only studies with minimal description of methods and results (reliability 4) were presented.

Cyclohexylamine has a harmonised classification as **Acute toxicity Category 4* H312 Harmful in contact with skin.**

The registrant concludes that the substance is acutely toxic via the oral route and classified, in the registration dossier, the substance as **Acute toxicity Category 3 H311 Toxic in contact with skin**.

Based on the available information, the eMSCA concludes that there is no need to request further information under this substance evaluation.

Other routes :

Table 14 : Summary of acute toxicity studies via others route

Method	Route	Results	Reference
In mouse Test material (CAS number) : 108-91-8	IV	LD50 : 200 mg/kg bw	Takahashi A. (1976)
In mouse	SC	LD100 : 2000 mg/kg bw	Pliss G.B. (1958)
In rat Test material (CAS number) : 108-91-8	IP	LD50 : 164-199 mg/kg	Registration dossier (study report 1978)
In mouse	SC	LD50 : 1150 mg/kg	Pliss G.B. (1958)
In mouse Test material (CAS number) : 108-91-8	IP	LD50 : 300 mg/kg bw	Bopp B.A. *et al.* (1986)
In rat Test material (CAS number) : 108-91-8	IP	LD50 : 300 mg/kg bw	Japanese journal of pharmacology (1969)
In rabbit	SC	No info	Registration dossier (study report 1929)
In dog Test material (CAS number) : 108-91-8	IV	LD50 : 200 mg/kg bw	Miyata T. *et al.* (1969)

In rabbit	IV	No info	Registration dossier (study report 1929)
In rat	IP	No info	Registration dossier (study report 1929)
In mouse Test material (CAS number) : 108-91-8	IP	LD50 : 465 mg/kg bw	Bopp B.A. *et al.* (1986)
In mouse Test material (CAS number) : 108-91-8	IP	LD50 : 770 mg/kg bw	Bopp B.A. *et al.* (1986)
In mouse Test material (CAS number) : 108-91-8	IP	LD50 : 520 mg/kg bw	Bopp B.A. *et al.* (1986)
In mouse	IP	LD50 : 48 mg/kg bw	Registration dossier (study report 1979)
In mouse Test material (CAS number) : 108-91-8	IP	LD50 : 477 – 806 mg/kg bw	Miyata T. *et al.* (1969)
In rabbit Test material (CAS number) : 108-91-8	IV	LD50 : 150 mg/kg bw	Bopp B.A. *et al.* (1986)
In mouse Test material (CAS number) : 108-91-8	IP	No info	Lee I.P. and Dixon R.L. (1972)
Mammal Test material (CAS number) : 108-91-8	IP	LD50 : 200 mg/kg bw/d	Mallette F.S. and Von Haam E. (1952)
In mouse Test material (CAS number) : 108-91-8	No info	LD50 : 129 mg/kg bw	Pharmaceutical chemistry Journal (1988)
Rabbit	Injection	No info	Carswell T.S. and Morill H.L. (1937)
In mouse	SC	LDLo : 1000 mg/kg bw	Pliss G.B. (1958)
In rat Test material (CAS number) : 108-91-8	IP	LD50 : 74 – 95 mg/kg bw	Registration dossier (study 1978)
Review Many studies	IP SC IV	Rats : I.P. 350 mg/kg bw Mice : I.P. 619 mg/kg bw, S.C. 1150 mg/kg bw Dogs : I.V. 200 mg/kg bw	Bopp B.A. *et al.* (1986)

Only studies with minimal description of methods and results were presented and no concern was identified.

7.9.2.2. Corrosion/irritation

Skin :

Table 15 : Summary of irritation studies

Method	Result	Rel.	Reference
Human three-dimensional *in vitro* model Skin2 ZK 1350	Viability : 1.33 +- 3.1% Corrosive	2	Liebsch M. *et al.* (1995)

10sec, 15µg Test material (CAS number) : 108-91-8			
In vivo Rabbit Undiluted test substance Coverage : no information Observation period : 24h and 8d Exposure : up to 20h Test material (CAS number) : 108-91-8	After 1min exposure : Necrosis After 5 and 15min exposure : marked necrosis After 20h exposure : marked necrosis rounded by significant erythema, Not reversible	2	Registration dossier (study report 1970)
In vivo Rabbit 0.5 ml Undiluted test substance, 4h Obsvertion period : up to 17d Semiocclusive Test material (CAS number) : 108-91-8	After 4h : severe erythema and edema Within 14 to 17d : loosening about edges of scrab showing injury in depth Not reversible Corrosive	2	Registration dossier (Study report 1977)
In rabbit No more information available	Corrosive No other information available	2 in the registration dossier eMSCA supports a reliability of 3 (no other information available)	Registration dossier (study report 1959)
In vivo Rabbit Occlusive (50%) Exposure : 1, 5 and 15min Test material : cyclohexylamine	Erythema score : 2/4 after 5 and 15min (not fully reversible within 15min) + scar formation observed	2	Registration dossier (study report 1959)
In vivo Rabbit Test material (CAS number) : 108-91-8	Erythema score : 4/4 Edema score : 0/4	4	Registration dossier (microfiche : 1967)
In vivo Mammal Test material (CAS number) : 108-91-8	Highly irritating	4	Mallette F.S. and Von Haam E. (1952)
In vivo Rabbit Exposure : 24h Open Test material (CAS number) : 108-91-8	Grade 7 : severe necrosis	4	Smyth H.F. *et al.* (1969)
In vivo Rabbit Exposure : 4h Semiocclusive : 0.5ml Test material (CAS number) : 108-91-8	Erythema score : 4/4 (not reversible) (+slight eschar formation) Edema score : 2/4 after 1d and ¼ after 2d Necrosis observed in	4	Registration dossier (study report 1973)

	all animals		
In vivo Rabbit Doses : 20mg and above Test material (CAS number): 108-91-8	Immediately : corrosive effects (fully reversible within 4w)	4	Lomonova G.V. (1963)
Rabbit	Irritating	eMSCA supports a rel. of 4 (no information available)	Registration dossier (study report 1970)
Rabbit Exposure 24h, 2mg Test material (CAS number) : 108-91-8	Severely irritating	eMSCA supports a rel. of 4 (no information available)	Marhold J. (1986)
Guinea pig	Corrosive	eMSCA supports a rel. of 4 (no information available)	Registration dossier (study report 1929)

Studies showed non-reversible necrosis.

Cyclohexylamine is classified as **Skin Corrosive 1B H314: causes severe skin burns and eye damage**. And based on the available information, the eMSCA supports this classification and concludes that there is no need to request further information under this substance evaluation.

Eye :

Table 16 : Summary of the eye irritation/corrosion studies

Method	Results	Rel.	Reference
In rabbit 0.5 ml undiluted test substance Observation period : up to 8d No GLP Test material (CAS number) : 108-91-8	Overall irritation (at 1h, 24h and 8d) : mucous membranes etched, marked erythema, edema, cornea opacity, not reversible (scores not given) Additional findings : 1h : haemorrhage 8d : staphyloma	2	Registration dossier (study report 1970)
In rabbit (New Zealand withe) 0.1ml during 1min Observation period : up to 24h Test material (CAS number) : 108-91-8	Immediatly after application : severe discomfort with pawing, squealing, thrashing After 10min and 1h : moderate corneal cloudiness, iris congestion, severe erythema with a slight discharge After 24h : corrosive Not reversible (Scores not given)	2	Registration dossier (study report, 1977)
In rabbit Test A : exposure of 5min and reading at 7min Test B : exposure of 24h and reading at 24h No GLP	Test A : Score : corneal opacity 4/4, iritis 2/4, conjunctivae 4/4 Test B : Score : corneal opacity 4/4, iritis 2/4, conjunctivae 4/4	2	Registration dossier (study report 1987)

Test material (CAS number) : 108-91-8			
In rabbit No GLP Test material (CAS number) : 108-91-8	Overall irritation : severe burn from 0.5ml of a 1% solution Corneal necrosis No data about time point	4	Smyth H.F. *et al.* (1969)
In rabbit Doses : 50 µg Exposure period : 24 hours Test material (CAS number) : 108-91-8	Severely irritating		Registration dossier (study report 1986)

Studies of reliability 2 showed severe eye irritation. The classification in Skin Corrosive category 1B H 314 covers the eye damages.

