SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2,2′-methyliminodiethanol

EC No 203-312-7

CAS No 105-59-9

Evaluating Member State(s): UK

Dated: August 2017

Template Version 2.1
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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

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

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

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

Reproductive toxicity: This was identified as an area of concern for human health. Adverse toxicity to reproductive/developmental parameters was observed in the oral reproduction/developmental toxicity screening study (rat, OECD 421) at the highest dose (1000 mg/kg bw/day MDEA). However, a complete set of reproductive toxicity information was not available for MDEA. Instead, a two-generation reproductive toxicity study (rat, similar to OECD 416) and a pre-natal developmental toxicity study (rabbit) was read across from another substance (2-aminoethanol (MEA), CAS No 141-43-5 (EC No 205-483-3)). Therefore, the validity of the proposed read across should be assessed during the evaluation.

In addition, the available pre-natal developmental toxicity studies (one study conducted with MDEA and one study read across from MEA) were conducted via the dermal route. Therefore, an assessment should be made as to whether the dermal route is appropriate.

The DNEL (derived no effect level) for long-term inhalation exposure is based on route-to-route extrapolation from dermal data. Therefore, further assessment is warranted to confirm that the DNEL provides adequate basis to assess local and systemic effects from long-term inhalation exposure.

During the evaluation other concerns regarding human exposure were identified. Differences were identified between registrants in the exposure values that have been calculated for scenarios that are common to more than one registrant and there was not enough information in the CSRs to understand the reasons for these differences. Also, in some cases it was not possible for the eMSCA to reproduce the exposure values quoted in the CSR based on the information given. It is therefore not clear if the Risk Management Measures (RMM) that are being recommended are appropriate in all cases. Concerns were also identified about the efficiency of gloves that has been assumed where this RMM has been recommended.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

MDEA was not identified as a priority substance under the Existing Substances Regulation and no other regulatory processes have been initiated for this substance. No occupational exposure limit values are listed for this substance in the IFA GESTIS International Limit Values database[2].

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**

[2] http://limitvalue.ifa.dguv.de/

Need for follow-up regulatory action at EU level *[if a specific regulatory action is already identified then, please, select one or more of the specific follow-up actions mentioned below]*	
Harmonised Classification and Labelling	
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

On the basis of this evaluation the eMSCA does not consider that there is a need for regulatory action.

4.1.1. Harmonised Classification and Labelling

Not applicable.

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

Table 2

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

Clarification of hazard

The evaluation confirmed that adverse toxicity to reproductive/developmental parameters were observed at a high dose and only together with parental toxicity in the oral reproduction/developmental screening study conducted with MDEA; this finding is acknowledged by the Registrants.

No signs of developmental toxicity were observed in the pre-natal developmental toxicity study (rat, dermal route) conducted with MDEA. The exposure assessment indicated that there were no registered consumer uses for MDEA. Furthermore, as the substance has a very low vapour pressure, exposure via the inhalation route is unlikely. The dermal route is thus concluded to be the most relevant route of exposure. The eMSCA also notes that information on developmental toxicity was provided by the reproductive/developmental toxicity screening study, in which MDEA was administered by the oral route. Therefore, the concern that the dermal route might not be appropriate for the conduct of the developmental toxicity studies has been clarified.

The concerns for reproductive/developmental toxicity were clarified. No further information is requested under this evaluation.

The eMSCA considered that route-to-route extrapolation from a dermal study to a long-term inhalation DNEL was not appropriate. As systemic effects were seen via oral exposure, the route-to-route extrapolation from oral exposure is considered to be more applicable and was used to derive a worker systemic long-term DNEL for the inhalation route.

Human health exposure

For MDEA, the eMSCA has performed its own exposure assessment. Instead of relying on Tier 1 modelling tools it has used the ART to estimate inhalation exposures for aerosol generating processes (PROCs 7, 11, 17 and 18). In order to generate predictions using this tool, several assumptions have been made about the nature of the activities being performed and the nature of the workspaces and the eMSCA accepts that this introduces uncertainty into its exposure assessment. For all other processes where MDEA is present as a liquid, the eMSCA has set an upper limit of 1.5 mg/m3 (approximately 10% of the SVC). This upper limit has not been modified to take account of any risk management measures e.g. LEV, and therefore represents a realistic worst case. The eMSCA does not consider that it is necessary to quantify exposure to residual MDEA in cured foams or solidified concrete. In these situations, the greater risk posed to workers will arise from process generated dusts and as such, the control measures that are applied to limit exposure to this dust will also manage any risks arising from residual MDEA.

For its dermal exposure assessment, the eMSCA has used estimates generated by the ECETOC TRA tool version 3 (a recently published validation study indicated that the performance of this tool was similar to the performance of other dermal exposure estimation tools). The eMSCA has applied the lowest glove efficiency in its calculations (80%) and has also estimated dermal exposure without gloves where one or more registrants indicates this option in their exposure scenarios.

Although the eMSCA has obtained RCRs > 1 for several scenarios using its own DNELs and exposure predicitons, these RCRs are mainly driven by conservativism in the DNEL calculations and conservative assumptions about the effectiveness of gloves at limiting dermal exposure. For these reasons, the RCRs > 1 are not considered to signify serious risks to workers health under the working conditions described in exposure scenarios. However, there is a possibility that mild skin irritation may occur if sufficient attention is not paid to managing dermal exposure, particularly for situations where gloves are not identified as a necessary risk management measure. It will therefore be helpful if the registrants update registrations with the following (this takes into account information requested in the draft decision which has not been provided):

- To help limit dermal exposure it is important that registrants emphasise the need to implement effective glove management programmes and adopt good housekeeping practices in their exposure scenarios. It would also be useful to revisit situations where gloves are not currently worn to see (in discussion with downstream users) if tasks can be modified and additional risk management measures implemented to reduce opportunities for skin contact.

- Where gloves are required, all registrants must provide the information about suitable glove materials, thicknesses and breakthrough times described in the IR and CSA Guidance Chapter R14, section R.14.5.3.

- To help reduce the uncertainties in the exposure assessment registrants should seek more information from downstream users about the conditions of use and risk management measures that are typically applied. This is particularly important for spraying activities. The information should be presented transparently in their CSRs.

- Registrants should also transparently describe how cleaning and maintenance activities have been covered in each scenario.

- Given the likelihood that the Tier 1 exposure modelling tools that registrants are using will overestimate potential inhalation exposure, it would be useful if registrants gave further thought to the way they assess potential airborne concentrations associated with each use.

5.2. Other actions

Not applicable

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

Not applicable

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

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

Reproductive toxicity: This was identified as an area of concern for human health. Adverse toxicity to reproductive/developmental parameters was observed in the oral reproduction/developmental toxicity screening study (rat, OECD 421) at the highest dose tested (1000 mg/kg bw/day MDEA). However, a complete set of reproductive toxicity information was not available for MDEA. Instead, a two-generation reproductive toxicity study (rat, similar to OECD 416) and a pre-natal developmental toxicity study (rabbit) was read across from another substance (2-aminoethanol (MEA), CAS No 141-43-5 (EC No 205-483-3)) in order to meet the information requirements. The plausibility of the read-across argument was assessed to determine if it lent support to the eMSCA's conclusion.

In addition, the available pre-natal developmental toxicity studies (one study conducted with MDEA and one study read across from MEA) were conducted via the dermal route. Therefore, an assessment should be made as to whether the dermal route is appropriate.

The Registrant's proposed DNEL (derived no effect level) for long-term inhalation exposure is based on route-to-route extrapolation from dermal data. Therefore, further assessment is warranted to confirm that the DNEL provides an adequate basis to assess local and systemic effects from long-term inhalation exposure.

During the evaluation other concerns were identified. The additional concerns were:

For human exposure, differences were identified between registrants in the exposure values that have been calculated for scenarios that are common to more than one registrant and there was not enough information in the CSRs to understand the reasons for these differences. Also, in some cases it was not possible for the eMSCA to reproduce the exposure values quoted in the CSR based on the information that has been given. It is therefore not clear if the Risk Management Measures (RMM) that are being recommended are appropriate in all cases. Concerns were also identified about the efficiency of gloves that has been assumed where this RMM has been recommended.

Table 3

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Human Health – Reproductive toxicity	*The evaluation confirmed that adverse toxicity to reproductive/developmental parameters was observed at a very high dose together with parental toxicity in the oral reproduction/developmental screening study conducted with MDEA; this finding is acknowledged by the Registrants.* *No signs of developmental toxicity were observed in the pre-natal developmental*

	toxicity study (rat, dermal route) conducted with MDEA. As the substance has a very low vapour pressure, the dermal route is concluded to be the most relevant route of exposure for workers; there are no consumer uses for which a consideration of exposure via the oral route would also be necessary. Notwithstanding, some information on the developmental toxicity of MDEA via the oral route is available from the reproduction / development screening study. Therefore, the concern that the dermal route might not be appropriate for the conduct of the toxicological studies has been clarified. *The concerns for reproductive/developmental toxicity were clarified. No further information was requested.*
Human Health - DNEL	*The eMSCA considered that route-to-route extrapolation from a dermal study to a long-term inhalation DNEL was not appropriate. As systemic effects were seen via oral exposure, the route-to-route extrapolation from oral exposure is considered to be more applicable and was used to derive a worker systemic long-term DNEL for the inhalation route.*
Human Exposure	*Owing to uncertainties in the exposure information presented in registrations, the eMSCA has calculated its own exposure estimates. Using these exposure estimates the eMSCA has been able to reach a conclusion about potential risk. Therefore, although it does not have all of the information requested in the draft decision, the eMSCA does not intend to take further regulatory action. To cover the possibility that mild skin irritation could occur in certain situations and to help lessen the uncertainty in the registrants (and eMSCA's) exposure assessments, a series of recommendations have been made for further information to be provided in registration updates.*
Environment	*A brief review of all of the relevant environmental fate, behaviour and toxicity data was performed. This confirmed the low environmental hazard profile of the substance – a high level of biodegradation and low ecotoxicity. Two studies were targeted for a more in depth evaluation. The first was the study used to provide the aquatic PNEC. The second was a related acute aquatic study where effects were observed, but it was only used a supporting study (in contrast to the key study where no toxicity was observed).*

7.2. Procedure

Initial assessment period: evaluation of existing information 20th March 2013 to 19th March 2014

The evaluation focussed on the information provided in the registration dossier and CSR.

The evaluating MSCA (eMSCA) met with the lead registrant in March 2013 to discuss the substance evaluation procedure and the justification for inclusion of MDEA in the CoRAP. Subsequent to this meeting, two of the registrants updated their registration dossier (May 2013) to include a justification for read across to data on 2-aminoethanol (MEA) and further information on the uses of MDEA. For these two registrants, the updated registration dossier formed the basis of the evaluation. There were no other updates to the registration dossiers during the initial assessment period.

During the initial evaluation period the Registrants extended the read-across to also include 2,2',2"-Nitrilotriethanol (TEA) and 2,2'-iminodiethanol (DEA). Both MEA and TEA were on the CoRAP for evaluation in 2014-2015 so we agreed with the Polish CA (which produced the justification documents for these two substances) to take over those evaluations in order to consider the three substances together. DEA was evaluated by the German REACH CA in 2012-2013.

Following consultation with ECHA, a draft decision for MDEA was issued to the Registrants but the evaluation was put on hold pending the evaluations of MEA and TEA so that the conclusions of the three evaluations and any information requests could be aligned. In April 2014, we informed the Registrants that this was our intention. In the interim some of the information requested in the draft decision was provided by the registrants.

Once the evaluations of MEA and TEA were concluded, both with no action, the remaining information requests in the draft decision for MDEA were reconsidered. Subsequently, as this information would not result in regulatory risk management, it was decieded to terminate the evaluation without issuing a formal decision. ECHA was informed of this by e-mail on 5 September 2016.

Chemistry

Analytical information provided in the dossiers (submitted up to August 2017) was assessed to confirm substance identity and composition.

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

Human health

The grounds for concern were the focus of the human health assessment. However, an evaluation of all the available information was undertaken to identify other possible areas of concern and inform on the proposed read-across to data on MEA for reproductive/developmental toxicity. The initial evaluation was based on information contained in the IUCLID 5 file, CSR and justification document for read-across to MEA (May 2013). Where more detail was required, the original study reports/publications were requested from the registrants and evaluated in full.

During period 2013-2014: Following a discussion with the eMSCA, the Registrants provided additional information to support the proposed read-across and mode-of-action arguments.

A literature search conducted by the eMSCA in July 2013 identified one study (an eye irritation study (non-guideline)), which was not considered in the registration dossier; information from this study has been evaluated and included in the present evaluation report.

Human exposure

The initial exposure evaluation was based on the updated CSRs that were submitted by the lead registrant and one other registrant in May 2013 and the CSRs that were available

in REACH IT in March 2013 for the remaining three registrants. All of the human exposure information provided by each registrant in their CSR was assessed.

During period 2013-2014: The lead registrant and one of the four joint registrants updated their CSRs and the eMSCA assessed the information that was available in these updates.

The new information did not provide sufficient detail for the eMSCA to reach a conclusion about risk and the adequacy of the recommended RMMs and therefore a draft decision document was prepared asking for further information from each registrant which would help the eMSCA understand the reasons for the differences that have been identified between exposure assessments and to confirm that the PROC codes and input parameters that have been selected for each scenario match the processes, tasks and activities that the scenario is intended to cover. Additional information was also required from some individual registrants to enable the eMSCA to reproduce the exposure values quoted in their CSRs and to confirm that suitable RMMs are being recommended.

Some further information was provided during the period this evaluation was put on hold which enabled the eMSCA to finalise its evaluation. The exposure assessment takes account of the information provided in all registrations and updates submitted up to August 2017.

Environment

The substance was not evaluated on the basis of any environmental concern. Due to this, only a brief review of all of the relevant environmental fate, behaviour and toxicity data was performed. This confirmed the low environmental hazard profile of the substance – a high level of biodegradation and low ecotoxicity. Two studies were targeted for a more in depth evaluation. The first was the study used to provide the aquatic PNEC. The second was a related acute aquatic study where effects were observed, but it was only used a supporting study (in contrast to the key study where no toxicity was observed).

7.3. Identity of the substance

Information on substance identity as published on the ECHA dissemination site is given in the table below.

