LATVIJAS VIDES, ĢEOLOĢIJAS UN METEOROLOĢIJAS CENTRS

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

m-phenylenediamine

EC No 203-584-7

CAS No 108-45-2

Evaluating Member State(s): Latvia

Dated: 31.10.2019

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2018

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

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

Foreword

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

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

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

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

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

Contents

Information on toxicokinetics of m-phenylenediamine is limited to a few animal studies with unspecified strain of rats by application of structurally similar substance, C14 labelled benzene-1,4-diamine as read across (Registration dossier, study report, 1981). The substance is quite rapidly eliminated and excreted from the body - approximately 50 % of the dose was excreted in the urine and 35 % in the feces within a 72-hour period. Approximately 3-4 % of the dose remained in the animal at the 72-hour sacrifice. Based

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

M-phenylenediamine was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR/reprotoxic properties

- Exposure/Wide dispersive use (workers), high tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Harmonised Classification and Labelling (Annex VI of CLP Regulation section 3.1.) and the Seveso III Directive (Directive 2012/18/EU which repeals the Seveso II Directive 96/82/EC), Category E1, H2.

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

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

In addition to the existing harmonised classification, STOT RE 2, H373 (liver) classification is proposed by the eMSCA.

With regards to the initial concern on reproductive toxicity the eMSCA is not proposing further classification. Taking into account the new information in the updated registration dossier and additional clarifications provided by the Registrant, the evaluating Member State was able to conclude on endpoints of concern and found no potential, inadequately controlled risks. Hence, the evaluating Member State concludes that the initial concerns can be removed. The above proposal for classification is noted as an additional issue in the substance evaluation.

eMSCA notes that harmonised classification is a legal obligation that must be obeyed by the registrants.

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

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Not applicable.

5.2. Other actions

Not applicable.

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

Based on the severe liver effects at a low dose (7.9.3), the substance meet the criteria for classification as STOT RE 2 H373. So the harmonized classification is considered for this endpoint. However, the substance already have harmonised classification amongst others as Muta 2, H341, so the adequate risk management measures should be in place. Therefore, the official classification proposal for an update of an entry VI of CLP can be submitted depending on priority and available resources.

Part B. Substance evaluation

7. EVALUATION REPORT

According to Article 45(4) of the REACH Regulation Competent Authority of Latvia has initiated substance evaluation for m-phenylenediamine EC No 203-584-7 (CAS No 108-45-2), based on a registration submitted by the concerned registrant and prepared the decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to exposure to workers, high tonnage, wide dispersive use and possible CMR/reprotoxic properties m-phenylenediamine was included in the Community rolling action plan (CoRAP) for substance evaluation according to Article 44(2) of the REACH Regulation to be evaluated in 2018. The CoRAP was published on the ECHA website on 20 March 2018.

7.1. Overview of the substance evaluation performed

M-phenylenediamine was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR/reprotoxic properties

- Exposure/Wide dispersive use (workers), high tonnage.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
CMR/reprotoxic properties	Concern not substantiated. No further action.
Exposure/Wide dispersive use (workers), high tonnage	Acceptable. No further action.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, M-phenylenediamine was included on the Community rolling action plan (CoRAP) for evaluation in 2018. The Competent Authority of Latvia (eMSCA) was appointed to carry out the evaluation.

The evaluation of M-phenylenediamine was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP.

The reprotoxicity endpoint, exposure for workers, professional and industrial uses and high tonnage were evaluated by eMSCA. The evaluation was based upon the available data provided in the registration dossier(s) including the Chemical Safety report (CSR), Harmonised C & L inventory and Seveso Directive.

During the process, fluent communication was established between the eMSCA and the lead registrant. On 28.02.2018. the Lead Registrant submitted to ECHA an update of the registration dossier containing the information needed. This new information has been assessed by the eMSCA. Finally, on 18.03.2019 the eMSCA has concluded that the new information submitted by the registrants clarifies the concerns.