Based on the available information, the eMSCA supports this classification and concludes that there is no need to request further information under this substance evaluation.

7.9.3. Sensitisation

7.9.3.1. Skin

A study (Mallette F.S. and Von Haam E., 1952) with minimal description of method and results (reliability 4) was presented. This study was an *in vivo* patch test using cyclohexylamine. The laboratory animals (no more information available) were exposed to 100% of the test substance (undiluted test material). The clinical observations were dull-red discoloration with edema, slight maceration and possibly petechiae.

The eMSCA concludes that there is no concern for skin sensitisation and no need to request further information under this substance evaluation due to the corrosive properties.

7.9.4. Repeated dose toxicity

7.9.4.1. Repeated dose toxicity : Oral route

Table 17 : Summary of the repeated dose toxicity studies via oral route

Method	Results	Rel.	Reference
Chronic study (2years) in rats (Wistar)(48/sex/group) Doses : 0, 600, 2000, 6000 ppm Feed No GLP Test material (CAS number) : 4998-76-9	LOAEL : 600 ppm (approx. 18mg/kg bw/d) : decreased body weight, changes of some relative organ weight (gonads, thyroid, brain)	2	Gaunt I.F. *et al.* (1976)
Chronic study (2years) in rats (FDRL)(30/sex/group) Doses : 0, 15, 50, 100 and 150 mg/kg bw/d (cyclohexylamine) Feed Test material (CAS number) : 4998-76-9	NOAEL : 15 mg/kg bw/d of cyclohexylamine	2	Oser B.L. *et al.* (1976)
Chronic study (80weeks) in mice (ASH-CS1) (50 males and 48 females) Doses : 0, 300, 1000 and 3000 ppm (ca 0, 29, 102, 292 mg/kg bw/d) Feed Test material (CAS number) : 4998-76-9	BW : initial and terminal bw were significantly changed Histopathology : mild hepatic changes in females at the highest dose level Tumours found in all dose levels but not statistically significant differences. NOAEL : 1000 ppm eMSCA comment :Not possible to conclude on NOAEL based on the information available (no information in the registration dossier about the dose at which the effects were observed). However in the MAK Collection for Occupational Health and safety (Value Documentation 2006), a NOAEL of 29 mg/kg bw/d was indicated due to a decreased of body weight gain in males at 102 mg/kw bw/d)	2 in the registration dossier however eMSCA supports a reliability of 3 (no data available)	Hardy J. *et al.* (1976)
Chronic study (30 months) in rats (Sprague Dawley)(52/sex/dose) Doses : 0, 200 mg/kg bw/d Feed Test material (CAS number) : 108-91-8	NOAEL : 200 mg/kg bw/d No toxic effects, no tumours observed	4	Schmaehl D. (1973)
Chronic study (5 days) in male rats (30 receiving	Endpoint analyzed : mortality No animal died	4	Registration dossier (study

<table>
<tr><td>increasing dose) (Wistar)
Doses : 86, 130, 194, 292, 437 mg/kg bw/d
Feed
Test material (CAS number) : 108-91-8</td><td></td><td></td><td>report 1968)</td></tr>
<tr><td>Subchronic study (82 days) in rats, guinea pigs and rabbits
Doses : 100 mg/kg bw/d
Test material (CAS number) : 108-91-8</td><td>1 rabbit and 1 guinea pig died (pneumonia)
No other effects</td><td>4</td><td>Carswell T.S. and Morill H.L. (1937)</td></tr>
<tr><td>Study (9 weeks) in rats (15/doses)
Doses : 0, 200 mg/kg bw/d
Test material (CAS number) : 108-91-8</td><td>↓ bwg, food intake, motor activity
↓ testicular and seminal vesicles weights, testosterone concentration,
↓ spermatogenesis (pachytene spermatocytes, early and late spermatids)
↑ FSH concentration</td><td>4</td><td>James R.W. et al. (1981)</td></tr>
<tr><td>Chronic study (2years) in dogs (3/sex/dose)
Doses : 0, 0.15, 1.5, 15 mg/kg bw/d
Test material (CAS number) : 27817-50-1</td><td>NOAEL : 15 mg/kg bw/d
No effects</td><td>4</td><td>Bopp B.A. et al. (1986)</td></tr>
<tr><td>Subchronic study (90days) in male rats (Wistar and Sprague Dawley)(25/dose)
Doses : 0, 600, 2000 and 6000 ppm (ca 0, 30, 105, 343 mg/kg bw/d cyclohexylamine)
Feed
Test material (CAS number) : 4998-76-9</td><td>NOAEL : 600 ppm
Significant decrease of bwg (Wiaster rats : 323, 341, 269, 181g and SD 438, 422, 380, 255g respectively at 0, 600, 2000 and 6000ppm)
Organ weight :6000 ppm : decrease weight (no more information available) of prostate, adrenals, pituitary, thyroid, heart, liver, kidneys and testes
Histopathology : 6000 ppm : significant increase of testicular damage, no or immobile spermatozoa, increased number of decapitated sperms in wistar rats
Loss of germinal cells leading to a reduction of spermatogenesis in over 80% of tubules</td><td>eMSCA supports a reliability of 4</td><td>Mason P.L. and Thompson G.R. (1977)</td></tr>
<tr><td>Subchronic study (13weeks) in rats (CFE) (15/sex/dose)
Doses : 0, 600, 2000 and 6000 ppm (ca 0, 41, 143</td><td>2000 and 6000 ppm : significant decrease of bw and food consumption
<table><tr><td></td><td></td><td>0ppm</td><td>600ppm</td><td>2000ppm</td><td>6000ppm</td></tr></table></td><td>eMSCA supports a reliability of 2</td><td>Gaunt I.F. et al. (1974)</td></tr>
</table>