Table 4

SUBSTANCE IDENTITY	
Public name:	2,2'-methyliminodiethanol
EC number:	203-312-7
CAS number:	105-59-9
Index number in Annex VI of the CLP Regulation:	603-079-00-5
Molecular formula:	$C_5H_{13}NO_2$
Molecular weight range:	119.1622
Synonyms:	Methyldiethanolamine N- Methyldiethanolamine MDEA MethylDEA

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

Structural formula:

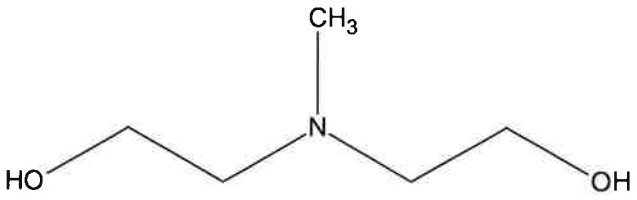

Table 5

Choose the appropriate title from this dropdown menu.			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
2,2'-methyliminodiethanol (203-312-7)	> 80%		Exact composition confidential

7.4. Physico-chemical properties

The physico-chemical properties reported in the registration dossiers are summarised in Table 6.

Many of the values are from in-house methods and are reported with very little detail. In most cases literature values are provided as supporting information and generally these are in agreement. It would be helpful if more detail regarding the methods used was included in the dossier & where there is disagreement between the measured and literature values this should be commented on.

Three physico-chemical properties are used in other areas of this evaluation and are described in more detail below;

Water Solubility;

The two solubility results were taken from secondary literature respectively giving values of 1000 g/l at 25°C and >1000 g/l at 20°C. Neither specifies purity or method of measurement.

Octanol-water Partition Co-efficient;

The key study provided gave a measured value of -1.16 at 23°c and pH 10.5 using the OECD Guideline 107; Partition Coefficient (n-octanol / water), Shake Flask Method.

An older in-house method determined the content of amine in the equilibrium phases of octanol and water using titration and gave a measured log Pow of -1.08 (mean of 3 values). According to the registrant the analysed mixtures are in a protolytic equilibrium, therefore the partition coefficient is strongly pH-dependent (pH of the aqueous equilibrium phase = 9.9-10.4 (mean value 10.1)).

Additionally a calculated value (using KOWWIN v1.67) and a literature value were included in the dossier and gave similar values.

Vapour Pressure;

The key study is an in-house dynamic method with an argon atmosphere, no other details are provided, however, the measured value is outside the recommended range of this

method. Three other supporting values are given in the dossier, all taken from secondary literature sources. Two values measured at 25°C are both an order of magnitude lower (0.0027 and 0.0003 hPa). The third, measured at 20°C gives a value of 0.013 hPa, an order of magnitude higher. None specifies purity or the method used. The registrants have not commented on these differences or suitability of the method used.

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	colourless liquid ammonia-like odour
Melting/freezing point	-21.3 °C at 1013 hPa Measured value using in-house method but no details given. Value consistent with supporting literature value.
Boiling point	243.3 °C at 1013 hPa Measured value using in-house method but little detail given (dynamic method with argon atmosphere). Value consistent with supporting literature value.
Relative density	1.04 g/cm^3 at 20 °C Measured value using in-house method but no details given. Value consistent with supporting literature value.
Vapour pressure	0.0031 hPa at 20°C Measured value using in-house method but little detail given (dynamic method with argon atmosphere).
Water solubility	miscible in any proportion at 20°C 1000 g/L at 20 °C miscible Literature values
Partition coefficient n-octanol/water (Log Kow)	-1.16 at 23°c and pH 10.5 Measured value OECD Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method)
Flash point	138 °C at 1013 hPa Measured in house using method DIN 51758. Consistent with supporting data included.
Autoflammability / self-ignition temperature	280 °C at 1013 hPa Measured in house using method DIN 51794. Consistent with supporting data included.
Flammability	Non flammable upon ignition. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water. Non flammable (derived from flash point). Expert judgement - Based on chemical structure pyrophoric properties and flammability in contact with water are not predicted.
Explosive properties	Waiver – predicted to be non-explosive. There are no chemical groups associated with explosive properties present in the molecule.

Oxidising properties	Waiver - predicted to be non-oxidising. The Substance is incapable of reacting exothermically with combustible materials on the basis of the chemical structure.
Granulometry	Not applicable. Substance is a liquid
Stability in organic solvents and identity of relevant degradation products	Waiver - Not applicable - the stability of the substance is not considered as critical.
Dissociation constant	8.68 at 25°C Calculation of pKa using SPARC v4.6. Consistent with supporting literature value.
Viscosity	99.05 mm2/s at 20°C (static) In house study using capillary method; Ubbelohde viscosimeter. Literature values for dynamic viscosity also included in the dossier.

7.5. Manufacture and uses

7.5.1. Quantities

Information as given on the ECHA dissemination site (August 2017).

Table 7

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 8 lists the uses for MDEA which were identified on ECHA's dissemination site in August 2017.

Table 8

USES	Use(s)
Uses as intermediate	Use as an intermediate in industrial settings
Formulation	Formulation of preparations
Uses at industrial sites	Distribution Use as a processing aid (catalyst) in polymerisation reactions Use in lubricants and metal working fluids Use in gas treatment Laboratory work Use as an additive in coatings
Uses by professional workers	Use as a processing aid (catalyst) in polymerisation reactions. Use in lubricants and metal working fluids

	Laboratory work Use as an additive in coatings Use as an additive in concrete and cement
Consumer Uses	None identified
Article service life	None identified

Use as an intermediate

MDEA is an amino alcohol which means that it has the properties of both amines and alcohols. This makes it useful as an intermediate in the manufacture of a variety of substances. It is used as a precursor for fatty ester quaternaries (esterquats) which are used as fabric softeners and in detergents[3],[4]. MDEA based esterquats are a possible alternative to esterquats manufactured using triethanolamine (TEA). Hydroxy functionalized quaternary ammonium compounds based on MDEA can be reacted with epichlorohydrin and formic acid to produce cationic polyurethanes which are used as paper sizing agents. MDEA may also be used as a precursor in the manufacture of a range of pharmaceutical actives.

Industrial and professional use as a processing aid (catalyst) in polymerisation reactions

MDEA may be used as a catalyst in the production of polyurethane foams and epoxy resins which have applications in building and construction.

Use in gas treatment

MDEA is widely supplied for use as a gas scrubbing and extracting agent to remove hydrogen sulphide, carbon dioxide and carbonyl sulphide from natural gas and refinery off-gas[5]. Its low vapour pressure makes it particulary attractive for this use because it can be used in higher quantities without appreciable losses during the process, it is resistant to thermal and chemical degradation and is largely immisible with hydrocarbons. MDEA also has antifoaming applications to control foams caused by contamination from liquid hydrocarbons, particulates or surfactants.

Use as an additive in coatings

In waterborne coatings e.g. acrylic polymer disersions, MDEA is used to increase resin solubility, aid pigment dispersion and improve the stability of the solution by reducing pH drift.

Use in lubricants

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3 http://magnumsolvent.com/productdata/Product%20Literature/Dehydration%20and%20Acid%20Gas%20Removal/Product%20Data%20Sheet%20-%20MDEA.pdf (accessed 31 August 2018)

4 http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_096d/0901b8038096dc16.pdf?filepath=productsafety/pdfs/noreg/233-00470.pdf&fromPage=GetDoc (accessed 31 August 2017)

5 http://www.dow.com/en-us/oil-gas-mining/markets/gas-processing-midstream/acid-gas-removal?arrowMenu=453c70f0-aef5-4e8a-ab93-ce1cb59b6a15_d2e44b01-0fa8-4dd6-96d0-e388f0db04a6 (accessed 31 August 2017) see also http://www.dow.com/en-us/oil-gas-mining/markets/refining/amine-treating-technology?arrowMenu=af0e913c-f6ed-47f0-a6de-42ded437681c_23cf3c57-5789-4076-9926-7dbe3500f344 (accessed 31 August 2017)

The addition of MDEA to lubricants lowers the pour point of lubricating oils thereby improving their handling characteristics.

Use as an additive in concrete and cement

MDEA may be used in accelerants that are used to speed up the setting time and/or increase early strength development[6]. One product brochure indicates the concentration in the finished cement may be of the order of 0.01 – 0.05%[7].

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 9

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)**		
603-079-00-5	2,2'-(methylimino)diethanol N-methyldiethanolamine	203-312-7	105-59-9	Eye Irrit. 2;	H319		

7.6.2. Self-classification

- In the registration(s):

The registrants classify MDEA in accordance with Annex VI to CLP.

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

Not classified
Acute Tox. 4 H302
Aquatic Chronic 3 H412
STOT SE 3 H335 (lung)

[6] https://www.sintef.no/globalassets/sintef-byggforsk/coin/sintef-reports/sbf-bk-a07025_accelerating-admixtures-for-concrete.pdf (accessed 9 October 2017)

[7] https://www.huntsmanservice.com/performance_products/Media%20Library/a_MC348531CFA3EA9A2E040EBCD2B6B7B06/Home_MC348531CFA8BA9A2E040EBCD2B6B7B06/Key%20markets_1_MC348531CFD2FA9A2E040EBCD2B6B7B06/Functional%20Chemicals_MC348531D02E6A9A2E040EBCD2B6B7B06/Concrete%20%20%20asphalt%20a_MC348531CFDC9A9A2E040EBCD2B6B7B06/files/Additives_Brochure_EN_Apac_20130801_page.pdf (accessed 9 October 2017)

7.7. Environmental fate properties

Only a brief review of all of the relevant environmental fate, behaviour and toxicity data was performed. All studies assessed were included in the registration dossier unless otherwise stated. Unpublished studies are not referenced in this report.

7.7.1. Degradation

Key study: OECD 301A: 96% biodegradation by day 10 in a 28-d study

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

None of the aquatic ecotoxicity tests provided in the registration dossier have analytical support. The substance is readily biodegradable. It is highly soluble, and has a low calculated Koc value. The registrant should consider including some justification for why the substance concentrations would remain stable during the ecotoxicity studies.

7.8.1.1. Fish

Short term toxicity to fish

Key study: DIN 38412 part 15 using Leuciscus idus 96-h LC100 = 2150 mg/l; 96-h NOEC = 1000 mg/l

Long term toxicity to fish

Waived: In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation.

7.8.1.2. Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Key study: OECD 202 using Daphnia magna 48-h EC50 = 125 mg/l; 48-h NOEC = 233 mg/l

A 48-h study using the copepod Acartia tonsa is provided in the registration dossier as a supporting study for the short-term toxicity to aquatic invertebrates endpoint. The study was conducted according to ISO 14669 and was to GLP. It was performed using static conditions and filtered natural seawater (31% salinity). Nominal concentrations of 0, 10, 18, 32, and 56 mg/l were run and there was no analytical support. Due to lack of analysis the registrant assessed the test as validity 2. There was one animal per replicate with ten replicates per concentration. The results based on nominal concentrations were reported as NOEC = 10 mg/l; EC50 = 45 mg/l; EC100 = 100 mg/l.

It is unclear why this study, where effects were seen, was not considered to be the key study for aquatic invertebrates. Therefore the registrant should provide justification for this choice in the registration dossier. There appears to be an error in the treatment levels listed, as the results discuss a further nominal concentration of 100 mg/l.

Long-term toxicity to aquatic invertebrates

A 96-h reproduction study using Acartia tonsa is provided in the registration dossier, which was judged validity 2 by the registrant. This was to GLP but not performed to a specific test guideline. It was conducted using semi-static conditions and filtered natural seawater (31.1% salinity). One mature female was added to each pot, with 12 replicates per concentration, including controls. Nominal test concentrations of 0, 5.6, 10, 18, 32, 56, and 100 mg/l were run, without analytical support. Due to lack of analysis the registrant assessed the test as validity 2. A NOEC ≥ 100 mg/l based on nominal concentrations was derived for both reproduction and mortality.

There is no statistical analysis provided to support the derivation of the NOECs. For example 30% mortality occurred at 56 mg/l at 96 h but was not judged to be significant; number of offspring per female was 70% of the control value at 100 mg/l but again not judged to be significant. In addition the mortality results from the 48-h acute test using the same species (EC50 = 45 mg/l) contradict the findings of this test, which is not discussed in the IUCLID or CSR. The registrant is therefore required to address both aspects in an updated RSS.

The registrant uses the study to fulfil the chronic invertebrate endpoint. The ISO 14669 test guideline is referenced but this is a protocol for a 48-h acute study. Generally the duration of invertebrate reproduction tests (e.g. Daphnia magna, Ceriodaphnia and mysids) mean that three broods are produced during the study (see R7.8.4.1 of the REACH endpoint guidance 7B). It is unclear how many broods would be produced by Acartia tonsa over the 96-h duration of this study. Given the short duration of the test, the registrant needs to update their RSS providing clear justification for why these data can be considered to provide a chronic rather than sub-acute endpoint.

7.8.1.3. Algae and aquatic plants

Key study: DIN 38412 part 9 using Desmodesmus subspicatus: 96-h ErC50 >100 mg/l; 96-h ErC10 = 19 mg/l

7.8.1.4. Sediment organisms

Waived: As direct exposure of sediment is unlikely and because the substance is readily biodegradable, no tests on sediment organisms are performed.

7.8.1.5. Other aquatic organisms

7.8.2. Terrestrial compartment

All testing waived: The test substance is not supposed to be directly applied to soil. Further, the test substance is readily biodegradable and hence, in case of indirect exposure of soil, MDEA is expected to rapidly degrade. Therefore soil is not expected to be a compartment of concern. The risk to soil dwelling organisms is considered to be negligible.

7.8.3. Microbiological activity in sewage treatment systems

7.8.4. PNEC derivation and other hazard conclusions

Not assessed

The registrant should provide justification for the assessment factor used to derive the aquatic PNEC once issues for the long term invertebrate study have been considered.

7.8.5. Conclusions for classification and labelling

On the basis of this evaluation the eMSCA does not propose any classification and labelling.

7.9. Human Health hazard assessment

The initial focus of the human health evaluation was the effect of MDEA on reproductive/developmental parameters, as reproductive toxicity was identified as an area of concern on the basis of findings in the available reproduction and development screening test by the oral route at the highest tested dose of 1000 mg/kg bw/d. A developmental toxicity study conducted by the dermal route was also available for MDEA, in which no adverse effects on development were observed up to the limit dose; the evaluation also aimed to assess if it was appropriate to conclude on the developmental toxicity of this substance on the basis of dermal studies.