7.3. Identity of the substance

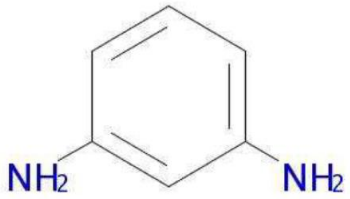
Table 4

SUBSTANCE IDENTITY	
Public name:	m-phenylenediamine
EC number:	203-584-7
CAS number:	108-45-2
Index number in Annex VI of the CLP Regulation:	612-147-00-3
Molecular formula:	C6H8N2

Molecular weight range:	108.1 g/mol
Synonyms:	m-diaminobenzene m-aminoaniline benzene-1,3-diamine

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid
Melting/freezing point	63.2°C at 101 325 Pa According to guideline OECD 102
Boiling point	284°C at 101 325 Pa Experimental data according to ASTM Method D 1120
Relative density	0.709 g/mL at 22°C Experimental data according to ASTM Method No. E-727
Vapour pressure	0.038 Pa at 20°C According to guideline OECD 104
Water solubility	429000 mg/L at 20°C According to guideline OECD 105
Partition coefficient n-octanol/water (Log Kow)	-0.39 at 20°C Data is calculated
Flammability	Non flammable Experimental data according to EU test method A.10 (Baker, 2010).
Explosive properties	Non explosive In accordance with column 2 of REACH Annex VII, the study is not required, no chemical groups associated with explosive properties present in molecule.
Oxidising properties	Non oxidising

	The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with oxidising properties and hence.
Granulometry	11.1% <180 µm According to HSE Guidance
Stability in organic solvents and identity of relevant degradation products	In accordance with column 1 of REACH Annex IX, the study is not required, as the stability of the substance is not considered to be critical.
Dissociation constant	4.58 pKa at 20°C Data is calculated
Surface tension	The study does not need to be conducted because surface activity is not a desired property of the material.
Flash point	The study does not need to be conducted because the substance is a solid
Autoflammability/self-ignition temperature	The study does not need to be conducted because the substance is a solid having a melting point <= 160°C
Viscosity	The study does not need to be conducted because the substance is a solid

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

7.5.2. Overview of uses

Table 7

USES	Use(s)
Uses as intermediate	01 - Industrial use as intermediate
Formulation	-
Uses at industrial sites	02 – Transported isolated intermediate used under Strictly Controlled Conditions 03 – Manufacture of polymer 04 – Industrial processing

Uses by professional workers	-
Consumer Uses	-
Article service life	-

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)***		
612-147-00-3	m-phenylenediamine	203-584-7	108-45-2	Acute Tox. 3 Acute Tox. 3 Skin Sens. 1 Eye Irrit. 2 Acute Tox. 3 Muta 2 Aquatic Acute 1 Aquatic Chronic 1	H301 H311 H317 H319 H331 H341 H400H410		

*H301: Toxic if swallowed.
H311: toxic in contact with skin.
H331: Toxic if inhaled.
H319: Causes serious eye irritation.
H317: May cause an allergic skin reaction.
H341: Suspected of causing genetic defects <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>.
H400: Very toxic to aquatic life.
H410: Very toxic to aquatic life with long lasting effects.

7.6.2. Self-classification

- In the registration(s)*:*

- In the individual submission of registration for intermediate the harmonised classification of m-phenylenediamine is used. However, in the section of labelling H400 and H410 are not indicated, instead of that the H411 (Toxic to aquatic life with long lasting effects) is included.

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

  STOT RE 2, H373
  Aquatic Chronic 2, H411

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Information on toxicokinetics of m-phenylenediamine is limited to a few animal studies with unspecified strain of rats by application of structurally similar substance, C14 labelled benzene-1,4-diamine as read across (Registration dossier, study report, 1981). The substance is quite rapidly eliminated and excreted from the body - approximately 50 % of the dose was excreted in the urine and 35 % in the feces within a 72-hour period. Approximately 3-4 % of the dose remained in the animal at the 72-hour sacrifice. Based on the study results, it is concluded that the test substance has a low bioaccumulation potential and is primarily excreted in the urine as an N,N'-diacetyl metabolite.