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<tr>
<td>and 468 mg/kg bw/d cyclohexylamine)
Test material (CAS number) : 4998-76-9</td>
<td>
<table>
<tr><td>Bw gain (g) at D84</td><td>Males</td><td>372</td><td>377</td><td>338*</td><td>274*</td></tr>
<tr><td></td><td>Females</td><td>201</td><td>190</td><td>160*</td><td>133*</td></tr>
<tr><td>Food consumtpion (g/rat/d)</td><td>Males</td><td>21.4</td><td>20.5</td><td>20.0*</td><td>18.6*</td></tr>
<tr><td></td><td>Females</td><td>16.5</td><td>14.9*</td><td>14.3*</td><td>13.9*</td></tr>
<tr><td>Rel. brain weight (g/100g bw)</td><td>Males</td><td>0.42</td><td>0.41</td><td>0.44</td><td>0.50*</td></tr>
<tr><td></td><td>Females</td><td>0.62</td><td>0.63</td><td>0.70*</td><td>0.80*</td></tr>
<tr><td>Rel. stomach weight (g/100g bw)</td><td>Males</td><td>0.38</td><td>0.39</td><td>0.39</td><td>0.45*</td></tr>
<tr><td></td><td>Females</td><td>0.49</td><td>0.49</td><td>0.52</td><td>0.59*</td></tr>
<tr><td>Rel. gonads weight (g/100g bw)</td><td>Males</td><td>0.81</td><td>0.80</td><td>0.81</td><td>0.67*</td></tr>
<tr><td></td><td>Females</td><td>43</td><td>45</td><td>56*</td><td>55*</td></tr>
<tr><td>Rel. thyroid weight (g/100g bw)</td><td>Males</td><td>5.1</td><td>5.2</td><td>5.1</td><td>5.1</td></tr>
<tr><td></td><td>Females</td><td>6.1</td><td>7.1</td><td>7.2</td><td>7.4*</td></tr>
<tr><td>Rel. small intestine weight (g/100g bw)</td><td>Males</td><td>1.67</td><td>1.72</td><td>1.71</td><td>1.81*</td></tr>
<tr><td></td><td>Females</td><td>2.21</td><td>2.31</td><td>2.16</td><td>2.40</td></tr>
<tr><td>Rel. caecum weight (g/100g bw)</td><td>Males</td><td>0.23</td><td>0.21</td><td>0.21</td><td>0.21</td></tr>
<tr><td></td><td>Females</td><td>0.25</td><td>0.26</td><td>0.27</td><td>0.31*</td></tr>
<tr><td>Rel. adrenal weights (g/100g bw)</td><td>Males</td><td>14.4</td><td>14.0</td><td>14.5</td><td>15.8</td></tr>
<tr><td></td><td>Females</td><td>23.4</td><td>24.8</td><td>25.5*</td><td>26.5*</td></tr>
</table>
Histopathology : reduced spermatogenesis and tubular atrophy in testes at the mid and high dose groups (respectively 4/11males and 18/20males).

NOAEL : 600 ppm (ca 30 mg/kg bw/d)
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<td>Subchronic study (13 weeks) in rats (15 or 16males/dose)
Doses : 0.01, 0.05, 0.1, 0.2, 0.5, 1.0 and 2.5% (ca. 3.5 – 434 mg/kg)
Feed
Test material (CAS number) : 4998-76-9</td>
<td>Mortality : 2.5% : all rats died
Bwg : 0.2% and above: significant decrease
Organ weight : many organ weights were decreased
Testes : absolute weight decreased at 1.0 and 2.5% while relative weight increased at 0.5% and decreased at 1%
Histopatholgy : degeneration of the tubular epithelium in both testes at 1% in 13 of 15 rats (with ≥95% of the tubules being affected in 8 rats, ≥70% in 4 rats and ≥40% in 1 rat)
NOAEL : 0.1% in diet</td>
<td>4</td>
<td>Collings A.J. et Kirby W.W. (1974)</td>
</tr>
<tr>
<td>Multi generation (F6) study in mouse (Swiss SPF)
Doses : 0, 600 mg/kg Feed
Test material (CAS number) : 27817-50-1</td>
<td>Short term study (4 months) :
Bwg decreased
Histopatholigy : no effect observed
Long term study :
Bw decreased</td>
<td>4</td>
<td>Kroes R. et al. (1977)</td>
</tr>
</table>

	No effects on food intake, haematology, histopathology		
Study (9 weeks) in dogs (4males/dose) Doses : 0, 250 mg/kg bw/d	Decrease motor activity, body weight, food intake Pachytene spermatocytes, early and late spermatids decreased Reversible effects	4	James R.W. *et al.* (1981)
Chronic study (52 weeks) in rats Doses : 114 mg/kg bw/d Test material (CAS number) : 108-91-8	Degenerative changes in livers and kidneys No more information available No tumours observed	4	Pliss G.B. (1958)
Study in monkeys (5males) Exposure : 7w Doses : 1w : 17 mg/kg bw/d; 1w : 34 mg/kg ; and 5w : 50 mg/kg bw/d + follow up study of 4w : 17 mg/kg bw/d Test material (CAS number) : 108-91-8	No NOAEL identified Testicular damage 2/5 monkeys with minimal effects on spermatogenesis Decrease food intake	4	Scientific Committee on food (1995)
Chronic study (2years) in rats (Charles river) (25/sex/dose) Doses : 0, 0.15, 1.5, 15 mg /kg bw/d Test material : cyclohexylamine sulphate	No significant changes between test and control animals for food intake, mortality and haematological parameters Slight depression of bwg in males At the highest dose : 1 bladder tumour in 1 of 8 animals	4	Price J.M. *et al.* (1970)

In the key study Gaunt I.F. *et al.* (1976), rats (48/sex/dose) were exposed to 0, 600, 2000 and 6000 ppm of cyclohexylamine hydrochloride during 2 years. The doses in ppm correspond to 0, 24, 82 and 300 mg/kg bw/d in males and 0, 35, 120 and 440 mg/kg bw/d in females of cyclohexylamine hydrochloride and then to 0, 18, 60 and 219 mg/kg bw/d in males and 0, 26, 88, 321 mg/kg bw/d in females of cyclohexylamine. A significant decrease of body weight in all dose groups were noted. The tested haematological parameters were Hb, PCV, RBC, Retics and leucocytes. At the end of the study, the haematology evaluation revealed in the male highest dose group an increase of Hb and PCV and a decrease of reticulocytes and in all dose groups a significant dose dependent decrease of total leucocytes. Signifcant changes in clinical chemistry analysis (urea an albumin) were shown in all doses in males. At necropsy, the organ weight analysis indicated some changes in males and females and the histopathological examination showed modification in the highest dose group (in lungs : significant increased incidence of rats which had alveoli with foamy macrophages and in testes : significant increased incidence of rats with bilateral atrophy. Moreover, at mid dose group an increase of incidence of testes with tubules showing few or no spermatids were observed).

Table 18 : summary of the significant changes in the chronic study (Gaunt I.F. *et al.*, 1976)

	Sex	0 (controls)	600 ppm	2000 ppm	6000 ppm
Mortality	Males	24	21	18	5
	Females	16	10	4	7
Terminal body weight	Males	646g	623g	575g*	451g*
	Females	399g	360g*	311g*	240g*
Clinical chemistry : urea	Males	48	30*	32*	23*
Clinical chemistry : albumin	Males	2.97	3.16*	3.34*	4.09*
Relative brain weight (mg/100g bw)	Males	0.34	0.36	0.39*	0.48*
	Females	0.50	0.56*	0.65*	0.82*
Relative liver weight (mg/100g bw)	Males	2.65	2.64	2.43	2.32*
Relative spleen weight (mg/100g bw)	Males	0.29	0.28	0.27	0.21*
Relative kidneys weight (mg/100g bw)	Males	0.72	0.66	0.63	0.56*
Relative gonads weight (mg/100g bw)	Females	32.6	36.1	43.8*	54.4*
Relative thyroid weight (mg/100g bw)	Females	7.9	8.1	9.8*	9.1*
Lungs : alveoli with foamy macrophages (number of affected animals/number of examined animals)	Males	6/34	8/40	12/39	19*/46
	Females	5/38	13/43	8/47	21*/41
Testes : bilateral atrophy (number of affected animals/number of examined animals)		0/34	2/40	2/39	18*/46
Testes : tubules with few or no spermatids (number of affected animals/number of examined animals)		2/34	6/40	10*/39	7/46

In the second key study, Oser B.L. *et al.* (1976), 30 rats/sex/doses received in diets cyclohexylamine hydrochloride (corresponding to 0, 15, 50, 100 and 150 mg/kg bw/d of cyclohexylamine) during 2 years (113w). The treatment had no influence on the mortality rate, on clinical signs, on hematology, on clinical chemistry and on urinalysis parameters.