The registrants proposed to fill the requirements for an oral two-generation study (rats, OECD 416) and pre-natal developmental toxicity study (rabbits, OECD 414) with information from the structurally-related substance, 2-aminoethanol (MEA); CAS No 141-43-5 (EC No 205-483-3). The registrants' CSR and read-across justification document also highlighted other structurally-similar substances: 2,2'-iminodiethanol (DEA), CAS No 111-42-2 (EC No 203-868-0) and 2,2',2"-nitrilotriethanol (TEA), CAS No 102-71-6 (EC No 203-049-8), for which they used an informal grouping approach to address selected human health endpoints. The eMSCA considers that there is sufficient information on MDEA itself to conclude on the concern for reproductive toxicity; however the plausibility of the read-across justification has been assessed to lend support to the conclusion.

A screen of all the available information on other toxicological endpoints was conducted to identify any additional concerns.

The evaluation of the human health toxicity has been based on data presented by the registrants in their registration dossier and on reviews conducted by a variety of international bodies/regulatory programmes (IARC, OECD, etc.) and original publications. Where the original publications have been obtained this is stated in the specific hazard sections. Unpublished studies available in the dossier have not been referenced in this report.

7.9.1. Toxicokinetics

Toxicokinetic information from two studies in rats was presented in the registration dossier. The results of both studies have been evaluated to inform on the extent of absorption and fate of MDEA in rats. No further studies were identified through a literature search conducted by the eMSCA.

Original publications were obtained for both toxicokinetic studies (Leung *et al.*, 1996).

7.9.1.1. *In vitro* data

The pharmacokinetics of MDEA (99.5% purity) have been studied in the Fischer 344 rat after exposure to a single intravenous (50 or 500 mg/kg bw) or cutaneous dose (500 mg/kg bw for 6 or 72 h contact) (both studies summarised in Leung *et al.*, 1996). The results of both studies have been evaluated below:

Intravenous dosing

To investigate the pharmacokinetics of MDEA (99.5% purity) via the intravenous route (Leung *et al.*, 1996), adult Fischer 334 rats (4 males/dose) were cannulated (jugular vein) with a single dose of 50 or 500 mg/kg bw [^{14}C] MDEA (10 µCi, volume of 2 ml/kg) and held in metabolism cages for 72 hours. Blood, urine, faeces and expired $^{14}CO_2$ were collected at regular intervals for up to 72 hours post-dosing. Total radioactivity levels for each fraction were measured by liquid scintillation spectrometry. Unchanged MDEA concentrations in the plasma and urine were determined by HPLC (High Performance Liquid

Chromatography) combined with an in-line radioactivity monitor. Analysis/identification of metabolites was not conducted. Pharmacokinetic distribution parameters (including maximum concentration, volume of distribution at steady state, rate constant, half-lives and area under the concentration-time curve) were estimated using RSTRIP (a personal computer-driven polyexponential curve stripping/least squares parameter estimation programme, Micropath Inc).

Total recovery of radioactivity was 91.1% and 87.6% in the 50 and 500 mg/kg bw dose groups, respectively. Radioactivity was rapidly distributed (plasma t ½ = 0.3 hr and 0.8 hrs after dosing with 50 and 500 mg/kg bw, respectively), but more slowly excreted (excretion t ½ = 7.12 and 35.1 hrs after dosing with 50 and 500 mg/kg bw, respectively). Excretion occurred primarily via the urine (59.9% and 67.6% radioactivity excreted via the urine at 50 and 500 mg/kg bw, 72 hrs), but was slow (urine t ½ = approximately 18 hr for both 50 and 500 mg/kg bw). After exposure to 50 mg/kg bw, the major urinary component was metabolites of [^{14}C] MDEA. However, after exposure to 500 mg/kg bw urine radioactivity consisted predominantly of unmetabolised [^{14}C] MDEA, indicating that metabolism of MDEA may be saturated at high doses.

Percutaneous dosing

In the percutaneous dosing study (Leung *et al,* 1996), 500 mg/kg bw (equivalent to 62.5/83 mg/cm^2 (males/females)) [^{14}C] MDEA (25 µCi, >99% purity) was applied (occluded) to an 8/6 cm^2 (males/females) area of shorn dorsal skin in two groups of Fischer 334 rats (4/sex/group). In one group the test substance was removed after 6 hours, while in the other group exposure was maintained for 72-hours. Blood, urine, faeces and expired $^{14}CO_2$ were collected in both groups at regular intervals for up to 72 hours. Animals were sacrificed after collection of the last blood/excreta samples, and portions of liver, kidney, bone marrow, spleen, brain, heart, lung, muscle, fat, uterus, and ovaries/testes were collected. Total radioactivity levels for each tissue/fraction were measured by liquid scintillation spectrometry. Unchanged MDEA concentrations in the plasma and urine were determined by HPLC combined with an in-line radioactivity monitor. Analysis/identification of metabolites was not conducted.

Total recovery of radioactivity was acceptable (100 ± 10%) in both groups. A significant proportion of the radioactivity (73-74% and 44-50.4% after 6 and 72 hours exposure) was recovered from the occlusive device (tape, sheeting and bandage) and skin surface. An average of 17-21% (6 hours exposure) and 41-50% (72 hours exposure) of the applied radioactivity was absorbed (based on excreta, tissue and carcass) over the 72 hr sampling period. However, it is noted that the applied dose per area was very high (recommended guideline amount - OECD 427: 5 mg/cm^2), meaning that the exposure area could have been overloaded with the test substance.

Radioactivity absorbed from the skin surface appeared to be sequestered in the skin matrix; evidenced by its delayed and steady release into the blood stream. In the 6-hour exposure group, plasma radioactivity levels continued to rise from 30-60 hours post-dosing, despite removal of the test substance after 6 hours exposure. As MDEA is not lipophillic (octanol/water partition coefficient: -1.16 at 23^{O}C, pH 10.5), the study authors hypothesised that the observed skin retention was due to incorporation of radioactivity in membrane phospholipids. The structurally similar substance, DEA, has been shown to act in this manner.

A large portion of radioactivity remained in the carcass 72 hours post-dosing (approximately 14% and 30% after 6 and 72 hours exposure). Of the tissues examined, the highest concentrations were measured in the liver and kidneys. The principle route of elimination was in the urine (2.9-4.8% and 7.5-8.5% total radioactivity after 6 and 72 hr exposure), which was slow (urinary elimination t ½: ≥32 hours). Metabolites of [^{14}C] MDEA (not identified) constituted the major portion of urinary radioactivity, indicating that metabolism plays an important role in MDEA elimination.

The registrants used this study to set a dermal absorption value of 20% for DNEL calculation.

7.9.1.2 Summary and discussion of toxicokinetics

The pharmacokinetics of MDEA was studied in the Fischer 344 rat after a single intravenous (50 or 500 mg/kg bw) or cutaneous dose (500 mg/kg bw for 6 or 72 h contact; Leung *et al.*, 1996). No information was available via the inhalation or oral routes of exposure.

Absorption

Oral

No data on the absorption of MDEA after oral exposure is available. Therefore, the registrants adopted the default absorption value for DNEL derivation (i.e., 100% absorption). In the absence of available data, the eMSCA agrees with this approach.

Inhalation

No data on the absorption of MDEA after inhalation exposure is available. Therefore, the registrants adopted the default absorption value for DNEL derivation (i.e., 100% absorption). In the absence of available data, the eMSCA agrees with this approach.

Dermal

Based on the available *in vivo* percutaneous study, the registrants set a dermal absorption value of 20%. As the percutaneous study used a very high dose (MDEA)/area it is likely that the exposure area was overloaded with test substance, meaning that the derived dermal absorption value (calculated as a percentage of the total applied dose) may not provide a realistic estimate (i.e. likely to be an underestimate) for use in DNEL derivation. However, as the use of 20% for dermal absorption is more precautionary for route-to-route extrapolation in DNEL derivation than the default value of 50%, the eMSCA accepts the use of this value for the risk assessment.

Distribution

Distribution of MDEA and/or its metabolites was measured in the available dermal toxicokinetic study. In this study, distribution was relatively uniform, with highest concentrations measured in the liver and kidney.

Metabolism

Plasma and urine concentrations of parent MDEA and total radioactivity (MDEA and/or metabolites) were measured in both dermal and intravenous toxicokinetic studies. However, no analysis/identification of metabolites is available. In both studies, MDEA was well metabolised; however, metabolism may be saturated at high doses.

Excretion

In both dermal and intravenous toxicokinetic studies, the predominant route of excretion was in the urine. Urinary excretion was slow for both routes; however, rates were slower following cutaneous dosing. Metabolites (not-identified) constituted the major fraction of urine radioactivity at 50 mg/kg bw (intravenous) and 500 mg/kg bw (percutaneous) MDEA indicating that metabolism plays an important role in MDEA elimination.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity was not identified as a concern for MDEA. It is noted that inconsistent notifications for acute oral toxicity were submitted to the classification and labelling inventory.

7.9.2.1. Acute toxicity: oral

Two acute oral toxicity studies have been included in the registration dossier. Of these studies, the registrants identified one older study as the key study and one newer study as a supporting study. Information from the supporting study was not used by the registrants for hazard classification and was not included in the CSR. No further studies were identified through a literature search conducted by the eMSCA. The results of both studies are summarised in the table below.

Table 10. Summary of oral acute toxicity studies in rats

Method	LD_{50}	Observations and Remarks	Reference
Rat (strain not specified) 10/sex/dose Gavage 208, 1664, 3328, 4160, 5200, 6656 mg/kg bw MDEA Observation period= 7 days Vehicle= water Purity=98% Pre-GLP Similar to OECD Guideline 401	LD_{50}: 4680 mg/kg bw (combined for males and females)	Mortalities reported at ≥3328 mg/kg bw/day. *Clinical signs observed during the post-dosing period:* squatting posture, ruffled fur, gasping, bloody eyes & nose. *Necropsy for those animals that died:* smeared snouts and urogenital tract, droopy GI tract with bloody contents. Surviving animals showed bronchitis and bronchiectasis.	Original study report was not available during the evaluation process. The evaluation was based on the registrants' summary in the dossier.

Method	LD_{50}	Observations and Remarks	Reference
Rat/Sprague-Dawley 5/sex/dose Gavage (undiluted MDEA) No information on dose, volume and purity of test substance. Observation period= 14 days Similar to OECD Guideline 401	M: 1945 mg/kg F: 1945 mg/kg	*Clinical signs observed during the post-dosing period:* sluggishness, lacrimation, chromodacryorrhea, diarrhoea, kyphosis and prostration. All survivors recovered within 2-3 days post-dosing and gained weight over the 2-week observation period. *Necropsy of the animals that died revealed*: distended stomachs containing blood and having dark red or purple discolouration of the glandular portion. Intestines contained blood and had variable degrees of congestion. Lungs showed dark red mottling. Survivors had no gross pathology at necropsy.	Ballentyne and Leung (1996) Original publication was obtained for evaluation.

7.9.2.2. Acute toxicity: inhalation

Two acute toxicity studies via the inhalation route (vapour) have been included in the registration dossier. Of these studies, one older study was identified by the registrants as the key study and one newer study as a supporting study. No further studies were identified through a literature search conducted by the eMSCA. The results of both studies are summarised in the table below.

Table 11. Summary of inhalation acute toxicity studies in rats

Method	LC_{50}	Observations and remarks	Reference
Rat (strain not specified) 6/sex/dose Vapour (saturated atmosphere) MDEA Exposure: 8 hours Observation period: 7 days Purity= 98% Pre-GLP	No deaths	No clinical or pathological signs of test substance-related toxicity were observed. Animals gained normal weight. No substance was lost but an increase in substance weight was recorded. This is considered to be an indicator that the test substance is hygroscopic and only a marginal fraction of the substance may be volatile. Therefore, it is unlikely that significant exposure via inhalation occurred in this study. Analytical verification of the test atmosphere was not conducted.	Original study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary in IUCLID and the CSR.
Rat/Sprague-Dawley 5/sex/dose Vapour (120 L chamber previously saturated with 50	No deaths	No significant signs of toxicity were observed. MDEA is a hygroscopic substance with a low volatility; therefore, it is unlikely that significant exposure to the test substance occurred during this study.	Ballantyne and Leung (1996) Original publication was obtained for evaluation.

Method	LC_{50}	Observations and remarks	Reference
g of MDEA for 18 hours) Exposure : 6 hours Observation period: 14 days No information on purity or GLP compliance.		It is not stated if analytical verification of the test atmosphere was conducted.	

7.9.2.3. Acute toxicity: dermal

Three acute toxicity studies via the dermal route have been included in the registration dossier. No further studies were identified through a literature search conducted by the eMSCA. The results of the available acute dermal toxicity studies are summarised in the table below.

Table 12. Summary of dermal acute toxicity studies in rabbits

Method	LD_{50}	Observations and Remarks	Reference
Rabbit/New Zealand White 5/sex/dose Coverage: occlusive Exposure:24 hours Observation period: 14 days No information on dose used, volume or purity. Non-GLP	M: 10244 mg/kg F: 11336 mg/kg	*Clinical signs observed during the post-doing period:* sluggishness, unsteady gait, emaciation and prostration. Survivors recovered between days 3-5 post dosing. Animals lost weight during the first post-dosing week, with partial recovery during the second week. *Local signs of toxicity*: moderate to severe erythema and oedema with ecchymoses, necrosis and ulceration. These effects in general persisted to the end of the observation period. During the second post-application week, local desquamation, alopecia and scaring had developed. *Necropsy of the animals that died:* dark red-mottled lungs, dark red livers and mottled kidneys. Most survivors at necropsy did not reveal any gross pathology, but a few showed red-mottled lugs and dark red livers.	Ballantyne and Leung (1996) Original publication was obtained for evaluation.
Rabbit (strain not specified) 4 males Coverage: occlusive	LD50: 5990 mg/kg bw	No information was reported on deaths, clinical signs, body weight or gross pathology.	Smyth H. *et al.* (1954) Benya *et al.* (1994) Original publication was not available

Method	LD_{50}	Observations and Remarks	Reference
Exposure: 24 hours Observation period: 14 days No information on dose or purity of the test substance.			during the evaluation process. The evaluation was based on the registrants' robust study summary
Rabbit /New Zealand White 2/sex/dose 2000 mg/kg bw/day MDEA 96% purity Observation period: 14 days No information on type of coverage, vehicle or duration of exposure.	LD50: > 2000 mg/kg bw (male/female)	No deaths or treatment-related clinical signs were observed.	Study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary

7.9.2.4. Skin irritation

Two skin irritation/corrosion studies have been included in the registration dossier. Of these studies, the registrants identified one older study as the key study and one newer study as a supporting study. No additional information was found via a literature search conducted by the eMSCA. The results of both studies are summarised in the table below.