7.9.2. Acute toxicity and Corrosion/Irritation

The registrants self-classify the substance as Acute Tox Cat. 4 for all three routes of exposure – oral (harmful if swallowed), inhalation (harmful if inhaled) and dermal (harmful in contact with skin) This assessment is based on the following animal studies:

- on male rats (Crl:CD BR) by application of m-phenylenediamine by means of oral gavage: estimated Approximate Lethal Dose (ALD) 450 mg/kg bw (Registration dossier, study report, 1996) (study characterized with Klimisch score 2);
- on male rats (Crl:CD) by m-phenylenediamine aerosol inhalation (only nose): estimated 4-hr LC50 3.2 mg/L air (Registration dossier, study report, 1982) (study characterized with Klimisch score 2);
- on albino rabbits by means of dermal occlusive coverage of structurally similar substance benzene-1,4-diamine with vehicle hydrophilic ointment or polypropylene glycol (read across approach): estimated ALD 1500 mg/kg/bw (Registration dossier, study report, 1970) (study characterized with Klimisch score 2).

The eMSCA notes that there is some discrepancy with the result values for acute toxicity and the current harmonised classification. Current classification is Acute Tox Cat 3 (Toxic if swallowed, in contact with skin and if inhaled), but the studies in the dossier imply milder category 4. The eMSCA does not have the historical knowledge on the underlying information that was used to establish the current harmonised classification. However, it is an obligation to follow the established harmonised classification.

The substance has harmonized classification and labelling as an eye irritant category 2, H319 (causes serious eye irritation) according to CLP criteria, and based on the available information, the eMSCA supports this classification. No relevant information is available concerning respiratory system.

Sensitisation

One key animal study on female CBA mice skin sensitization is provided performed similar to OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay (LLNA)) and characterized with Klimisch score 2 (Ashby et al., 1995). m-phenylenediamine was tested at concentrations of 2, 5, and 10 % and was found to have a stimulation index - test/control ratio of 11.7, 15.4, and 19.2, respectively. The overall stimulation index (EC3) - the effective concentration of the test substance required to produce a three-fold increase in

the stimulation index compared to vehicle-treated controls was calculated to be 0.49 % (Gerberick et al., 2005, based on original data obtained by Ashby et al., 1995). Based on this information, the substance is considered to be a sensitising agent in the LLNA assay. The substance has the harmonized classification as Skin Sens. Cat. 1, H317 (may cause an allergic skin reaction) according to the CLP Regulation. Based on available data, the eMSCA can support this classification.

No data are available for respiratory sensitisation, but there were no observations of respiratory sensitisation during inhalation exposure with the substance.

7.9.3. Repeated dose toxicity

The Registrant(s) concluded that the m-phenylenediamine should not be classified as repeated dose toxicant according to the CLP Regulation. This conclusion is based on 90 days repeated dose toxicity study on male and female rats (OFA(SD)SPD) by oral gavage performed similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) and characterized with Klimisch score 2 (Registration dossier, study report, 1982). Rats were orally gavaged with the test substance for 90 days at levels between 2 and 18 mg/kg bw (6 days per week). The statistically significant test-substance related effects were observed in the 18 mg/kg bw group (increase in the absolute and relative liver weight (both sexes) as well as increase in the kidney weight for females, increase in the amount of serious degenerative liver damage (nuclear pyknosis)). Based on this information, the NOAEL of 6 mg/kg bw was determined. This NOAEL for repeated dose toxicity was further used for risk assessment of m-phenylenediamine.

Based on the data obtained, eMSCA considers that STOT RE 2, H373 (liver) classification is warranted.

7.9.4. Mutagenicity

One in vitro key study on mutagenicity submitted by the registrants - bacterial reverse mutation assay with S. typhimurium TA 1535, TA 1537, TA 1538 and TA 100 with and without metabolic activation performed similar to OECD Guideline 471 (Registration dossier, study report, 1975) (reliability 2). Dose levels between 1 and 1000 µg/plate of m-phenylenediamine have been tested, and a number of positive controls with 4-o**-**tolylazo-o-toluidine and N-methyl-N'-nitro-N-nitrosoguanidine were applied. The test result was positive for S. typhimurium TA 1538 with metabolic activation and negative for all other applications (S. typhimurium strains).