Whereas the body weight was significantly reduced at dose of 50 mg/kg bw/d and above in females and at dose of 100 mg/kg bw/d and above in males (No more data available). Some organ weights were changed, however relative organ weights were not modified indicating an effect of the lower terminal body weight. The gross pathology revealed some change.

Table 19 : Summary of gross pathology examination

Doses (mg/kg bw/d)			0	15	50	100	150
Body weight	Males		562	540	508	436	415
	Females		392	383	333	292	287
Kidney weight	Males	Abs.	4.19	3.83	4.15	3.91	3.38
		Rel.	0.75	0.71	0.82	0.90	0.81
	Females	Abs.	2.93	2.79	2.58	2.57	2.55
		Rel.	0.75	0.73	0.78	0.88	0.89
Gonads weight	Males	Abs.	3.47	4.09	2.76	3.07	2.31
		Rel.	0.62	0.76	0.54	0.70	0.56
	Females	Abs.	277.6	237.7	207.1	208.3	210.7
		Rel.	70.8	62.1	62.2	71.3	73.4
Incidence of renal calcification			2/33 (male+female/number of animals examinated)	5/24	11/35	10/27	8/41
Thickening of urinary bladder mucosa			8/57 (male+female/number of animals examinated)	9/58	13/56	9/56	13/56
Testicular atrophia			5/19 (male/males examinated)	6/15	9/13	3/10	12/20
Abnormal germinal epithelium			0/19 (male/males examinated)	0/15	1/13	1/10	3/20

Abs. : Absolu (g); Rel. : Relative (g/100 g bw)

In the third key study, Hardy J. *et al.* (1976), mice (50 males and 48 females) were exposed by diets to cyclohexylamine hydrochloride (0, 300, 1000 and 3000 ppm) during 80 weeks. No difference for mortality, body weight gain, haematological examination or incidence of tumors. The only histopathological change was an increased incidence on minor hepatic changes in females of the highest dose group.

Other studies with minimal description of methods and results (reliability 4 or no score assigned) were presented.

The data presented result from older studies, not following a guideline and therefore, several parameters are missing. The data however show only a concern for testes, which is covered by the harmonised classification as repr. Cat. 2. Moreover, due to the known corrosive property and the specific fishy smell of the substance, the eMSCA concludes that there is no need to request further information under this substance evaluation.

7.9.5. Mutagenicity

7.9.5.1. In vitro

Table 20 : summary of the *in vitro* mutagenicity studies

Method	Result	Rel.	Reference
Gene mutation *S. Typh*. TA 98, TA 100, TA 1535, TA 1537. OECD 471 (bacterial reverse mutation assay) Test material (CAS number) : 108-91-8	Genotoxicity : negative Cytotoxicity : yes	1	Mortelmans K. *et al.* (1986)
Gene mutation Mammalian cell gene mutation assay Chinese Hamster ovary cells International guidelines and EPA GeneTox Test material (CAS number) : 108-91-8	Genotoxicity : negative Cytotoxicity : yes	2	Brusick D. *et al.* (1989)
DNA damage and/or repair, unscheduled DNA synthesis Adult males rat hepatocytes Internaltional guidelines and EPA GeneTox Test material (CAS number) : 108-91-8	Without met. act. Genotoxicity : negative Cytotoxicity : yes	2	Brusick D. *et al.* (1989)
Bacterial reverse mutation assay *S. Typh.* TA 98, 100, 1535, 1537. Cyclohexylamine hydrochloride	Genotoxicity : negative Cytotoxicity : no	2	Herbold B.A. and Lorke D. (1980)
Adenovirus transformation in hamster cells Hamster embryo cells Test material (CAS number) : 108-91-8	Genotoxicity : positive Cytotoxicity : no data	4	Casto B.C. (1981)
Sister chromatid exchange assay in mammalian cells (human lymphocytes)	Genotoxicity : positive Cytotoxicity : no data	3	Wolff S. (1983)
DNA damage and/or repair, unscheduled DNA synthesis in mammalian cells (Hela cells)	Genotoxicity : sign increase in grains at 100µg/ml compared to control (2277 vs 1748) Cytotoxicity : sign. decrease in grains at 200µg/ml compared to controls (906 vs 1748)	4	Koizumi A. *et al.* (1971)
In vitro mammalian chromosome aberration test Test material (CAS number) : 108-91-8	Genotoxicity : positive Cytotoxicity : no data	3	Dixon C.H. (1973)
Gene mutation Microsome assay *S. Typh*. TA 98, 100, 1535, 1537, His G46, C207, C3076	Genotoxicity : positive Cytotoxicity : no data Positive result only in the presence of additional liver	4	Rao V.S. and Aiyar A.S. (1975)

Test material (CAS number) : 108-91-8	microsomal fraction		
In vitro mammalian chromosome aberration test Rat bone marrow cells	Genotoxicity : negative	2	Dick C.E. *et al.* (1974)
Gene mutation *S. Typh*. G46, serratia marcescens Hy a 21	Genotoxicity : negative Cytotoxicity : no data	4	Buselmaier W. *et al.* (1972)
Bacterial gene mutation assay S. Typh. TA 98, 100, 1535, 1538 Test material (CAS number) : 108-91-8	Genotoxicity : negative Cytotoxicity : no data	2	Anderson D. and Styles JA. (1978)
Gene mutation Various strains of S. Typh.	Genotoxicity : negative Cytotoxicity : no data	4	Rao V.S. and Aiyar A.S. (1975)
Gene mutation (E. Coli)	Genotoxicity : negative Cytotoxicity : no data	4	Fluck E.R. *et al.* (1976)
Chromosome aberration Human leucocytes	Genotoxicity : negative Cytotoxicity : no data	4	Brewen J.G. *et al.* (1971)
No information avalaible	No information avalaible		Cattanach B.M. (1976)

Generally, negative results were found in bacterial reverse mutation assay and in mammalian chromosome aberration test.

Other studies with minimal description of methods and results (reliability of 3 or 4) were presented.

Based on the available information, the eMSCA concludes that there is no concern for mutagenicity and no need to request further information under this substance evaluation.

7.9.5.2. In vivo

Table 21 : Summary of *in vivo* mutagenicity studies

Method	Results	Rel.	Reference
Chromosome aberration (dominant lethal assay in male rats) Exposure : Ip Test substance (CAS number) : 108-91-8	the average of 35 % of the ova flushed 48h after insemination from the oviducts of females mated with CHA-treated males showed no cleavage and did not exhibit 2 pro-nuclei. This indicated that fertilization had not occurred . The pre-implantation loss in females mated with CHA treated males results from some mechanism other than that of dominant lethal mutations	2	Green S. *et al.* (1972)
Chromosome aberration (rat)	Genotoxicity : negative Toxicity : no effects	2	Khera K.S. *et al.* (1971)
Chromosome aberration (rat) Exposure : Ip Test substance (CAS number): 108-91-8	Genotoxicity : positive Toxicity : no data Mean percent breakage for the spermatogonial cells : 4.4, 7.6, 11.2, 16.2, 19.2 (respectively at 1, 10, 20, 40, 50 mg/kg bw/d) vs 1.8 controls	2	Legator M.S. *et al.* (1969)
Chromosome aberration (mouse)	Genotoxicity : negative Toxicity : no effects	2	Lorke D. and Machemer L.