Table 13. Summary of skin irritation studies in rabbits

Method	Results	Reference
Rabbit/Vienna White 2 animals Undiluted MDEA Exposure period: 1, 5, 15 minutes and 20 hours Observation period: 8 days No information on volume Purity= 98% Coverage: occlusive	Mean scores over 24-72 hours for two rabbits (animal 1 – animal 2 (mean)): <u>1 minute exposure</u> Erythema: 0 - 0 (mean: 0) Oedema: 0 – 0 (mean: 0) <u>5 minute exposure</u> Erythema: 0 - 0 (mean: 0) Oedema: 0 – 0 (mean: 0) <u>15 minute exposure</u> Erythema: 0 - 0 (mean: 0) Oedema: 0 – 0 (mean: 0) <u>20 hour exposure</u> Erythema: 3 - 2 (mean: 2.5) Oedema: 2.67 – 0 (mean: 1.3)	Study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary

Method	Results	Reference
Similar to OECD 404, pre-GLP		
Rabbit/New Zealand White 0.5 ml undiluted MDEA Exposure period: 4 hours Observation period: 21 days Coverage: occlusive No information on number of animals, purity and GLP compliance. Similar to OECD 404	Mean scores over 24-72 hours: Erythema: mean: 0.2 Oedema: mean: 0.2 A few scattered ecchymoses but no necrosis was observed. All effects had reversed within 3 days post-dosing. Scores are not available for individual animals.	Ballantyne B. and Leung H-W. (1996) Original publication was obtained for evaluation.

7.9.2.5. Eye irritation

One eye irritation/corrosion study was included in the registration dossier. A second study (Ballentyne and Leung, 1996) was also identified by the eMSCA, but was not included in the registration dossier. The results of both studies are summarised in the table below.

Table 14. Summary of eye irritation studies in rabbits

Method	Results	Reference
Rabbit/Vienna White 2 animals 50 µl undiluted MDEA Exposure period: single application - eyes were not washed out Observation period: 8 days No information on volume Purity= 98% Similar to OECD 405, non-GLP	Mean scores over 24-72 hours for 2 rabbits (animal 1 – animal 2): Opacity: 1 – 1 (mean: 1) Iritis: 0 – 0 (mean: 0) Conjunctiva- Erythema: 1.7 – 1.7 (mean: 1.7) Conjunctivia- Chemosis: 0.7 – 0.7 (mean: 0.7) Conjunctival bleeding was also reported. All effects reversed within the 8-day observation period.	Study report was not available during the evaluation process. The evaluation was based on the registrants' robust study summary

Method	Results	Reference
Rabbit/New Zealand White 6 animals 0.005 ml undiluted MDEA Exposure period: Observation period: No information on number of animals	A slight to moderate conjunctival hyperemia and chemosis was seen within an hour of contaminating the eye and resolved within 1-3 days. The iris showed mild injection, which persisted for approximately 3-days. Corneal opacity, just detectable and affecting ¼ or less of the surface, was seen at 24 hours post application in 1/6 rabbits. This reversed within 3 days. No other effects were reported.	Ballantyne B. and Leung H-W. (1996) * Original publication was obtained for evaluation.

* The eMSCA notes that this study has not been reported in the dossier

7.9.2.6 Summary and discussion of acute toxicity and irritation

No human data on the acute toxicity of MDEA is available. In animals, the acute toxicity of MDEA has been investigated by the oral, inhalation and dermal routes.

Acute Oral Toxicity

MDEA has a moderate to low acute oral toxicity. In the key study, a combined oral LD_{50} value of 4680 mg/kg bw was derived for male and female rats. This LD_{50} value is above the cut off for classification for acute oral toxicity.

In a supporting study, a LD_{50} of 1945 mg/kg bw was derived for both male and female rats (Ballantyne and Leung, 1996). This LD_{50} value is just within the cut off criteria for classification as Acute Tox. 4; H302 ($300 < ATE \leq 2000$ mg/kg). However, limited reporting details were included in the original publication (no information on dose, volume and purity of test substance), making the toxicological significance of this study unclear.

Inconsistent notifications were submitted to the classification and labelling inventory for the classification of MDEA for acute oral toxicity. Based on the available data, the eMSCA agrees that no classification is justified.

Acute Inhalation Toxicity

Vapour

Two acute inhalation toxicity studies were available for MDEA. In both studies, rats were exposed to vapours of MDEA and no mortalities were observed. However, it is unlikely that the animals were exposed to significant concentrations of MDEA vapour as the substance is hygroscopic and has a low vapour pressure. In addition, it is not stated if analytical verification of the test atmosphere was conducted; therefore, exposure to MDEA vapour cannot be confirmed.

As MDEA has a low vapour pressure, significant human exposure is not anticipated. Consequently, the eMSCA does not consider acute inhalation (vapour) toxicity to be a concern for MDEA.

Acute Dermal Toxicity

In the three available acute dermal toxicity studies, all LD_{50} values were above 2000 mg/kg bw. Based on the available data, the eMSCA agrees with the registrants that no classification is justified for acute dermal toxicity.

Skin irritation/corrosion

No human data was available to evaluate the skin irritation/corrosion potential of MDEA. In animals, one laboratory study and one published study were included in the registration dossier. Further information on skin effects was also available in an acute toxicity study carried out by the dermal route and a skin sensitisation study in guinea pigs.

In a patch test, the skin of two rabbits (Vienna White) was exposed to undiluted MDEA for 1, 5, 15 minutes or 20 hours under occlusive conditions. No signs of skin irritation/corrosion were observed after 1, 5 and 15 minutes of exposure, while widespread reddening and scale formation (in one animal) was observed after 20 hours' exposure. The mean erythema and oedema scores after 20 hours' exposure were reported as 2.5 and 1.3, respectively. However, this study was conducted under occlusive conditions and the 20-hour exposure time significantly exceeds the guideline recommended exposure time (4 hours), which would exaggerate the potential for irritation/corrosion.

In a second test, rabbits (New Zealand White, number of animals not specified) were exposed to undiluted MDEA for 4 hours under occlusive conditions (the OECD test guideline states that a semi-occlusive dressing should be used). Slight erythema (mean score: 0.2), oedema (mean score: 0.2) and ecchymoses (few, scattered) was observed. However, there were no signs of necrosis and all symptoms reversed within the 21-day observation period.

In a guinea pig maximisation skin sensitisation test, both control and treated animals showed a skin irritation response after occlusive exposure to MDEA for 48 h. Details of the exact nature of the skin irritation observed are not available.

Two skin irritation studies and a study to investigate skin sensitisation indicate that MDEA is mildly irritating to the skin; the eMSCA notes, however, that the exposure conditions employed in all of these studies exceeded the requirements of the OECD test guideline for skin irritation in terms of exposure duration, concurrent use of an irritant substance and/or occlusive conditions. The results of an acute toxicity study carried out via the dermal route in rabbits suggests treatment with MDEA causes a corrosive effect (necrosis, ulceration and alopecia). However, in this study the exposure time far exceeded that recommended in the criteria of CLP and the concentrations of MDEA applied were very high. In the study that most closely follows the guidelines for the testing of skin irritation, the severity scores for skin irritation after ≤ 4 hours of exposure were below those specified in the classification criteria. Therefore, the eMSCA agrees with the registrants that no classification is justified.

Eye irritation/damage

No human data were available to evaluate the eye irritation/damage potential of MDEA. In animals, one laboratory study (key study) and one published study (Ballantyne and Leung, 1996) was available.

In the key study, the eyes of two animals were exposed to a single dose of undiluted MDEA and were not subsequently washed out. Observations included redness, swelling, clouding of the cornea and conjunctival bleeding. However, all symptoms reversed within the 8-day observation period. Mean irritation scores for opacity, iritis, erythema and chemosis were reported as 1, 0, 1.7 and 0.7, respectively.

A second study was also identified by the eMSCA, but was not included in the registration dossier. This test reported comparable results when undiluted MDEA was added to the eyes of 6 rabbits. Adverse effects included conjunctival hyperemia, chemosis, mild injection of the iris and corneal opacity. All symptoms had resolved within 3 days post dosing. No information on eye damage severity scores were reported (Ballantyne and Leung, 1996).

The observations of both eye irritation tests are consistent with the harmonised classification of MDEA as Eye Irrit. 2; H319.

Respiratory tract irritation

MDEA is irritating to the eye indicating that it may also be irritating to the respiratory tract. However, no information on respiratory tract irritation was presented in the registration dossier and none of the available repeated-dose toxicity studies were conducted via the inhalation route. Two acute toxicity studies are available for the inhalation route (vapour); however, it is unlikely that significant exposure to the respiratory tract occurred (see Section 7.9.2.2.).

The eMSCA notes that inconsistent notifications have been submitted to the classification and labelling inventory for classification of MDEA as STOT SE 3; H335/no classification. However, in the absence of valid data on MDEA toxicity via the inhalation route, the eMSCA agrees with the registrants that no classification is required.

MDEA did not demonstrate corrosive properties in the available skin and eye irritation studies. Therefore, the eMSCA agrees with the registrants that no classification is justified.

7.9.3. Sensitisation

Sensitisation was not identified as an area of concern for MDEA.

No human data was available to evaluate the skin sensitisation potential of MDEA. In animals, one guinea pig maximisation study was included in the registration dossier. No additional studies were identified through a literature search conducted by the eMSCA. The results of this study is summarised in the table below.

Table 15. Summary of skin sensitation study in guinea pigs

Method	Doses	Results
Guinea pig / Durkin Hartley Albino 10/sex in test group 5/sex in positive and irritation controls Coverage: occlusive Vehicle= propylene glycol No information on purity. Similar to OECD 406-Magnusson and Kligman maximisation study, GLP Leung *et al.* (1998).	*Induction* Intradermal= 5% w/v Epidermal= 100% w/v *Challenge* 100% w/v *Re-challenge* 50% or 10% w/v 10% sodium lauryl sulphate in petrolatum was massaged on to skin of all animals to produce a mild inflammatory response.	*Challenge* **Equivocal** 100% challenge= 90% response at 48 hours Irritation control= 100% response at 48 hours Due to the positive response observed in the irritation control group, animals were re-challenged with 50% and 10% MDEA at separate sites. *Re-challenge* **Negative** 50% re-challenge= 0% response at 48 hours 10% re-challenge= 0% response at 48 hours Positive control = responded appropriately.

7.9.3.1. Summary and discussion of sensitisation

Skin sensitisation

In the adjuvant-type guinea pig maximisation study, MDEA induced a positive response in 90% of animals challenged with 100% MDEA. However, a 100% response was also observed in the irritation control group, indicating that the observed response may be the result of irritation rather than sensitisation.

As the results in the challenge group were equivocal, a re-challenge was conducted with 10% and 50% MDEA. No animals responded to both re-challenge concentrations; therefore, the criteria for classification (positive response in ≥30% of animals) were not met.

The eMSCA agrees with the registrants that the available data do not support classification for skin sensitisation in accordance with CLP.

Respiratory sensitisation

No information on respiratory sensitisation was included in the registration dossier. No repeated-dose toxicity studies are available via the inhalation route. As MDEA was not sensitising in a guinea pig maximisation study, the eMSCA does not consider respiratory sensitisation to be a concern for MDEA.

7.9.4. Repeated dose toxicity

Repeated dose toxicity was not highlighted as an initial concern for MDEA but the available information was evaluated to supplement the reproductive toxicity studies, and to inform on the identification of points of departure for DNELs.

7.9.4.1. Oral

The registrants have included a waiver for the conduct of a repeated-dose toxicity study via the oral route, as existing data is available for the dermal route. Some information on toxicity following oral exposure can be obtained from the reproductive toxicity screening study. This information is summarised in the table below. The reproductive / developmental findings are discussed in Section 7.9.7.

Table 16. Summary of oral repeated-dose toxicity in rats

Method	Dose Levels	Remarks
Reproduction/ Developmental screening test Rat/Wistar 10/sex/dose Oral (Gavage) OECD Guideline 421, EPA OPPTS 870.3550, GLP Purity= >99.9% Original study report available for evaluation.	0, 100, 300 and 1000 mg/kg bw/day MDEA Volume= 10 ml/kg bw/day Vehicle= drinking water Duration of treatment= 2-week pre-mating period to post natal day (PND) 4.	**Parental toxicity** 1000 mg/kg bw/day- *Clinical*: Reduced food consumption (F:↓37% during lactation days 1-4), reduced body weight gain (M:↓29% during weeks 0-3 and M:↓57% during weeks 2-3, F:↓≤46% gestation days 7-20), reduced body weight (F:↓≤14% on gestation days 14 and 20), reduced terminal body weight (M:↓7% and F:↓5%). *Liver*: increased liver weight (absolute: M:↑32% and F:↑26%; relative: M:↑41% and F:↑33%), lymphoid infiltration (M:9 and F:10). 300 mg/kg bw/day- *Clinical*: reduced body weight gain (M:↓45% during weeks 1-2), reduced terminal body weight (M:↓4% and F:↓5%). *Liver*: increased liver weight (absolute: M:↑11% and F:↑12%; relative: M:↑17% and F↑16%), lymphoid infiltration (M:2 and F:7). 100 mg/kg bw/day- *Liver:* increased liver weight (absolute: F:↑9%; relative: F:↑11%), lymphoid infiltration (M:1 and F:1). NOAEL (general toxicity)= 100 mg/kg bw/day due to body weight reductions and liver weight changes at ≥300 mg/kg bw/day.

In the reproduction/developmental screening test, Wistar rats (10/sex/dose) were dosed (gavage) with aqueous solutions of 0, 100, 300 or 1000 mg/kg bw/day MDEA. Treatment covered a two-week pre-mating period (males and females), two-week mating period (males and females), gestation (females only) and post-natal days 1-4 (females only). Gross pathology/histopathology examinations were conducted on gross lesions and the reproductive organs. Haematology and clinical chemistry parameters were not assessed.