In addition, one key in vivo erythrocyte micronucleus assay (chromosome aberration assay) in Crl:CD-1(ICR)BR male and female mice is performed similar to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) (Registration dossier, study report, 1991, reliability 2). m-phenylenediamine was administered by oral gavage at the following doses between 16 and 65 mg/kg/day. A positive control with cyclophosphamide was applied as well. No genotoxicity was detected at any exposure level in the presence of general toxicity at the same time.

The substance is classified as Muta 2, H341 according to CLP Regulation (suspected of causing genetic defects). Neither further information nor additional classification is requested in this substance evaluation.

7.9.5. Carcinogenicity

Only one supportive study on carcinogenicity by oral route in B6C3F1 mice (both male and female) assessed as "reliable" (Klimisch score 2) is provided by the registrants (Amo et al., 1988). m-phenylenediamine was administered in drinking water at concentrations of 0.02 % and 0.04 % giving calculated doses of 23 mg/kg bw/day for females and 19.8 mg/kg bw/day for males at the 0.02 % concentration level and 41.8 mg/kg bw/day for

females and 38.2 mg/kg bw/day for males at the 0.04 % concentration level. The animals were treated for 78 weeks, after which all mice were given purified water until 83-85 weeks. Necropsy was performed on all mice and histology was performed on selected tissues. Organ-weight ratios were determined as well. No neoplastic effects have been observed at any dose levels. Therefore, the NOAEL was estimated to be 41.8 mg/kg bw/day for females and 38.2 mg/kg bw/day for males (the highest doses tested).

No data are available on carcinogenicity after exposure via inhalation, dermal or other routes as well as no human data are available. Based on results of the repeated oral study with drinking water the registrants claim that m-phenylenediamine does not need to be classified for carcinogenicity according to CLP Regulation, and the eMSCA can support this conclusion taking into account the negative results from in vivo mutagenicity studies also. Thus, neither further information nor additional classification is requested in this substance evaluation.

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

Effects on fertility

No human or animal data are available. The eMSCA considers that request for additional information on fertility is not necessary in this substance evaluation as the uses are demonstrated to be under controlled conditions in the occupational environment.

Effects on development

No human data are available. With respect to animal studies, one supportive study on OFA (SD) SPF rats conducted similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study) and characterised as reliability 2 study is submitted (Registration dossier, study report, 1981).

m-phenylenediamine was administered daily by oral gavage on days 6-15 of gestation applying the following concentrations: 10, 30, and 90 mg/kg bw/day. Different adverse developmental toxicity effects - reduction in the number of litters with live pups, lower average placenta weights, fewer total number of live pups, fewer live pups per litter, lower average body weight of a live pup as well as an increase in the total resorptions, greater total number of late-dying embryos, greater total number of early dying embryos, higher percentage of dams with foetuses having minor alterations and greater frequency of foetuses having minor malformations occurred in the 90 mg/kg bw/day exposure group only. These detrimental effects can be attributed to general maternal toxicity in the same 90 mg/kg bw/day exposure group characterized by lethality of maternal animals - six of the test animals died before the 20th gestation day.

The NOAEL for maternal systemic effects as well as for foetal developmental effects was estimated to be 30 mg/kg bw/day.

Considering that the exposure potential of this substance seems to be very low, neither further information nor additional classification is requested in this substance evaluation.

7.9.7. Hazard assessment of physico-chemical properties

m-phenylenediamine is not explosive and oxidising substance based on its structural assessment. Furthermore, based on the available study the substance is not flammable.

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

The eMSCA acknowledges that the estimated NOAEL for repeated dose toxicity 6 mg/kg bw/day is a proper point of departure (POD) for further risk assessment of m-phenylenediamine as it covers all other possible critical endpoints including mutagenicity, carcinogenicity and reprotoxicity. In addition, skin sensitisation endpoint for assessment of acute local effects shall be considered.