	No pre- or post-implantation loss. The treatment did not damage the males and did not impair their mating capacity and fertility		(1974)
Chromosome aberration (rat)	Genotoxicity : negative Toxicity : no data	2	Dick C.E. *et al.* (1974)
Chromosome aberration (mouse) Test substance (CAS number): 108-91-8	Genotoxicity : negative Toxicity : yes	2	Chauhan P.S. *et al.* (1975)
Chromosome aberration (mouse) Test substance (CAS number): 108-91-8	Genotoxicity : negative Toxicity : no data	2	Cattanach B.M. and Pollard C.E. (1971)
Chromosome aberration (rat)	Genotoxicity : negative Toxicity : no effects	2	Khera K.S. *et al.* (1971)
Chromosome aberration (Chinese hamster) Test substance (CAS number): 108-91-8	Genotoxicity : positive Toxicity : no data	2	Van Went-de-Vries G.F. *et al.* (1975)
Chromosome aberration (rat) Test substance (CAS number): 108-91-8	Genotoxicity : positive Toxicity : yes Mean percent breakage for the bone marrow cells : 4.0, 5.12, 8.0, 12.16, 16.28 (respectively at 1, 10, 20, 40, 50 mg/kg bw/d) vs 2.72 of controls	2	Legator M.S. *et al.* (1969)
Chromosome aberration (mice) Test substance (CAS number): 108-91-8	Genotoxicity : positive Toxicity : no data	2	Petersen K.W. *et al.* (1972)
Chromosome aberration	Genotoxicity : negative Toxicity : no effects	2	Lorke D. and Machemer L. (1975)
Chromosome aberration (Chinese hamster) Ip Test substance (CAS number): 108-91-8	Genotoxicity : negative Toxicity : no data	4	Brewen J.G. *et al.* (1971)
Chromosome aberration (pregnant sheep) Test substance (CAS number): 108-91-8	Genotoxicity : positive Toxicity : no data Clastogenic	4	Turner J.H. and Hutchinson D.L. (1974)
Chromosome aberration (rat) Test substance (CAS number): 108-91-8	Genotoxicity : negative Toxicity : no effects	4	Mostardi R.A. *et al.* (1972)
Chromosome	Genotoxicity : positive	4	Khera K.S.

aberration (rat)	Toxicity : yes Decrease numbers of implantations due to pre-implentation loss		And Stoltz D.R. (1970)
Gene mutation (mouse spot test) According OECD 484 Test substance (CAS number): 108-91-8	Genotoxicity : positive (weakly) Toxicity : no data	/	Fahrig R. (1982)
Chromosome aberration (Chinese hamster)	Genotoxicity : negative Toxicity : no data	/	Machemer L. and Lorke D. (1976)

In most of the studies no genetic damage from cyclohexylamine has not been detected.

Based on the available information, the eMSCA concludes that there is no concern for mutagenicity and there is no need to request further information under this substance evaluation.

7.9.6. Carcinogenicity

Table 22 : Summary of the carcinogenicity studies

Method	Results	Rel.	Reference
In mouse By feed (80 weeks) Doses : 0, 300, 1000 and 3000ppm (ca. 0, 40, 140 and 400 mg/kg bw/d) Test material (CAS number) : 4998-76-9	No carcinogenic effect NOAEL (toxicity) : 1000 ppm	2	Hardy J. *et al.* (1976)
In rats (30/sex/dose) By feed (2 years) Doses : 0, 15, 50, 100, 150 mg/kg bw/d Test material (CAS number) : 4998-76-9	No carcinogenic effect	2	Oser B.L. *et al.* (1976)
In rat (48/sex/dose) By feed (2 years) Doses : 0, 600, 2000, 6000 ppm (ca. 0, 40, 133, 400 mg/kg bw/d) Test material (CAS number) : 4998-76-9	No carcinogenic effect	2	Gaunt I.F. *et al.* (1976)
In mouse By feed (84 weeks) Doses : 0, 0.5% (ca. 0, 600 mg/kg bw/d) Test material (CAS number) : 27817-50-1	No carcinogenic effect	4	Kroes R. *et al.* (1977)
In rat By feed (52 weeks) Doses : 0, 114 mg/kg bw/d Test material (CAS number) : 108-91-8	No carcinogenic effect Degenerative changes in liver and kidneys	4	Pliss G.B. (1958)
In rat By feed (2 years) Doses : 0, 0.15, 1.5, 15 mg/kg	15 mg : 1/8 rats showed an invasive transitional cell tumour of grade 2	4	Price J.M. *et al.* (1970)

bw/d Test material (CAS number) : 27817-50-1			
In rat By feed (30 months) Doses : 0, 200 mg/kg/d Test material (CAS number) : 108-91-8	No carcinogenic effect		Schmaehl D. (1973)
In dog Capsule (2 years) Doses : 0, 0.15, 1.5, 15 mg/kg bw/d Test material (CAS number) : 27817-50-1	No evidence of tumour development	4	Bopp B.A. *et al.* (1986)
In vitro test Mammalian cells (Human WI 38, Rodent BHK 21) Doses : 250 – 0.08µg/ml Test material (CAS number) : 108-91-8	No cell transformation activity	4	Styles J.A. (1978)
Principe : Degranulation test sebaceous-gland test tetrazolium reduction test Imlant test	All tests were negative	4	Purchase IFH (1978)

There is no evidence that cyclohexylamine is carcinogenic in rats, mice or dogs.

Based on the available information, the eMSCA concludes that there is no concern for carcinogenicity and no need to request further information under this substance evaluation.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

7.9.7.1. Toxicity to reproduction

Table 23 : Summary of the fertility studies

Method	Results	Rel.	Reference
In mouse Doses : 0.11% in diet = ca. 136 mg/kg bw/d Exposure : >10w Feed Test material (CAS number) : 108-91-8	No effects on behaviour and weight Fertility was normal No important increase in pre- and post-implantation losses	eMSCA supports a reliability of 4 (no more information available)	Lorke D. and Machemer L. (1975)
Multigeneration study (F1-F4) In mouse	No NOAEL identified ↑ mortality of the offsprings during the first 21days of their lifes ↓ body weight gain Effects dose dependent	4	Gondry E. (1973)

Doses : 0, 0.1, 0.5 and 1% (ca. 0, 143, 715 and 1430 mg/kg bw/d) Feed Test material (CAS number) : 108-91-8			
Mutligeneration study (3) In mouse (10 males and 40 females) Doses : 0, 600, 2000, 6000 ppm (ca. 0, 86, 286, 857 mg/kg bw/d) Exposure : feed Test material (CAS number) : 4998-76-9	NOAEL (fertility : P, F1, F2) : 600ppm NOAEL (general toxicity : P) : 600ppm NOAEL (general toxicity F1, F2) : 600ppm Parental : ↓ body weight gain in females (P-generation at 2000ppm; F1 generation : in all dose groups) Offspring : ↓ viability index (D4) (F1 generation : 68.8, 81.7*, 31.7*, 41.9*% at 0, 600, 2000 and 6000ppm; F2 generation : 81.3, 83.2, 57.3* and 35.0% at 0, 600, 2000 and 6000ppm; F3 generation : 84.3, 63.3* and 61.8*% at 0, 600and 2000ppm)	3	Registration dossier (study report, 1983)
In rats (5 males/group) Doses : 0, 6000 ppm (ca. 0, 343 mg/kg bw) Exposure : 10 months and were caged for 10days with 3 young untreated females Test material (CAS number) :	NOAEL(male) : 6000 ppm No significant difference between test and control groups in the number of fertile males, in litter size and in growth	4	Gaunt I.F. *et al.* (1974)