Parental toxicity was observed at ≥300 mg/kg bw/day and included statistically significant reductions in body weight, body weight gain, and food consumption. An increase in absolute (≥11%) and relative (≥16%) liver weight was also reported at ≥300 mg/kg bw/day in males and females. The study authors considered that the increase in liver weight was a non-adverse adaptive phenomenon, as no treatment related pathomorphological changes were reported in the liver.

The registrants set a NOAEL of 100 mg/kg bw/day (general toxicity) for this study based on a reduction in body weight observed at ≥300 mg/kg bw/day. The eMSCA agrees with the NOAEL set by the registrants.

7.9.4.2. Inhalation

No information available. The registrants have included a waiver for the conduct of a repeated dose toxicity study via the inhalation route because existing data via the dermal route is available.

7.9.4.3. Dermal

Three dermal repeated-dose toxicity studies (all conducted in the rat) were presented in the registration dossier. No additional studies were identified through a literature search conducted by the eMSCA. The results of the available studies are summarised in the table below.

Table 17. Summary of dermal repeated-dose toxicity in rats

Method	Results	Remarks
9-day study Dermal (Occlusive) Rat/Fischer 344 20/sex/dose 0, 260, 1040 and 2080 mg/kg/day undiluted MDEA (6hr/day, 5days/week) Control-deionised water Purity: >99.7% No information on GLP compliance.	2080 mg/kg/day *Clinical*: reduced bodyweight gain (M:↓ 53.1% and F:↓ 26.1%), reduced food consumption (M:↓ 6.4% during days 1-8). *Haematology*: increased segmented neutrophils (F:↑ 39.3%). *Clinical Chemistry*: increased glucose (F:↑ 13.2%), increased urea nitrogen (F:↑ 20.1%). *Skin*: erythema (transient and barely perceptible - M:1/20 and F:1/20), exfoliation (M:17/20 and F:20/20), excoriation (M:20/20 and F:17/20), necrosis (M:16/20 and F:20/20), fissuring (F:5/20), acanthosis, hyperkeratosis, multifocal areas of superficial dermatitis, exocytosis of polymorphonuclear leukocytes into the overlying stratum corneum. *Kidney*: increased weight (absolute F:↑ 10.1% and relative to body weight F:↑ 13.5%). *Adrenal gland*: increased weight (absolute F:↑ 12.0% and relative to body weight F:↑ 15.5%). 1040 mg/kg/day *Clinical*: reduced body weight gain (M:↓ 35.6% and F:↓ 18.2%), reduced food consumption (M:↓ 6.4% during days 1-8). *Haematology*: reduced hematocrit (M:↓ 3.0%). *Clinical Chemistry*: increased glucose (F:↑ 10.0%), increased urea nitrogen (F:↑ 18.7%). *Skin*: erythema (transient and barely perceptible - M:1/20, F:1/20), exfoliation (M:14/20 and F:20/20), excoriations (M:20/20 and F:20/20), necrosis (M:9/20 and F:19/20), fissuring (F:5/20) acanthosis, hyperkeratosis, multifocal areas of superficial dermatitis, exocytosis of polymorphonuclear leukocytes into the overlying stratum corneum. *Kidney*: increased weight (relative to bodyweight F:↑ 5.6%). 260 mg/kg/day *Clinical*: reduced body weight gain (M:↓ 26.3% and F:↓ 8.0%). *Skin*: oedema (barely perceptible F:1/20 on day 5), exfoliation (M:5/20 and F:19/20), excoriations (M:12/20 and F:14/20), necrosis (M:1/20 and F2/20), acanthosis, hyperkeratosis, multifocal areas of superficial dermatitis, exocytosis of polymorphonuclear leukocytes into the overlying stratum corneum.	Werley *et al*, 1997 Original publication available for evaluation.

Method	Results	Remarks
	LOAEL(general toxicity): 260 mg/kg bw/day (male/female) based on a dose-related reduction in body weight gain. LOAEL (local toxicity): 260 mg/kg bw/day (male/female) based on dose-related skin irritation.	
9-day study Dermal (Occlusive) Rat/Fischer 344 20/sex/dose 0, 100, 500 or 750 mg/kg/day MDEA (6hr/day, 5days/week) Vehicle- deionised water Volume- 1.0 ml/kg/day Purity: >99.7% No information on GLP compliance.	<u>750 mg/kg/day</u> *Clinical*: reduced body weight gain (M:↓ 25.4% and F:↓ 31.0% during days 1-8). *Clinical Chemistry*: increased aspartate aminotransferase (M:↑ 28.8%), increased alanine aminotransferase (M:↑ 29.6%), reduced sorbitol dehydrogenase (M:↓ 36.4% and F:↓ 45.5%). *Skin*: exfoliation (M:11/20 and F:20/20), excoriation (M:11/20 and F:16/20). *Adrenal Gland*: increased weight (relative to body weight F:↑ 12.8%). <u>500 mg/kg/day</u> *Clinical:* reduced body weight gain (M:↓ 19.7% and F:↓ 10.3% on days 1-8). *Clinical Chemistry*: reduced sorbitol dehydrogenase (M:↓ 63.6%). *Skin*: exfoliation (F:20/20), excoriation (F:4/20). *Adrenal Gland*: increased weight (relative to body weight F:↑ 15.4%). <u>100 mg/kg/day</u> *Clinical:* reduced body weight gain (M:↓ 13.1% and F:↓ 17.2% on days 1-8). <u>The following signs of local toxicity were also reported in the original study report, however, it is not clear which dose groups were affected:</u> erythema (barely perceptible to slight observed at irregular intervals), increased incidence and severity of acanthosis and hyperkeratosis, multifocal dermatitis, exocytosis of polymorphonuclear leukocytes into the stratum corneum. A LOAEL/NOAEL cannot be derived for this study owing to limited reporting details in the original publication.	Werley *et al*, 1997 Original publication available for evaluation.
90-day study Dermal (occlusive) Rat/Fischer 344 20/sex/dose (in control and high dose of which 10/sex were kept for a 4-week recovery period)	<u>750 mg/kg bw/day</u> *Clinical*: reduced body weight gain (males only, small, transient and variable). *Skin*: erythema (transient and slight), desquamation, excoriation, ulceration (minimal to marked), necrosis, eschar (minimal to marked), acanthosis, hyperkeratosis, parakeratosis, dermal fibrosis (minimal to marked), dermatitis (minimal to marked). <u>500 mg/kg bw/day</u> *Clinical*: reduced bodyweight gain (males only, small transient and variable).	Werley *et al*, 1997

Method	Results	Remarks
10/sex/dose (in low and mid dose) 0, 100, 500 or 750 mg/kg/day MDEA (6hr/day, 5days/week) Vehicle- deionised water Volume- 1.0 ml/kg/day Purity: >99.7% Similar to OECD 411. No information on GLP compliance.	*Skin*: desquamation, excoriation, ulceration (minimal to marked), necrosis, eschar (minimal to marked), acanthosis, hyperkeratosis, parakeratosis, dermal fibrosis (minimal to marked), dermatitis (minimal to marked). <u>100 mg/kg bw/day</u> *Clinical*: reduced body weight gain (transient and variable) *Skin*: desquamation (minimal), excoriation (minimal), ulceration (minimal), necrosis (minimal), eschar (minimal). A systemic LOAEL / NOAEL cannot be derived for this study because the observed body-weight effects have not been quantified in the robust study summary and original publication.	

*% change compared with control

Werley *et al* (1997) investigated the potential for toxicity of MDEA by repeated administration to the skin of Fischer 334 rats. The study was composed of three parts, including two short-term studies (9-day study) and one sub-chronic study (90-day study).

<u>First 9-day study</u>

In the first 9-day study, Fischer 334 rats (20/sex/dose) were cutaneously exposed to doses of 0, 260, 1040 or 2080 mg/kg bw/day/6 hr undiluted MDEA under occlusive conditions. Dose-related local toxicity was observed in all treatment groups and included exfoliation, excoriations, necrosis and fissuring (females only). Transient and barely perceptible erythema was also observed in one male and one female of the 2080 and 1040 mg/kg bw/day dose group. Oedema (barely perceptible) was observed in one female at 260 mg/kg bw/day.

Male and female body weight increased over the study period in all treatment groups. However, a dose-related reduction in body-weight gain was observed, being statistically significant and accompanied by reduced food consumption in mid- and high-dose males.

Small changes in haematological parameters were also observed in the mid and high dose, including increased segmented neutrophils and minor (<5% decrease) reductions in haemoglobin concentration, hematocrit and mean corpuscular haemoglobin. This was accompanied by increases in clinical chemistry parameters including glucose and urea nitrogen.

In females, increased relative and/or absolute kidney and adrenal weight was observed in the mid- and high-dose groups. The changes in kidney weight were not associated with microscopic or urinalysis findings and therefore do not represent a clear adverse effect. No significant organ weight changes were observed in males.

Pathological findings were limited to the treatment area and included a dose-related increase in the incidence and severity of acanthosis, hyperkeratosis, mutifocal areas of dermatitis (superficial) and exocytosis of polymorphonuclear leukocytes into the overlying stratum corneum.

The registrants have set a LOAEL of 260 mg/kg bw/day (males and females), based on dose-related skin irritation, haematological and clinical chemistry changes. The eMSCA agrees with the registrant's selection for the LOAEL. However, the registrants and study authors hypothesised that the body weight, clinical chemistry, haematological and adrenal gland changes were the consequence of local toxicity. In the absence of data showing that the MDEA was not systemically distributed, it is not possible to distinguish if these effects are the consequence of systemic toxicity or were secondary to local effects. In addition, adverse effects on body weight were also observed in the oral reproduction / developmental screening study, suggesting that the reduced body weight gain could be the consequence of systemic toxicity (see Section 7.9.4.1). The oral reproductive / developmental toxicity screening study cannot be used to inform on adrenal gland weight, kidney weight, haematology or clinical chemistry changes, as analysis of these parameters was not conducted.

Second 9-day study

Comparable findings were also observed in the second 9-day repeated dose toxicity study, using lower doses of MDEA (aqueous dilutions). In this study, Fischer 334 rats (20/sex/dose) were cutaneously exposed to doses of 0, 100, 500 or 750 mg/kg bw/day/6 hr MDEA under occlusive conditions. Dose related local toxicity including exfoliation and excoriations were observed in females of the mid and high dose groups. Barely perceptible to slight erythema (occurring at irregular intervals and affecting a few animals) is also reported in the original publication, however, it is not clear which dose groups were affected.

Body weight gain was reduced in a dose related manner, being statistically significant in high-dose females during week one. No statistically significant changes in haematological parameters were observed. Clinical chemical changes included increased aspartate aminotransferse (AST) and alanine aminotrasferase (ALT) (biomarkers of liver damage) at 750 mg/kg bw/day; however, this was not accompanied by other biochemical or morphological signs of liver toxicity. A reduction in sorbitol dehydrogenase was also observed at ≥500 mg/kg bw/day. In the presence of liver toxicity, serum levels of this enzyme would be expected to increase.

In females, an increase in relative adrenal weight was observed in the mid and high dose groups. However, no significant organ weight changes were observed in males.

Pathological findings were limited to the treatment area and included a dose related increase in the incidence and severity of acanthosis, hyperkeratosis, multifocal areas of dermatitis (superficial) and exocytosis of polymorphonuclear leukocytes into the overlying stratum corneum. However, it is not clear from the original publication which dose groups were affected.

The registrants set a NOAEL of 100 mg/kg bw/day for local toxicity. However, the eMSCA notes that there were limited reporting details provided in the robust study summary and original publication (e.g. does not state the doses at which some signs of toxicity were observed). Therefore, the eMSCA considers that a NOAEL/LOAEL cannot be set for this study.

In addition, the registrants and study authors hypothesised that body-weight gain, clinical chemistry and adrenal gland changes were secondary to local toxicity. However, in the absence of data showing that the MDEA was not systemically distributed, it is not possible to distinguish if these effects are the consequence of systemic toxicity or were secondary to local effects. In addition, adverse effects on body weight were also observed in the oral reproduction/developmental screening study, suggesting that the reduced body-weight gain may be the consequence of systemic toxicity (see Section 5.6.1.1). The oral reproductive/developmental toxicity screening study cannot be used to inform on adrenal gland weight or clinical chemistry changes, as analysis of these parameters was not conducted.

90-day study

In the 90-day repeated-dose toxicity study by the dermal route, Fischer 334 rats (20/sex/dose) were cutaneously exposed to 0, 100, 500 or 750 mg/kg bw/day MDEA (aqueous dilutions) for 6 hours/day under occlusive conditions. Twenty rats per sex were assigned to the control and high-dose groups and ten rats per sex to the low- and mid-dose groups. Half the rats of the high and control groups were retained for a 4-week recovery period.

No animals died and there were no clinical signs indicative of systemic toxicity. Dose related (incidence and severity) local toxicity was observed in all treatment groups and included desquamation, excoriations, uclerations, necrosis and eschar. Findings in the low-dose group were of minimal severity. Transient, minimal erythema was also observed in males and females of the high-dose group.

In contrast to the 9-day studies, no significant changes were reported in organ weights and hematologic/clinical chemistry/urinalysis parameters. No statistically significant changes in female body-weight and body-weight gain were observed. However, small, transient and variable reductions in body-weight gain were observed in high-, mid- (up to week 6) and low-dose (during weeks 1-2) males. These changes were not quantified in the registration dossier or original publication, and therefore, their statistical and toxicological significance is unclear.

Pathological findings were limited to the treatment area in mid- and high-dose rats. Common lesions included acanthosis, hyperkeratosis and parakeratosis. Minimal to marked dermal fibrosis, eschar, ulceration and dermatitis were noted. All lesions were dose-related and females were the most sensitive sex.

The registrants set a NOAEL of 100 mg/kg bw/day for local toxicity to the skin; the eMSCA notes, however, that local effects were observed at all doses. A NOAEL of 750 mg/kg bw/day was set for systemic toxicity as the registrants considered that no systemic effects were reported in this study. However, the eMSCA notes that there were limited reporting details provided in the robust study summary and original publication (e.g. effects not quantified). Therefore, an assessment of whether the reported effects are adverse cannot be made. On this basis, the eMSCA does not consider that a systemic NOAEL or LOAEL can be set for this study.