Table 9

CRITICAL DNELS/DMELS RECALCULATED BY THE EMSCA					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Workers					
Repeated dose toxicity	Long-term - systemic effects (inhalation route)	90 days repeated dose toxicity study on rats (OFA(SD)SPD) by oral gavage (Registration dossier, study report, 1982)	NOAEL: 6 mg/kg bw/day *	DNEL: 0.11 mg/m³ ***	AF=100 (dose response relationship "1" x difference in duration of exposure "1" x interspecies "2.5" x intraspecies "5" x uncertainty factor for the quality of the whole database "4" x remaining uncertainties "2")
Repeated dose toxicity	Long-term - systemic effects (dermal route)	90 days repeated dose toxicity study on rats (OFA(SD)SPD) by oral gavage (Registration dossier, study report, 1982)	NOAEL: 6 mg/kg bw/day	DNEL: 0.12 mg/kg bw/day	AF=50 (oral to dermal extrapolation "1" x interspecies "10" x intraspecies "5" x exposure duration "1")
Skin sensitisation	Acute local effects (dermal route)	Skin sensitisation study on CBA mice (Ashby et al., 1995;	Overall stimulation index: 0.49 % (122.5 µg/cm²)	DNEL: 0.49 µg/cm²	AF=250 (dose response relationship "2" x interspecies

		Registration dossier, 2005)			"10" x intraspecies "5" x remaining uncertainties "2.5")
General population					
Repeated dose toxicity	Long-term - systemic effects (inhalation route)	90 days repeated dose toxicity study on rats (OFA(SD)SPD) by oral gavage (Registration dossier, stydy report, 1982)	NOAEL: 6 mg/kg bw/day **	DNEL: 0.03 mg/m³	AF=200 (dose response relationship "1" x difference in duration of exposure "1" x interspecies "2.5" x intraspecies "10" x uncertainty factor for the quality of the whole database "4" x remaining uncertainties "2")
Repeated dose toxicity	Long-term - systemic effects (dermal route)	90 days repeated dose toxicity study on rats (OFA(SD)SPD) by oral gavage (Registration dossier, study report, 1982)	NOAEL: 6 mg/kg bw/day	DNEL: 0.06 mg/kg bw/day	AF=100 (oral to dermal extrapolation "1" x interspecies "10" x intraspecies "10" x exposure duration "1")
Skin sensitisation	Acute local effects (dermal route)	Skin sensitisation study on CBA mice (Ashby et al., 1995; Gerberick et al., 2005)	Overall stimulation index: 0.49 % (122.5 µg/cm²)	DNEL: 0.25 µg/cm²	AF=500 (dose response relationship "2" x interspecies "10" x intraspecies "10" x remaining uncertainties "2.5")
Repeated dose toxicity	Long-term - systemic effects (oral route)	90 days repeated dose toxicity study on rats (OFA(SD)SPD) by oral gavage (Registration dossier, stydy report, 1982)	NOAEL: 6 mg/kg bw/day	DNEL: 0.06 mg/kg bw/day	AF=100 (oral to dermal extrapolation "1" x interspecies "10" x intraspecies "10" x exposure duration "1")

* the dose descriptor starting point = 6 mg/kg bw/day x 1/(0.38 m³/kg bw/d) x 6.7 m³/10 m³ = 10.58 mg/m³, where:

- NOAEL for developmental toxicity through oral route 750 mg/kg bw/day
- route-to-route extrapolation factor from oral to inhalation "1"
- a standard breathing volume for the rat 0.38 m3/kg bw/d for 8 hours exposure
- correction factor for 8 hours exposure of workers – basic caloric demand 6.7 m³
- correction factor for 8 hours exposure of workers – caloric demand under light activity 10 m³

** the dose descriptor starting point = 6 mg/kg bw/day x 1 /1.15 m³/kg bw/d = 5.22 mg/m³, where:

- route-to-route extrapolation factor from oral to inhalation "1"
- a standard breathing volume for the rat 1.15 m³/kg bw/d for 24 hours exposure

*** instead of 0.24 mg/m³ wrongly calculated by the registrants

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

Harmonised classification according to CLP regulation:

Muta. 2, H341 (Suspected of causing genetic defects)
Acute Tox. 3 *, H331 (Toxic if inhaled)
Acute Tox. 3 *, H311 (Toxic in contact with skin)
Acute Tox. 3 *, H301 (Toxic if swallowed)
Eye Irrit. 2, H319 (Causes serious eye irritation)
Skin Sens. 1, H317 (May cause an allergic skin reaction)
Aquatic Acute 1, H400 (Very toxic to aquatic life)
Aquatic Chronic 1, H410 (Very toxic to aquatic life with long lasting effects)

Additional harmonized STOT RE 2, H373 (liver) classification is proposed by the eMSCA.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not applicable.