<table>
<tr><td>4998-76-9</td><td></td><td></td><td></td></tr>
<tr><td>In rats (30/sex/group) Doses : 0, 15, 50, 100, 150 mg/kg bw/d Feed Exposure : 2years. (F4) Test material (CAS number) : 4998-76-9</td><td>NOAEL (general toxicity) : 15 mg/kg bw/d
NOAEL (reproductive toxicity) : 100 mg/kg bw/d
150 mg : growth retardation due to the lower food consumption
Reproduction parameters : normal in all dose groups
Slight reduce of the litter size and the weaning weight
In male : significant higher incidence of testicular atrophy at the high dose group however these rats continued to be fertile</td><td>4</td><td>Oser B.L. et al. (1976)</td></tr>
<tr><td>In rats and rabbits Doses : 0, 1.5 and 15 mg/kg bw/d Exposure : Before and during mating, gestation and lactation in both sexes, + during the critical period of organogenesis in females Test material (CAS number) : 27817-50-1</td><td>No NOAEL identified
Parental : No difference between test and control groups for number of corpora lutea, implantation sites, resorption sites, the ability to copulate, to reproduce
Offspring : No abnormalities observed during external, internal and skeletal examination</td><td>4</td><td>Kennedy G.L. et al. (1969)</td></tr>
<tr><td>Multigeneration study (F6) In mouse (Swiss) Doses : 0, 0.5% (ca. 0, 600 mg/kg bw/d) Exposure : feed,</td><td>Significant difference between test and control group in all generation : ↓sign of number of implantation sites, ↓sign number of live born foetuses, ↓sign body weight gain of the offspring and ↑sign perinatal mortality (decrease postnatal survivor ratio (D20/D0))
<table>
<tr><td></td><td></td><td>F1a</td><td>F2a</td><td>F3a</td><td>F3b</td><td>F4a</td><td>F5a</td><td>F6a</td></tr>
<tr><td rowspan="2">Mean no. of liveborn</td><td>Control</td><td>10.7</td><td>11.5</td><td>10.0</td><td>12.2</td><td>11.1</td><td>11.8</td><td>11.4</td></tr>
<tr><td>0.5</td><td>9.</td><td>8.</td><td>8.</td><td>10.</td><td>9.</td><td>10.</td><td>9.</td></tr>
</table></td><td>4</td><td>Kroes R. et al. (1977)</td></tr>
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<table>
<tr>
<td>Test material (CAS number) : 27817-50-1</td>
<td>
<table>
<tr><td>fetuses</td><td>%</td><td>2*</td><td>4*</td><td>3*</td><td>2*</td><td>3*</td><td>5*</td><td>9*</td></tr>
<tr><td rowspan="2">Postnatal survivors ratio (D5/D0)</td><td>Control</td><td>37</td><td>79</td><td>88</td><td>93</td><td>85</td><td>91</td><td>98</td></tr>
<tr><td>0.5 %</td><td>10</td><td>49 *</td><td>55 *</td><td>76*</td><td>75 *</td><td>60*</td><td>73 *</td></tr>
<tr><td>Mean bw D20</td><td>Control</td><td>2.3</td><td>2.4</td><td>3.0</td><td>2.6</td><td>3.2</td><td>2.9</td><td>3.0</td></tr>
<tr><td></td><td>0.5 %</td><td>0.8</td><td>2.0</td><td>2.4*</td><td>2.5</td><td>2.9*</td><td>2.5 *</td><td>2.5*</td></tr>
</table>
<table>
<tr><td></td><td>Control</td><td>0.5% cyclo</td></tr>
<tr><td>Mean no. of implantations</td><td></td><td></td></tr>
<tr><td>F2b</td><td>14.0</td><td>10.9*</td></tr>
<tr><td>F3c</td><td>14.1</td><td>11.3*</td></tr>
<tr><td>F4b</td><td>13.4</td><td>11.9*</td></tr>
<tr><td>F5b</td><td>13.1</td><td>11.0*</td></tr>
<tr><td>F6b</td><td>13.4</td><td>12.2</td></tr>
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Embryotoxic action
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<td></td>
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<tr>
<td>Mutligeneration study (3)
In mouse (10 males and 40 females)
Doses : 0, 600, 2000, 6000 ppm (ca. 0, 86, 286, 857 mg/kg bw/d)
Exposure : feed
Test material (CAS number) : 4998-76-9</td>
<td>NOAEL (fertility : P, F1, F2) : 600ppm
NOAEL (general toxicity : P) : 600ppm
NOAEL (general toxicity F1, F2) : 600ppm
Parental : ↓ body weight gain in females (P-generation at 2000ppm; F1 generation : in all dose groups)
Offspring : ↓ viability index (D4) (F1 generation : 68.8, 81.7*, 31.7*, 41.9*% at 0, 600, 2000 and 6000ppm; F2 generation : 81.3, 83.2, 57.3* and 35.0% at 0, 600, 2000 and 6000ppm; F3 generation : 84.3, 63.3* and 61.8*% at 0, 600and 2000ppm)</td>
<td>3</td>
<td>Registration dossier (study report, 1982)</td>
</tr>
</table>

Only older fertility studies with minimal description of methods and results (reliability 3 or 4) were presented.

The data presented result from older studies, not following a guideline and therefore, several parameters are missing. The data however show a concern for fertility, which is covered by the harmonised classification as repr. Cat. 2. Moreover, due to the known corrosive property and the specific fishy smell of the substance, in combination of the use which is limited to industrial and professional settings, the eMSCA concludes that no further testing is required.

7.9.7.2. Developmental toxicity

Table 24 : Summary of developmental toxicity studies

Method	Results	Rel.	Reference
NMRI Mice (25 inseminated virgin mice/group) Doses : 0, 10, 30, 100 mg/kg bw (ca. 0, 14, 42, 140 mg/kg of cyclohexylamine) Exposure : gavage, GD 6-15 Test material (CAS number) : 4998-76-9 Guideline : US-FDA	NOAEL (maternal toxicity) : 140 mg/kg bw/d No effects NOAEL (developmental toxicity) : 140 mg/kg bw/d No effects on the average number of implantations, resorption rate, sex ratio of the fetuses, average foetus weight, average placenta weight, incidence of foetus with skeletal variation, runts, malformation rate	2	Lorke D. and Machemer L. (1983)
Long Evans Rats (25 inseminated virgin rats/group) Doses : 0, 10, 30, 100 mg/kg bw (ca. 0, 14, 42, 140 mg/kg of cyclohexylamine) Exposure : GD 6-15, gavage Test material (CAS number): 4998-76-9 Guideline : US-FDA	NOAEL (maternal toxicity) : 42 mg/kg bw/d ↓sign bwg at 140mg during the treatment period (39.9** vs 56.6g in control group) and during the entire pregnancy (133.8* vs 146.0g in control group) NOAEL (developmental toxicity) : 42 mg/kg bw/d ↓sign at 140mg of fetal weight (3.37**g vs 4.03 in control group) and placental weight (0.47**g vs 0.56 in control group) No effects on the average number of implantations, resorption rate, sex ratio of the fetuses, incidence of foetus with skeletal variation, runts, malformation rate	2	Lorke D. and Machemer L. (1983)
Rats (Wistar-Imamichi) (15/group) Doses : 0, 1.8, 3.6, 18, 36 mg/kg bw/d Exposure : gavage, GD7-13 Test material (CAS number) : 108-91-8	NOAEL (maternal toxicity) : 18mg/kg bw/d ↓ bwg, food consumption NOAEL (developmental toxicity) : 36 mg/kg bw/d No abnormalities	eMSCA supports a reliability of 4 (no more information available)	Tanaka S. *et al.* (1973)
Mice Doses : 0, 61, 77, 122 mg/kg bw Exposure : IP, GD 11 Test material (CAS number) : 108-91-8	LOAEL (fetotoxicity) : 61 mg/kg bw ↓sign fetal bw (1.61g, 1.49, 1.47, 1.43g respectively at 0, 61, 77, 122 mg)	4	Gibson J.E. and Becker B.A. (1971)
Mice Doses : 0, 20, 50, 100 mg/kg bw/d Exposure : GD 6-11,	NOAEL (maternal toxicity) : 50 mg/kg bw/d Midly lethal at 100 mg NOAEL (embryotoxicity) : 50	4	Takano K. and Suzuki M. (1971)