7.9.4.4. Summary and discussion of repeated-dose toxicity

Oral Repeated-Dose Toxicity

No oral repeated-dose toxicity studies are available for the registered substance. Some information can be obtained from the reproductive/developmental toxicity screening study, in which systemic effects (reductions in body weight gain in males and increases in liver weight) were reported at doses ≥ 300 mg/kg/d.

Dermal Repeated-Dose Toxicity

Based on the results of the sub-chronic study, the registrants set a NOAEL of 100 mg/kg bw/day and 750 mg/kg bw/day for local and systemic toxicity, respectively. These values were applied for derivation of dermal DNELs.

7.9.5. Mutagenicity

Mutagenicity was not identified as an area of concern for MDEA.

7.9.5.1. *In vitro* data

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

Table 18. Summary of the available *in vitro* genotoxicity data

***In vitro* data**			
Method	**Organism/Strain**	**Concentrations Tested**	**Result**
Bacterial Reverse Mutation Assay (Ames Test) Purity: 99.8% Similar to OECD Guideline 471, no data on GLP compliance. Leung & Ballantyne (1997) *	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538)	0.1, 0.3, 1, 3, 5 and 10 mg/plate	**Negative** ± S9 metabolic action Cytotoxicity observed. Valid positive and negative controls.
Mammalian Cell Gene Mutation Test Purity: 99.8% Equivalent or similar to OECD 476, no data on GLP compliance. Leung & Ballantyne (1997)*	Chinese Hamster Ovary cells	0.1, 0.3, 0.6, 1.0, 1.5, 2.0 and 33.0 mg/ml	**Negative** ± S9 metabolic activation No cytotoxicity observed. Valid positive and negative controls.
Bacterial Reverse Mutation Assay (Ames Test) Purity: 99.8% Similar to OECD Guideline 471, no data on GLP compliance. Zeiger *et al.* (1987) Original publication not available. Evaluation based on robust study summary	*Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537)	0, 33, 100, 333, 1000, 2000, 3333, 10000 µg/plate	**Negative** ± S9 metabolic action Cytotoxicity observed at ≥3333 µg/plate. Valid positive and negative controls.
Sister Chromatid Exchange Assay in Mammalian Cells Equivalent or similar to OECD guideline 479, no data on GLP compliance. Leung & Ballantyne (1997)*	Chinese Hamster Ovary Cells	0.3, 0.6, 1.0, 2.0 mg/ml	**Negative** ± S9 metabolic activation No cytotoxicity observed. Valid positive and negative controls.

* Original publication available for evaluation.

7.9.5.2. *In vivo* data

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

Table 19. Summary of the available *in vivo* genotoxicity data

***In vivo* data**			
Method	**Species/Strain**	**Concentrations Tested**	**Result**
Mouse Micronucleus Assay Intraperitoneal Equivalent or similar to OECD guideline 474. Leung & Ballantyne (1997) Original publication available for evaluation.	Mouse/Swiss Webster	175, 350, 560 mg/kg bw/day	**Negative** No signs of substance-related toxicity observed. Valid positive and negative controls.

7.9.5.3. Summary and discussion of mutagenicity

The *in vitro* genotoxicity of MDEA has been investigated in two Ames Tests, a mammalian cell gene mutation test and a sister chromatid exchange assay. Negative results were reported in all studies. Negative results were also obtained from an *in vivo* mouse micronucleus test in which the test substance was administered by the intra-peritoneal route.

Based on the available data, the eMSCA agrees with the registrants that no classification is required in accordance with CLP.

7.9.6. Carcinogenicity

No data is available to measure the carcinogenic potential of MDEA.

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

Reproductive toxicity was identified as one of the initial areas of concern, because of findings in an oral reproduction/development screening study. Therefore, a thorough evaluation of the available data on the reproductive toxicity of MDEA was conducted.

A two-generation/extended one-generation study and a prenatal developmental toxicity study in a second species were not available for MDEA. Instead, the registrants presented studies on the related substance, MEA. A justification for the read-across approach was provided in Section 13 of the updated registration dossier (17th May 2013). Upon detailed evaluation, the eMSCA concluded that sufficient information was provided by the available reproduction/screening test on MDEA, and thus did not rely on supportive information from the studies on the related substance MEA to clarify the concern for reproductive toxicity. Nevertheless, the eMSCA assessed the plausibility of the proposed read-across against ECHA's read-across assessment framework to determine if it lent support to the conclusion. Analysis of the provided argument indicates consistency in effects caused by the four structurally-related substances. Overall, the read-across appears plausible.

7.9.7.1. Fertility

No two-generation/extended one-generation studies are available to investigate the effect of MDEA on reproductive parameters. The available reproduction/developmental screening test conducted with MDEA is summarised in the table below.

Table 20. Summary of available data on fertility

Method	Dose Levels	Remarks
Reproduction/ Developmental screening test Rat/Wistar 10/sex/dose Oral (Gavage) OECD Guideline 421, EPA OPPTS 870.3550, GLP Purity= >99.9% Original study report available for evaluation.	0, 100, 300 and 1000 mg/kg bw/day MDEA Volume= 10 ml/kg bw/day Vehicle= drinking water Duration of treatment= 2-week pre-mating period to post-natal day (PND) 4.	**Parental toxicity** 1000 mg/kg bw/day- *Clinical*: Reduced food consumption (F:↓37% during lactation days 1-4), reduced body weight gain (M:↓29% during weeks 0-3 and M:↓57% during weeks 2-3, F:↓≤46% gestation days 7-20), reduced body weight (F:↓≤14% on gestation days 14 and 20), reduced terminal body weight (M:↓7% and F:↓5%). *Liver*: increased liver weight (absolute: M:↑32% and F:↑26%; relative: M:↑41% and F:↑33%), lymphoid infiltration (M:9 and F:10). 300 mg/kg bw/day- *Clinical*: reduced body weight gain (M:↓45% during weeks 1-2), reduced terminal body weight (M:↓4% and F:↓5%). *Liver*: increased liver weight (absolute: M:↑11% and F:↑12%; relative: M:↑17% and F:↑16%), lymphoid infiltration (M:2 and F:7). 100 mg/kg bw/day- *Liver:* increased liver weight (absolute: F:↑9%, relative: F:↑11%), lymphoid infiltration (M:1 and F:1). **Fertility/reproduction effects** 1000 mg/kg bw/day- increased duration of gestation (22.8 d vs. 21.9 d in control), reduced number of implantation sites (6.7 vs. 12.9 in control), increased number of resorptions (21 vs. 8 in control), increased post-implantation loss (31.0% vs. 6.0% in control), reduced number of delivered pups (4.6 vs. 12.9 in control), total litter loss (4/10 dams), undelivered pups palpable (2/10 dams). 300 mg/kg bw/day- reduced mating index (90% compared with 100% in other treatment groups because of 1 infertile male), testes seminiferous tubule atrophy (1 male), aspermia in the epididymides (1 male). 100 mg/kg bw/day- No test substance-related toxicity. **Offspring toxicity** 1000 mg/kg bw/day- reduced number of pups per dam (4.6 vs. 12.1 in control), reduced pup viability index (62% vs. 99% in control), increased number of dead pups (5 vs. 0 in controls), increased number of cannibalised pups (12 vs. 1 in controls), reduced pup body weight (↓20% on PND 4), reduced pup body weight gain (↓52%). 300 mg/kg bw/day- No test substance-related toxicity. 100 mg/kg bw/day- reduced viability index (87% vs. 99% in control) owing to 1 dam that cannibalised 11/14 pups. Increased number of runts owing to one dam not nursing pups properly and total litter loss by PND 2. NOAEL (general toxicity) = 100 mg/kg bw/day owing to body weight reductions at ≥300 mg/kg bw/day.

		NOAEL (reproductive performance/fertility) = 300 mg/kg bw/day based on litter loss, insufficient lactation behaviour and an increased duration of gestation at 1000 mg/kg bw/day. NOAEL (developmental toxicity) = 300 mg/kg bw/day based on reduced viability index and reduced post-natal offspring weight gain at 1000 mg/kg bw/day.

In the reproduction/developmental screening test, Wistar rats (10/sex/dose) were dosed (gavage) with aqueous solutions of 0, 100, 300 or 1000 mg/kg bw/day MDEA. Treatment covered a two-week pre-mating period (males and females), two-week mating period (males and females), gestation (females only) and post-natal days 1-4 (females only). An adverse effect on reproductive/development parameters was observed at the high dose of 1000 mg/kg bw/day but was observed in the presence of severe maternal toxicity.

In females, a statistically significant increase in gestation duration (22.8 d vs. 21.9 d in control), number of resorptions (21 vs. 8 in control) and post-implantation loss (31.0% vs. 6.0% in controls) was reported at 1000 mg/kg bw/day. This was accompanied by statistically significant reductions in the number of implantation sites (6.7 vs. 12.9 in control) and delivered pups (4.6 vs. 12.9 in control). Four dams of the 1000 mg/kg bw/day dose group lost their entire litters. Offspring of two of these dams had no or less milk in their stomachs, indicating that pup deaths may have been the consequence of insufficient dam and/or pup lactation behaviour. The other two dams had undelivered pups palpable in their abdomen.

Parental toxicity was observed at ≥300 mg/kg bw/day and included statistically and toxicologically significant reductions in body weight (up to 14 % in females), body-weight gain (up to 46 % in females), and food consumption (up to 37 % in females). An increase in liver weight was also reported at ≥300 mg/kg bw/day.

No weight or substance-related pathomorphological changes were observed in the reproductive organs (testes, epididymides and ovaries), except for a single incidence of testicular seminiferous tubule atrophy and aspermia in the epididymides at 300 mg/kg bw/day (1/10 males). However, because of the lack of a dose-response-relationship this is considered by the eMSCA to be a spontaneous finding.

It is noted that all substance-related adverse effects on reproductive parameters/offspring toxicity were observed at doses also causing maternal toxicity (reduced body weight and food consumption). No such effects were observed at lower doses in the absence of parental toxicity.

7.9.7.2. Developmental toxicity

No prenatal developmental toxicity studies are available to assess the effect of MDEA on development after oral or inhalation exposure. However, an oral reproduction/developmental screening test on MDEA is available (see above) in the rat. A dermal prenatal developmental toxicity study in the rat is also available; this study is summarised in the table below.

Table 21. Summary of available data on development

Method	Dose Levels	Remarks
Prenatal developmental toxicity study	0, 250, 500 and 1000 mg/kg bw/day MDEA	Maternal toxicity 1000 mg/kg bw/day- Skin: exfoliation, excoriation, crusting, ecchymoses and necrosis.

Rat/ CD 25 pregnant females/dose OECD Guideline 414, no data on GLP compliance Purity= >99.5% Leung & Ballantyne (1998)*	Volume= 4 ml/kg bw/day Vehicle= water Duration of treatment= 6 hrs/day during gestation days 2-15.	Haematology: reduced erythrocyte count, reduced hematocrit, reduced haemoglobin (↓6%). 500 mg/kg bw/day- Skin: exfoliation, excoriation, crusting, ecchymoses and necrosis. 250 mg/kg bw/day- No test substance related toxicity. Developmental toxicity 1000, 500 and 250 mg/kg bw/day- No adverse effects on embryo or developmental toxicity was observed. NOAEL (maternal toxicity)= 250 mg/kg bw/day. NOAEL (teratogenicity)= 1000 mg/kg bw/day.

* Original study report was not available. Evaluation was based on the robust study summary in the dossier

Reproduction/developmental screening test

In the reproduction/developmental toxicity screening study (also discussed in Section 7.9.7.1), Wistar rats (10/sex/dose) were dosed (gavage) with aqueous solutions of 0, 100, 300 or 1000 mg/kg bw/day MDEA. Treatment covered a two-week pre-mating period (males and females), two-week mating period (males and females), gestation (females only) and post-natal days 1-4 (females only). An adverse effect on reproduction / development was observed at 1000 mg/kg bw/day, a dose that also produced maternal toxicity.

Maternal toxicity observed at ≥300 mg/kg bw/day included statistically significant reductions in body weight, body weight gain, and food consumption. An increase in absolute and relative liver weight was also reported at ≥300 mg/kg bw/day.

A statistically significant increase in gestation length (22.8 d vs. 21.9 d in control), number of resorptions (21 vs. 8 in control) and post-implantation loss (31.0% vs. 6.0% in controls) was reported at 1000 mg/kg bw/day. This was accompanied by statistically significant reductions in the number of implantation sites (6.7 vs. 12.9 in control) and delivered pups (4.6 vs. 12.9 in control). Four dams of the 1000 mg/kg bw/day dose group lost their entire litters. Offspring of two of these dams had no or less milk in their stomachs, indicating that pup deaths may be the result of insufficient dam and/or pup lactation behaviour. The other two dams had undelivered pups palpable in their abdomen.

Offspring toxicity was observed at 1000 mg/kg bw/day and included reductions in pup viability (62% vs. 99% in control), pup body weight (↓ 20% on PND 4), pup body weight gain (↓ 52%) and an increased number of dead (5 vs. 0 in the control)/cannibalised (12 vs. 1 in controls) pups. A reduction in the pup viability index (87% vs. 99% in controls) was also observed in the 100 mg/kg bw/day dose group. However, this was caused by one dam, which cannibalised 11 of its 14 pups and consequently is not considered treatment related.

All substance-related adverse effects on reproductive parameters/offspring toxicity were observed at doses also causing maternal toxicity (reduced body weight and food consumption).

Prenatal developmental toxicity study – rats

In a prenatal developmental toxicity study (Leung & Ballentyne, 1998), pregnant rats (CD, 25/dose) were cutaneously exposed to 0, 250, 500 and 1000 mg/kg bw/day MDEA for 6 hrs/day under occlusive conditions during gestation days 2-15.

No animals died and there were no clinical signs of systemic toxicity. Local toxicity included skin exfoliation, excoriation, crusting, ecchymoses and necrosis at 500 and 1000 mg/kg bw/day. Small changes in erythrocyte count, haemoglobin and hematocrit were observed at 1000 mg/kg bw/day (Hermansky *et al*, 1995).

No developmental toxicity was observed up to the highest dose of 1000 mg/kg bw/day.

7.9.7.3. Summary and discussion of reproductive toxicity

Reproductive toxicity was identified as an initial ground for concern, based on a manual screen of the findings from a reproduction / developmental toxicity screening study (OECD 421).