7.10.2. Endocrine disruption - Human health

Not applicable.

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

Not applicable.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

In confidential annex, which is removed from this public version of the report.

7.13. Risk characterisation

7.13.1. Human health

Workers

Risk characterisation for workers is based on possible risk from long-term exposure having potential to cause repeated dose toxicity effects. The related reference values - DNELs for inhalation and dermal exposure are applied. It is considered that oral exposure cannot cause any concern in occupational environment. In addition, risk from acute local dermal exposure is assessed based on the DNEL for skin sensitisation.

Risk characterisation for repeated dose toxicity (long-term systemic exposure)

		Major use at industrial sites as intermediate, manufacture of plastic products	Minor use – industrial processing
Inhalation exposure	The highest exposure concentration estimated (mg/m³)	6.76E-02	6.31E-02
	DNEL (mg/m³)	0.11	
	RCR	**0.61**	**0.57**
Dermal exposure	The highest exposure concentration estimated (mg/kg bw/day)	2.54E-01	6.86E-02
	DNEL (mg/kg bw/day)	0.12	
	RCR	**2.11**	**0.57**
Total exposure	**RCR**	**2.72**	**1.14**

Risk characterisation for acute local effects (skin sensitisation)

	Major use at industrial sites as intermediate,	Minor use – industrial processing

		manufacture of plastic products	
Dermal exposure (skin sensitisation)	Exposure concentration estimated (µg/cm^2)	0.2 *	0.2 *
	DNEL (µg/cm^2)	0.49	0.49
	RCR	**0.41**	**0.41**

* highly protective PPE - nitrile gloves are used

According to the eMSCA's evaluation, the Risk Characterisation Ratio (RCR = Exposure concentration/DNEL) for workers through inhalation route is well below "1" for both industrial usages based on the highest exposure estimate within each use. Following, all other PROCs included in the specific use do not pose long – term inhalation risk for workers.

As regards the dermal exposure, with assumption that PPE is not used the estimated highest exposure values exceed the RCR value "1". Following, highly protective PPE - nitrile gloves shall be applied to reduce the dermal exposure. In addition, protection against skin sensitisation is ensured as well.

General population

Risk characterisation for general population is based on possible risk from long-term exposure man via environment having potential to cause repeated dose toxicity effects. The related reference values - DNELs for inhalation and oral exposure are applied.

Risk characterisation for repeated dose toxicity (long-term systemic exposure)

		Major use at industrial sites as intermediate, manufacture of plastic products	Minor use – industrial processing
Inhalation exposure	The estimated PEC_{local} (mg/m³)	3.84E-14	4.42E-14
	DNEL (mg/m³)	0.03	
	RCR	**1.28E-12**	**1.47E-12**
Oral exposure	Estimated local oral exposure (mg/kg bw/day)	2.23E-06	5.24E-07
	DNEL (mg/kg bw/day)	0.06	
	RCR	**3.71E-05**	**8.73E-06**

Total exposure	**RCR**	**3.71E-05**	**8.73E-06**

According to the eMSCA's evaluation, the RCR for general population is extremely low and well below "1" for both industrial usages.

7.14. References

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7.15. Abbreviations

ALD - Approximate Lethal Dose

eMSCA – evaluating Member State Competent Authority

CMR - Carcinogenic, mutagenic or toxic to reproduction

CSR - Chemical Safety Report

DNEL - Derived no-effect level

NOAEC - No observed adverse effect concentration

NOEL - No observed effect level

OECD - Organisation for Economic Co-operation and Development

SVHC – Substance with very high concern