gavage Test material (CAS number) : 108-91-8	mg/kg bw/d ↓sign body weight of living fetuses at 100mg No teratogenic effects observed		
In rats and rabbits Doses : 0, 1.5 and 15 mg/kg bw/d Exposure : Before and during mating, gestation and lactation in both sexes, + during the critical period of organogenesis in females Test material (CAS number) : 27817-50-1	No NOAEL identified More resporption site No skeletal, internal or external abnormalities	4	Kennedy G.L. *et al.* (1969)
Monkey Doses : 0, 25, 50, 75 mg/kg bw/d Oral Exposure : GD 20-45 Test material : cyclohexylamine	No significant teratogenic or embryotoxic effects.	eMSCA supports a reliability of 4 (no more information available)	Wilson J.G. (1972)

The data presented result from older studies, not following a OECD-guideline and therefore, several parameters are missing. The data however show a concern for fertility, which is covered by the harmonised classification as repr. Cat. 2. Moreover, due to the known corrosive property and the specific fishy smell of the substance, in combination of the use which is limited to industrial and professional settings, the eMSCA concludes that no further testing is required.

7.9.7.3. Other informations

Table 25 : summary of studies

Method	Result	Rel.	Reference
In vitro Primary cell cultures from testis Doses : 0, 0.1, 1, 3 and 10mM used with four culture dishes at each level Test material (CAS number) : 4998-76-9)	0.1 mM : no morphological changes throughout the 72h culture period 1 mM : 24h : foci of Sertoli cell vacuolation with eosinophilic inclusions but the germ cell populations appeared unaffected After 48h : occasional foci of more severe sertoli cell vacuolation associated with germ cell debris. 3 mM : changes in Sertoli cells and germ cells after 24h After 48 and 72h : Sertoli cell vacuolation was extensive and most germ cells were vacuolated. 10 mM : overtly toxic. After 24h : all Sertoli cells exhibited marked vacuolation + reduction in the number of cells present. After 72h : very few cells remained in the cultures and those present were abnormal		Creasy D.M. *et al.* (1990)
In male rat	Testis :	2	Creasy

<table>
<tr>
<td>(Wistar) : 10 for the control groups and 15 for treated groups
Exposure : 1, 3, 7, 9 and 13w
Doses : 0, 396 mg/kg bw/d, feed
Test material (CAS number) : 4998-76-9</td>
<td>After 3w of exposure : 4 out of 15 treated rats exhibited basal foci of Sertoli cell vacuolation + focal loss of spermatocytes or spermatogonia
Less than 10% of tubules was affected
After 7w of exposure : all treated rats showed Sertoli cell vacuolation. The proportion of affected tubules was greater and was more affected than after 3w. + focal depletion of germ cells.
1 rat exhibited a more severe lesion with extensive Sertoli cell vacuolation and a generalized degeneration and depletion of spermatocytes and spermatids.
After 9w : 5 rats exhibited generalized germ cell depletion affecting over 75% of tubules and 10 rats showed only focal germ cell depletion and sertoli cell vacuolation.
After 13w : in 5 rats, less than 10% of tubules were affected and in 10 rats generalized germ cell degeneration and depletion were observed
Epididymis :
After 7w and more : animals which showed prominent testicular lesions also showed a marked decrease or absence of spermatozoa and an increased numbers of exfoliated germ cells and cellular debris in the epididymal lumen.
After 13w : 3 treated rats showed cystic vacuolation of the epithelial lining in the caput epididymis
Spermatic cords : no abnormalities observed</td>
<td></td>
<td>D.M. et al. (1990)</td>
</tr>
<tr>
<td>DA and Wistar Rat and MF1 mice, male
Doses : 0, 400 mg/kg bw/d
Exposure : 13w, feed
Test material (CAS number) : 4998-76-9</td>
<td>↓ bwg in wistar and DA rats
↓ relative testes weight only in one species of rats (DA rats)
Histo : atrophy of testes in the 2 species of rats (Wistar and DA rats)
All DA rats and 6 wistar rats showed extensive germ cell loss with depletion of spermatogonia, spermatocytes and spermatids in 75-100% of tubules accompanied by varying degrees of apparent Leydig cell hypertrophy or hyperplasia.
In rats : epididymis showed a decreased sperm content and increased number of exfoliated germ cells in the lumen
<table>
<tr><td></td><td></td><td>0 mg</td><td>400 mg</td></tr>
<tr><td rowspan="3">Wistar rat</td><td>Bw (g)</td><td>385</td><td>287*</td></tr>
<tr><td>Testis weight (g)</td><td>1.70</td><td>1.21</td></tr>
<tr><td>Rel. testis</td><td>0.44</td><td>0.43</td></tr>
</table>
</td>
<td>2</td>
<td>Roberts A. et al. (1989)</td>
</tr>
</table>

			weight (g/100g)			
		DA rat	Bw (g)	278	214*	
			Testis weight (g)	1.29	0.55*	
			Rel. testis weight (g/100g)	0.47	0.26*	
		MF1 mouse	Bw (g)	33	37*	
			Testis weight (g)	0.11	0.13	
			Rel. testis weight (g/100g)	0.36	0.37	
In male rats : 0, 200 mg/kg bw/d In male dogs : 250 mg/kg bw/d Exposure : 9w, gavage Test material (CAS number) : 108-91-8	Rat : ↓ bwg, motor activity, testicular and seminal weight, testosterone concentration, spermatogenesis ↑ FSH concentration Dog : ↓ spermatids, spermatogenesis (reversible)					4	James R.W. *et al.* (1981)
Rat Doses : 0, 50, 100, 200, 300 mg/kg bw/d Exposure : 13w Test material (CAS number) : 108-91-8	NOAEL (testicular effects) : 100 mg/kg bw/d ↓ bwg in all groups ↓ sign Testicular weight (at 200 and 300 mg/kg bw/d) + testicular lesions (degenerative changes in the tubules, giant cell formation and atrophy)					4	Brune H. *et al.* (1978)
Rat Doses : 0, 600, 2000, 6000 ppm (ca. 0, 30, 105, 343 mg/kg bw/d) Exposure : 13w, diet Test material (CAS number) : 4998-76-9	↓sign bwg (males : 372, 338, 274g at 0, 2000 and 6000ppm, females : 201, 160, 133g at 0, 2000 and 6000ppm) ↓sign relative gonads weight (males : 0.67 at 6000ppm vs 0.81mg/100g bw in control group; females : 56 at 2000 and 55 at 6000 ppm vs 43mg/100g bw in control) Histo : ↓ spermatogenesis and tubular atrophy in testes at 2000 and 6000ppm					eMSCA supports a reliability of 4 (no more information available)	Gaunt I.F. *et al.* (1974)
Male Rat (Wistar and Sprague Dawley)	NOAEL (reproductive organs) : 2000 ppm ↓sign bwg at 6000 ppm (Wistar : 323, 314, 269 and 181g and Sprague Dawley 438, 422, 380 and 255g at 0, 600, 2000					eMSCA supports a reliability of 4 (no more	Mason P.L. and Thompson G.R. (1977)