This evaluation has confirmed that adverse effects on reproduction and developmental parameters were produced by MDEA in this screening study, occurring only at the high (limit) dose of 1000 mg/kg bw/d. The observed effects included reduced number of implantation sites, increased number of resorptions, increased post-implantation loss and reduced number of delivered pups. These effects occurred only in the presence of general systemic toxicity in the dams, which was reported from 300 mg/kg bw/d. It is considered that the effects on reproduction and offspring occurred as a consequence of the general toxicity occurring in dams and is therefore considered non-specific. The read-across argument put forward by the registrants proposes that the cause of the general toxicity of MDEA and other ethanolamines is due to a common mode of action (MOA) causing perturbation of choline homeostasis. The Registrants believe that this MOA may lack human relevance and have proposed further mechanistic work to investigate this. However, pending this information, the eMSCA cannot dismiss these effects as not being relevant to humans.

There were no indications of developmental toxicity in a dermal OECD 414-compliant study conducted on MDEA. The eMSCA notes that this substance has no registered consumer uses. Furthermore, as the substance has a very low vapour pressure, exposure via the inhalation route is unlikely. The dermal route is thus concluded to be the most relevant route of exposure. Therefore, the concern that the dermal route might not be appropriate for the conduct of the toxicological studies has been clarified. It is also pertinent that some information on developmental toxicity after oral exposure is provided by the reproduction / development screening study. Overall, the eMSCA concludes that additional information to investigate developmental toxicity via a route of exposure other than dermal is not required to clarify the concern for reproductive toxicity.

In conclusion, the eMSCA considers that there is sufficient information on MDEA to inform on the concern for reproductive toxicity (effects on development; embryo-foetal toxicity). The observed effects occurred only at the high dose of 1000 mg/kg bw/d (via the oral route) in the presence of significant maternal toxicity. There were no effects on fertility or any evidence of teratogenicity following treatment with MDEA. No further information is requested.

7.9.8. Hazard assessment of physico-chemical properties

MDEA is a colourless liquid with a boiling point of 243 °C and a low volatility (0.31 Pa at 20 °C). It is non-flammable with a flashpoint of 138 °C.

Based on the available data, MDEA does not meet the criteria for classification for any physico-chemical end points.

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

DNEL Derivation for MDEA.

Long-term systemic DNELs have been calculated for workers (dermal and inhalation routes). There are no consumer uses of this substance. MDEA has a harmonised classification for eye irritation and is a mild skin irritant (see section 7.9.2.). In the repeated-dose toxicity studies by the dermal route of exposure, local effects were evident; these occurred at all doses in the 90-day study. Therefore, qualitative risk assessment is appropriate for these effects.

Dermal route (worker)

The registrants proposed a DNEL based on a 90-day dermal study with a total AF of 40. In this study, no systemic toxicity was reported at doses up to 750 mg/kg bw/d. However, the eMSCA considered that there was insufficient reporting of the effects (for examples, magnitudes of changes) to determine if systemic toxicity was evident. Therefore, the eMSCA proposed not to set a NOAEL and LOAEL from this study.

A systemic NOAEL of 100 mg/kg bw/day is available from a reproduction / developmental screening study. This will be used as the basis for route-to-route extrapolation from an oral NOAEL to a systemic dermal DNEL for humans. The eMSCA recognises that, since there was no apparent systemic toxicity in the 90-day dermal study (body-weight effects that were stated to be small and transient, but further details not available; hence a systemic NOAEL was not set by the eMSCA), this approach is likely to be conservative.

Oral absorption is assumed to be 100% (default value) in rats and humans. Dermal absorption is considered to be equivalent in the test species (rats) and humans (20%; see section 7.9.1.).

Corrected dermal NOAEL = oral NOAEL x ABSoral-rat / ABSderm-human

= 100 x 100/20

= 500 mg/kg bw/d

Assessment factors

The following assessment factors have been used in the conversion of the NOAEL in the rat oral study to a human equivalent.

- Interspecies – 10
- Intraspecies – 5
- Duration of exposure – 6 (correction from sub-acute to chronic; exposures were for 28 days)
- Dose response relationship - 1 (NOAEL is highest dose tested)
- Quality of database – 1 (The database on MDEA is limited in terms of chronic studies. However, there is sufficient information to characterise the reproductive / developmental toxicity and the extrapolation to chronic duration has already been made. No additional factor is considered applicable.)
- Total AF = 300

Overall, the worker $DNEL_{long\text{-}term\ dermal\ systemic}$ = 500 mg/kg bw/d / 300

= 1.7 mg/kg bw/d

Inhalation route (worker)

The registrants proposed a DNEL based on a 90 day dermal study. As systemic effects were seen via oral exposure, the route to route extrapolation from oral exposure is considered to be more applicable.

A NOAEL of 100 mg/kg bw/day is available from an oral reproduction / developmental toxicity screening test (OECD 421). The key end-point is reduced body weight in both parental sexes.

Oral absorption is considered to be 50% (default in the absence of data) with 100% inhalation absorption (default in the absence of data).

To convert the NOAEL to mg/m^3 for workers a correction of 50/100 x 1/0.38 m^3/kg/8h x 0.67 = 0.88

Corrected inhalation NOAEC = 100 x 0.88 = 88 mg/m^3/8h

Assessment factors

The following assessment factors have been used in the conversion of the NOAEL in the rat oral study to a human equivalent.

- Interspecies – 2.5 (no factor for allometric scaling required)
- Intraspecies – 5
- Duration of exposure – 6 (correction from sub-acute to chronic; exposures were for 28 days)
- Dose response relationship - 1 (NOAEL, effects at LOAEL were not severe or irreversible)
- Quality of database – 1 (The database on MDEA is limited in terms of repeat dose oral studies and chronic oral studies. However, there is sufficient information to characterise the reproductive / developmental toxicity and the extrapolation to chronic duration has already been made. No additional factor is considered applicable.
- Total AF = 75

Overall, the worker DNEL$_{\text{long-term inhalation systemic}}$ = 88 mg/m^3/8h / 75 = 1.2 mg/m^3 /8h

Table 22

CRITICAL DNELS/DMELS				
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**
Worker dermal	Systemic	Oral screening study	500 mg/kg bw/d	1.7 mg/kg bw/d
Worker inhalation	Systemic	Oral screening study	88 mg/m^3/8h	1.2 mg/m^3/8h

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

MDEA has a harmonised classification of Eye Irrit. 2: H319. On the basis of the available data the eMSCA does not consider any further classification for human health is warranted.

7.10. Assessment of endocrine disrupting (ED) properties

Not assessed

7.11. PBT and VPVB assessment

Not assessed

7.12. Exposure assessment

By August 2017, six companies had submitted full registrations for MDEA. All are part of the same joint submission and the aggregated tonnage for all registrants is 10,000+ tpa. Of these six registrants, some have not revisited their dossiers since the initial submissions were made in 2010 whereas other companies have updated their registrations in light of discussions that took place during the initial evaluation in 2013/14. This exposure assessment takes account of the information provided in all registrations and updates submitted up to this date.

Note to registrants: To ensure accurate information is available to authorities in relation to the uses and the conditions of use that are supported, all registrants should ensure that they update their CSRs promptly when they receive new information. The opinions expressed by the eMSCA in this report about the quality and suitability of the exposure assessments performed by registrants constitute new information. The eMSCA expects that all registrants, including any submitting registrations for the first time after 31 August 2017, will ensure that the findings from this substance evaluation are taken into account in their chemical safety assessments.

7.12.1. Human health

The exposure assessments submitted by the registrants cover workers engaged in the manufacture and use of MDEA at industrial sites also professionals using MDEA and products containing MDEA. Consumers are not supplied with MDEA or products containing MDEA and exposure to this substance via articles is not expected based on the information provided by registrants.

The assessments are based on modelled data obtained using either the ECETOC TRA tool version 2 or 3 or the EASY TRA tool, no measured data were provided. Where MDEA is used in mixtures, a linear approach has been adopted to take account of the concentration in mixtures. This approach will produce lower exposure estimates than would be obtained using the concentration band approach that has been adopted in the ECETOC TRA tool and is therefore less precautionary. Dermal exposure predictions have not been adjusted to take account of LEV, which increases conservatism in the dermal exposure assessment.

Based on its hazard classification, short-term exposure to MDEA is not expected to result in adverse effects therefore the exposure assessment has only covered full-shift exposure. The eMSCA agrees that it is not necessary to perform a short-term exposure assessment for this substance.

Since MDEA is classified as an eye irritant and there is evidence to show that it may cause mild skin irritation and since it is not possible to establish robust dose response relationships for these effects, a qualitative assessment has been performed to ensure that any risks to health from these properties are suitably managed.

7.12.1.1. Worker

7.12.1.1.1 Observations made during the initial evaluation

The initial evaluation identified several areas of the registrants' exposure assessments that required further work. It was not clear to the eMSCA which activities and tasks were covered by each exposure scenario. Registrants were asked to provide further justifications for the choice of PROC codes and modelling parameters. In particular, a concern was raised for the use of the ECETOC TRA tool to assess aerosol forming processes given that MDEA is a low volatility substance and the applicability domain of the ECETOC TRA tool does not cover aerosol forming processes for substances with low vapour pressures. For the use of gloves, justifications were required to support the glove efficiency values that had been selected and registrants were asked to provide more information about glove materials, thicknesses and breakthrough times. Information was also needed to clarify how cleaning and maintenance activities are being addressed. In their response to the draft decision, the lead registrant agreed to provide the additional information that was requested. However, the majority of registrants have not updated their CSRs since the draft decision was issued.

One registrant was taking a unique approach to modifying the outputs of the TRA tool to take account of the low volatility of MDEA. The registrant provided a detailed justification for their approach. Having assessed this justification, the eMSCA considers it would be preferable to use an exposure modelling tool that has been validated for use for low volatility liquids rather than apply mathematical adjustments to the TRA tool.

In the light of the uncertainties in the registrants' exposure assessments and in order to progress this evaluation, the eMSCA has chosen to perform its own exposure assessment. This assessment is based on the information contained in all registrations as they stood in August 2017.

7.12.1.1.2 Exposure assessment performed by the eMSCA

The vapour pressure of MDEA (0.31 Pa at 20°C) is low. This vapour pressure places MDEA towards the lower end of the low vapour pressure band for the ECETOC TRA tool (0.01 – 500 Pa). The ECETOC TRA tool calculates vapour in air concentrations. Therefore, for substances with low vapour pressure, the tool has the potential to overestimate exposures. To illustrate the scale of the problem for MDEA, for PROC 3 (used to describe manufacture or formulation in closed batch processes with occasional controlled exposure or processes with equivalent containment condition), the tool estimates an air concentration of 14.9 mg/m^3 (activity performed for up to 8 hours, substance used undiluted, LEV and RPE are not used). This exceeds the saturated vapour concentration (SVC) reported by one registrant (13.4 mg/m^3) and matches the SVC calculated by the eMSCA using the EGRET[8] (14.9 mg/m^3). It is clearly unrealistic for vapour in air concentrations to reach levels that approach the SVC during normal operating conditions even for a very open process. PROC 3 is intended to describe a mainly closed process with limited worker interventions. The eMSCA has therefore attempted to find alternative ways of assessing inhalation exposure to MDEA.

In its assessment, the eMSCA is taking account of a small scale investigation which attempted to characterise the relationship between the calculated SVC and measured airborne concentrations for three substances (Pengelly and Johnson, 2012). The

[8] The EGRET (**E**uropean Solvents Industry Group **G**eneric Exposure Scenario **R**isk and **E**xposure **T**ool) has been devloped to assess consumer exposure to solvents. It includes the facility to calculate the saturated vapour concentration of solvents based on their molecular weight and vapour pressure. The tool and associated user guidance can be accessed at: http://www.esig.org/regulatory/reach-ges/consumers/ (accessed 5 September 2017).

substances chosen for the investigation were cinnamaldehyde, phenoxyethanol and 1-methylnaphthalene which have vapour pressures ranging from 1 – 10 Pa at 20°C.

The investigation included a series of bench scale baseline tests in which 50 µl substance was allowed to evaporate into sealed glass chambers of different sizes (2-litre vs 20-litre container) and using different air temperatures (20 or 35°C) over 6 or 24 hour periods. Further experiments were performed in which 1 ml of a 5% aqueous solution of phenoxyethanol was allowed to evaporate into a sealed or ventilated 20 litre container at 20°C for 6 hours. An experiment was also performed in which the surface temperature of the solvent was increased to 55°C and substances were allowed to evaporate for 6 hours into a sealed 4 litre container with an air temperature of 20°C. Samples were periodically collected from the test chamber onto Tenax TA sorbent tubes and were analysed using thermal desorption and gas ghromatography-mass spectrometry (GC-MS).

The experiments were then scaled up and further studies were performed with cinnamaldehyde and phenoxyethanol in a room sized test chamber measuring approximately 4m x 4m x 3m. This included tests in which amounts ranging from 1 - 5 ml of each substance were placed in a shallow dish situated approximately 50 cm above floor level and allowed to evaporate into an unventilated room with temperatures ranging from 17 – 21°C over periods of 2 or 3 hours. Tests were also performed which aimed to simulate typical work activities that may be performed with these substances. In the case of cinnamaldehyde, the experiment simulated its use as a deodorant in sanitary bins. In the case of phenoxyethanol, the experiment simulated its use in coatings applied by brush. Static sampling heads were placed directly above the source of exposure at a height of approximately 1.5 m and a series of 10, 20 or 30 minute samples were collected onto Tenax TA sorbent tubes over a 2 or 3 hour period with a flow rate of around 50 ml/min. As before samples were analysed with thermal desorption followed by GC-MS.

In the baseline tests, the air concentrations for the three substances ranged from 6 - 25% of the calculated SVC after 6 hours. Increasing the size of the chamber slowed the equilibration time but had relatively little effect on the final concentration. When the evaporation time was extended to 24 hours, the air concentrations continued to rise, but in no case did the air concentration approach the SVC including the tests where elevated surface temperatures were used. In the case of the tests with the 5% aqueous phenoxyethanol solution, when the solution was allowed to evaporate into a sealed chamber the air concentration reached 35% of the SVC within 2 hours. In contrast when the chamber was ventilated at a rate of around 0.1 air changes per hour, the air concentration had only reached 1.8% of the SVC after 6 hours. This illustrates the impact that even a low rate of ventilation can have on air concentrations.