Doses : 0, 600, 2000, 6000 ppm (ca. 0, 30, 105, 343 mg/kg bw/d) Exposure : 13w, feed Test material (CAS number) : 4998-76-9	and 6000ppm) ↓sign testes weight (no data available), ↑sign testicular damage in both strains at 6000ppm + no or immobile spermatozoa increased number of decapited sperms in Wistar rats	information available)	
Monkey Doses : 1w 2*17mg/kg bw/d, 1w 2*34mg/kg bw/d, 5w 2*50mg/kg bw/d, 4w 2*17mg/kg bw/d Exposure : 7w and 4w, oral	No NOAEL identified ↓ food intake Testicular damage, effects on spermatogenesis	eMSCA supports a reliability of 4 (no more information available)	Scientific Committee on Food (1995)

Some studies showed lesions in testis (Sertoli cells affected, decrease of testis weight, spermatogenesis affected, …).

The data presented result from older studies, not following a guideline and therefore, several parameters are missing. The data however show a concern for fertility, which is covered by the harmonised classification as repr. Cat. 2. Moreover, due to the known corrosive property and the specific fishy smell of the substance, in combination of the use which is limited to industrial and professional settings, the eMSCA concludes that no further testing is required.

7.9.7.4. Summary and conclusion

Old studies showed effects on testes such as decreased testes weight, testicular atrophy, degeneration of tubuli and reduced spermatogenesis.

The data presented result from older studies, not following a guideline and therefore, several parameters are missing. The data however show a concern for fertility (decreased testes weight, testicular atrophy, degeneration of tubuli and reduced spermatogenesis), which is covered by the harmonised classification as Repr. Cat. 2, H361f. No new data became available since. Moreover, due to the known corrosive property and the specific fishy smell of the substance, in combination of the use which is limited to industrial and professional settings, it seems that exposure to the substance at the workplace will not be unremarked and protective measures can be expected to be in place.

Based on all this information taken together in a weight of evidence approach, the eMSCA concludes that despite the questions that can be raised regarding the reliability of the available long term reproductive toxicity test, currently there is no concern that arises from the uses of the substance as explained above that would merit requiering further information under this substance evaluation or regulatory action.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated

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

Not evaluated

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

Based on the available data, the eMSCA agrees with the classification as Repr. 2; H361f (area of initial concern) and with the classification as Acute Tox. 4* H302, Acute Tox. H312 and Skin Corr. 1B H314.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated

7.10.2. Endocrine disruption - Human health

Not evaluated

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not evaluated

7.11. PBT and VPVB assessment

Persistence: The substance degraded 92% within 20 days in a ready biodegradable test. The P criterion is thus not fulfilled.

Bioaccumulation: The log Kow value is <3.7 and does not meet the screening criterion for B.

Toxicity: The substance is classified as Repr. 2, H361f and thus fulfills the T criterion according to Annex XIII.

Based on the available information, the eMSCA agrees with the conclusion of the registrant(s) that cyclohexylamine is not PBT/vPvB.

7.12. Exposure assessment

The registrant presented exposure scenarios for 3 different uses of the substance:

- Laboratory agent
- Corrosion inhibitor

- pH-regulating agents

The exposure and risk for the environment and for workers was assessed by the eMSCA for manufacture, formulation and use of the substance.

7.12.1. Human health

7.12.1.1. Worker

The eMSCA evaluated the dermal, oral and respiratory exposure to workers for all identified uses, using ECETOC TRA v3.1. The PROCs (1, 2, 3, 4, 8a, 8b, 9 and 15) and duration of exposure proposed by the registrant seemed acceptable. The eMSCA can accept the protective values for respiratory equipment and the use of chemical resistant gloves and these were also included in the eMSCAs assessment.

7.12.1.2. Consumer

No consumer exposure is expected as there are no consumer uses for the substance.

7.12.2. Environment

The eMSCA evaluated the exposure to the aquatic, terrestrial and atmospheric compartment using EUSES 2.1.1 for the manufacture, formulation and three use categories of the substance: laboratory agent, corrosion inhibitor and pH-regulating agents. The registration dossier also mentioned a use as cutting oil, but the registrant mentioned no known tonnage for this use and no evaluation of this use was included in the assessement of the registrant. The eMSCA did not include this use in its assessment.

The evaluation was based on default values or information provided by the registrant where appropriate. The tonnage used for manufacture was the highest tonnage mentioned in the registration dossier. The registrant states that all liquid and solid waste produced during manufacture is incinerated. The eMSCA therefor did not take any emission from manufacture into account.

The registrant indicated that a considerd amount of the manufactured substance is exported outside the EU or used as an intermediate under stricktly controlled conditions. The tonnage band for non-exported and non-intermediate uses is 100-1000 t/a. No information was available on the distribution of the tonnage to the different uses. As a worst case estimation the maximum tonnage was introduced in EUSES for each of the three use categories.

The registrant provided an estimation of the number of industrial sites the substance is used, but given the remaining uncertainty the eMSCA used the default values of EUSES in their evaluation. The registrant also provided an estimation of the number of emission days. As it was unclear how the registrant calculated the number of emission days, the eMSCA used the default values of EUSES. Due to the use of the default values for the number of industrial sites and the number of emission days, the RCRs calculated by the eMSCA are more conservative than those proposed by the registrant.

7.13. Risk characterisation

7.13.1. Human health

7.13.1.1. Worker

Based on the available hazard and exposure data, the eMSCA agrees with the registrant and concludes that no immediate risk to workers is expected.

7.13.1.2. Consumer

There are no consumer uses and therefore no risk to consumers is expected.

7.13.2. Environment

Based on the available data, a limited risk was calculated for the use of laboratory agents and pH regulating agents and the formulation and use of corrosion inhibitors and this for fresh water, fresh water sediment and soil (RCR values close to 1). Due to the application of default values regarding the tonnage distribution for the different uses, the number of industrial sites and number of emission days, these calculations probably present an overestimation of the risk.

Given the above considerations, the eMSCA concludes that there is probably no risk for the different enviromental compartments with the current uses and tonnage of the substance that would merit follow-up regulatory action at EU level.

7.14. References

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7.15. Abbreviations

AOP : Atmospheric Oxidation Program

Approx. : approximately

Bw : body weight

BWG : body weight gain

CHA : Cyclohexylamine

DA rat : Dark Agouti

EORGTS : Extended One Generation Reproductive Toxicity Test

FSH : Follicle Stimulating Hormone

GD : gestanional day

GLP : Good Lanoratory practice

Hb : Hemoglobin

IP : intraperitoneal

ISO : International Standard Organisation

IV : intravenous

LC50 : lethal concentration 50%

LD50 : dose lethal 50%

LOAEL : Lowest Observed Adverse Effect Level

Met. act. : metabolic activation

NADPH : Nicotinamide adenine dinucleotide phosphate oxidase

NOAEL : No Observed Adverse Effect Level

OECD : Organization for Economic Co-operation and Development

PCV : Packed Cell volume

RBC : Red Blood Cell

RD50 : 50% decrease in the respiratory rate

Rel. : reliability

SC : subcutaneous

SD : Sprague Dawley

SIEF : Substance Information Exchange Forums

Sign. : Significant

S. Typh : *Salmonella Typhimurium*

US-EPA : US environmental Protection Agency

US-FDA : USD Food and drug Administration