For the chamber studies, the highest vapour concentrations were achieved in simulated painting tests with phenoxyethanol. When 20 ml undiluted phenoxyethanol was spread across a piece of cardboard (30 cm x 30 cm) using a 2.5 cm paint brush for around 1 minute and an airflow of 1.6 – 2.0 m/s was blown across the painted surface during a 3-hour evaporation phase the air concentration rose to 1.4% of the SVC. When the evaporation phase was extended to 6 hours, the vapour concentration rose to 1.9% of the SVC. This test was repeated using 50 ml of a 10% aqueous solution of phenoxyethanol and after 3 hours the vapour concentration reached 0.84% of the SVC. Since the vapour pressure of phenoxyethanol (1.3 Pa at 25°C) is higher than that of MDEA (0.13 Pa at 20°C), these results suggest that under realistic working conditions, for non-aerosol forming processes, air concentrations of MDEA are likely to be very substantially below the SVC. If as a worst case, it is assumed that air concentrations for non-aersosl forming processes will not exceed 10% of the SVC under normal working conditions, this indicates a maximum concentration in air of around 1.5 mg/m^3 for such processes.

In the light of this information, rather than attempt to calculate airborne concentrations for each work activity that has been identified in registrations, the eMSCA will assume that exposures will not exceed 1.5 mg/m^3 (8-hr TWA) for non-aerosol forming processes. For

aerosol forming proceses, the eMSCA will derive airborne exposure estimates using the Advanced REACH Tool (ART) version 1.5.

The eMSCA will rely on the ECETOC TRA tool version 3 to assess dermal exposure for all activities. A recently published validation study reported that the performance of this tool appeared to be in the range of the performance of other dermal exposure models (Marquart *et al*, 2017). The tool was found to overestimate exposure for activities with a low potential for dermal exposure. Where dermal exposure is expected to be higher, e.g. activities which may generate significant surface contamination, the tool predicted lower exposures than the corresponding measured data. Where registrants have identified the need for gloves to be worn, the eMSCA will take a precautionary approach and apply an efficiency of 80% in its own calculations. The eMSCA will not take account of the use of LEV in its dermal exposure assessment.

7.12.1.1.2.1 Manufacture

MDEA is manufactured in the EU. Manufacture is described by PROCs 1, 2, 3, 8b and 15 which implies a predominantly closed process with limited opportunities for worker exposure. The registrants indicate LEV and RPE are not used. The qualitative assessment indicates gloves should be worn to protect the skin against incidental contact. The eMSCA'assessment will therefore take account of the use of gloves with an assumed efficiency of 80%. Eye protection may also be required if there is an opportunity for incidental splashing. It is assumed that all activities are performed for 8 hours per day.

Table 23: Exposure values for manufacture estimated by the eMSCA.

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), LEV and RPE are not used, glove efficiency is 80%.	1.5	<0.01
PROC 2			0.27
PROC 3			0.14
PROC 8b			2.74
PROC 15			0.07

The maximum concentration in air that is expected to arise during the manufacture of MDEA is 1.5 mg/m^3. The maximum dermal exposure that has been calculated is 2.74 mg/kg/day for PROC 8b. The risk characterisation for manufacture will therefore be based on the values for PROC 8b.

7.12.1.1.2.2 Use as an intermediate

MDEA is used as an intermediate in the manufacture of a range of substances. The majority of registrants supporting this use describe it with PROCs 1, 2, 3, 4, 8a, 8b and 9, although one company expects higher levels of containment and does not apply PROC 4. All registrants indicate that LEV (efficiency 90%) is required if open transfers are carried out (PROC 8a). The eMSCA will therefore assume that this risk management measure is implemented at all sites using MDEA as an intermediate. LEV and RPE are not required for other activities. Gloves are required to protect the skin against incidental contact and will be taken into account in the dermal exposure assessment. Eye protection is required where there is the potential for incidental splashing. As a worst case, it is assumed that the substance is used as such (i.e. the concentration is 100%). However, it may be handled as a more dilute solution at some stages of the process and hence exposure assessments based on the assumption that pure MDEA is being handled will overestimate exposure for these processes.

Table 24: Exposure values for use as an intermediate estimated by the eMSCA

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), LEV is only required for transfers covered by PROC 8a. RPE is not used, glove efficiency is 80%.	1.5	<0.01
PROC 2			0.27
PROC 3			0.14
PROC 4			1.37
PROC 8a			2.74
PROC 8b			2.74
PROC 9			1.37

The maximum concentration in air that is expected to arise during the use of MDEA as an intermediate is 1.5 mg/m³. The maximum dermal exposure that has been calculated is 2.74 mg/kg/day for PROCs 8a and 8b. The risk characterisation for use as a intermediate will therefore be based on the values for PROCs 8a and 8b.

7.12.1.1.2.3 Formulation of preparations

Formulation of preparations containing MDEA is described by PROCs 3, 5, 8a, 8b and 9. RPE is not required. All registrants indicate LEV is required for activities covered by PROCs 5 and 8a. All registrants also recommend the use of gloves to protect against incidential skin contact. The eMSCA has therefore taken account of the use of gloves with an assumed efficiency of 80% in its assessment. The use of LEV has not been taken into account in the dermal exposure assessments. Eye protection will be required where there is the potential for incidental splashing.

Table 25: Exposure values for formulation of preparations estimated by the eMSCA

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
PROC 3	Activity performed for up to 8 hours, substance used as such (100%), LEV is required for activities covered by PROC 5 and open transfers covered by PROC 8a. RPE is not used, glove efficiency is 80%.	1.5	0.14
PROC 5			2.74
PROC 8a			2.74
PROC 8b			2.74
PROC 9			1.37

The maximum concentration in air that is expected to arise during the formlation of products containing MDEA is 1.5 mg/m³. The maximum dermal exposure that has been calculated is 2.74 mg/kg/day for PROCs 5, 8a and 8b. The risk characterisation for formulation will therefore be based on the values for these three PROCs.

7.12.1.1.2.4 Distribution

Some registrants have included a scenario for "distribution" of the substance to cover storage, loading and unloading of vessels and repacking into smaller containers. These activities have been described with PROCs 1, 2, 3, 4, 8a, 8b, and 9. PROC 2 has been applied to cover sampling activities and PROC 8a to cover equipment cleaning and maintenance. Gloves with an assumed efficiency of 80% are taken into account for bulk transfers (PROC 8b) and cleaning and maintenance (PROC 8a) but not for other activities in the registrants' assessment. Since gloves may be worn at other times to protect against incidental skin contact, the eMSCA has calculated dermal exposure both with and without gloves. Eye protection is required for all stages of the process.

Table 26: Exposure values for distribution estimated by the eMSCA

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)	
			Glove efficiency 80%	No gloves
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), LEV and RPE are not required, gloves with an assumed efficiency of 80% are worn for activities covered by PROCs 8a and 8b.	1.5	<0.01	0.03
PROC 2			0.27	1.37
PROC 3			0.14	0.69
PROC 4			1.37	6.86
PROC 8a			2.74	n/a*
PROC 8b			2.74	n/a*
PROC 9			1.37	6.86

* n/a: not assessed. Since gloves have been identified as a mandatory measure for PROCs 8a and 8b, without glove exposures have not been calculated.

The maximum concentration in air that is expected to arise during distribution is 1.5 mg/m³. The maximum dermal exposure that has been calculated is 6.86 mg/kg/day for PROCs 4 and 9 if these activities are performed without gloves. The risk characterisation will be based on the values for PROCs 4, 9, 8a and 8b.

7.12.1.1.2.5 Industrial and professional use as a processing aid (catalyst) in polymerisation reactions

MDEA is used as a catalyst in the production of polyurethane foams and epoxy resins which are used in construction. Where this use takes place at industrial sites it is described by PROCs 7, 8a, 8b, 10, 14, 21 and 24c. Some registrants have assumed that MDEA may be used at concentrations of up to 100% for this purpose whereas others have set an upper limit of 1% for all stages of the process where MDEA is handled in a liquid state. PROCs 21 and 24c are applied to cover processing of cured foams and resins which may contain residues of MDEA. All registrants have assumed that the solids being processed are of high dustiness with some taking a worst case approach and assuming MDEA may be present in the matrix at up to 100% while others assume it is present at up to 10%.

Professional use is described by PROCs 8a, 8b, 10, 11, 13 and 14. Professionals are only supplied with mixtures containing MDEA and not pure MDEA. Some registrants are assuming that MDEA is present at a concentration of up to 5% while others have set an upper limit of 1%.

Registrants assuming MDEA may be used at concentrations of up to 100% indicate that LEV is required for spraying activities, open transfers and application using brushes or rollers (PROCs 7, 8a and 10). This is not required for other activities. No requirements for LEV are made where MDEA is used at concentrations of 5% or less.

The use of gloves has been taken into account in different ways. Some registrants take account of the use of gloves with an assumed efficiency of 90% for all activities performed by industrial workers and professionals. Others indicate gloves with an assumed efficiency of 98% should be worn for industrial spraying activities, gloves with an assumed efficiency of 90% should be worn for other industrial activities and by professionals spraying products containing MDEA. Professionals do not need to use gloves for other activities owing to the low concentration of MDEA in products.

Eye protection may be required to protect against incidental splashing during industrial activities, but is not deemed necessary for professional activities given the low concentration of MDEA in products.

Note to registrants: The eMSCA notes that 98% efficiency was assumed for the use of gloves in relation to PROC 7 in the scenario for the use of MDEA as a processing aid in polymerisation reactions. This value is not recognised as an option in the IR & CSR guidance or in the TRA tool. The use of this modifier is linked to the provision of specific activity training and intensive management supervision. Although gloves can provide this level of protection, the eMSCA does not expect that these conditions will be maintained consistently by all downstream users that may follow this scenario. Any registrant intending to rely on this efficiency value should provide a specific justification for its use. Alternatively they should revise their CSR with a new value that is recognised as an option in the IR & CSR guidance.

The registrants have chosen to use the ECETOC TRA tool version 2 or the EASY TRA tool to assess exposure during aerosol forming processes (PROCs 7 and 11). The developers of the ECETOC TRA tool state that it does not address such exposures. In the case of low volatility substances, it is foreseeable that an assessment that only takes account of the vapour phase could underestimate exposure. The eMSCA also questions whether the predictions that these tools have generated for PROCs 21 and 24c accurately reflect potential exposure to MDEA during processing of cured foams and resins. For these two PROCs, the eMSCA expects that the assumptions made by the registrants are very precautionary.

Note to registrants: The IR & CSA Guidance Chapter R14, section R.14.6.6[9] states that users of modelling tools should ensure the tool is used within the published boundaries. Where modelling tools are used for situations outside their applicability domains, the exposure estimates should only be used in the assessment as supporting evidence. The user guidance for the ECETOC TRA tool clearly states that aerosol forming processes are outside the applicability domain for the tool. Registrants should therefore update their CSRs with an appropriate assessment for aersol forming processes or a justification indicating why the exposures calculated by the ECETOC TRA tool or EASY TRA tool are representative for the use situation to which they are being applied. If indicated by a revised exposure assessment, registrants should amend the conditions of use described in their exposure scenarios.

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9 https://echa.europa.eu/documents/10162/13632/information_requirements_r14_en.pdf/bb14b581-f7ef-4587-a171-17bf4b332378 (version 3.0, accessed September 2017)

For its assessment, as previously indicated the eMSCA is assuming that for non-aerosol forming processes (PROCs 8a, 8b, 10, 13 and 14) airborne exposures will not exceed 1.5 mg/m^3 (8-hr TWA).

For aerosol forming proceses (PROCs 7 and 11), the eMSCA has used the Advanced REACH Tool (ART) version 1.5 to assess potential inhalation exposure. In the absence of specific information about the products that are used and processes that are operated, the eMSCA has made assumptions about the concentration of MDEA in the mixture, the scale of the process and the conditions under which processes are operated (the input parameters chosen by the eMSCA are listed in Appendix 1, table A1). Although some registrants have based their calculations on the assumption that MDEA may be present at up to 100% in mixtures used in industrial settings, the eMSCA considers that this is likely to be a very precautionary assumption and is basing its own calculations on the expectation that a catalyst is likely to be a minor component. It will take 5% as the upper limit for MDEA in mixtures that are used for spraying activities. Since the ART does not distinguish between use at industrial sites and use by professionals, the same input parameters are applied to both cases. The eMSCA has assumed that LEV is not in use since this risk management measure is not recommended by any registrant for professional spraying and not all registrants recommend the use of LEV for industrial spraying.

In the case of PROCs 21 and 24c, the eMSCA prefers to carry out a qualitative risk characterisation because it does not have sufficient information about the levels of residual MDEA that may be present in cured foams/resins to calculate meaningful exposure estimates.

For its dermal exposure assessment, with the exception of PROCs 21 and 24c, the eMSCA has relied on the ECETOC TRA tool. Although this tool has not been used to assess inhalation exposure for PROCs 7 and 11, the analysis of Marquart *et al* (2017) found that dermal exposure predictions for these PROCs was representative for the available measured data. The eMSCA has taken account of the use of gloves with an assumed efficiency of 80% for all industrial activities. For professional activities it has assesed dermal exposure both with and without gloves.

Table 27: Exposure values for industrial and professional use as a processing aid (catalyst) in polymerisation reactions estimated by the eMSCA.

Contributing scenario	Assessment parameters*	Inhalation value (8-hr TWA, mg/m^3)	Dermal value (mg/kg/day)	
			Gloves efficiency 80%	No gloves
Industrial				
PROC 7	Activity performed for up to 8 hours, substance used in a mixture (5%), LEV and RPE are not used, glove efficiency is 80%.	4.6	1.71	n/a
PROC 8a		1.5	0.55	n/a
PROC 8b			0.55	n/a
PROC 10			1.10	n/a
PROC 14			0.14	n/a
PROC 21	Insufficient information to establish suitable assessment parameters	Qualitative assessment		
PROC 24c				
Professional				
PROC 11	Activity performed for up to 8 hours, substance used in a mixture (5%), LEV and RPE are	4.6	4.29	21.4
PROC 8a		1.5	0.55	2.74

PROC 8b	not used, gloves are not worn.		0.55	2.74
PROC 10			1.10	5.49
PROC 13			0.55	2.74
PROC 14			0.14	0.69

* A complete list of the assessment parameters used for the ART assessment is given in Appendix 1, table A1.

The maximum concentration in air that is expected to arise during spraying is 4.6 mg/m^3 and spraying is also associated with the highest potential dermal exposures. For other activities a maximum concentration in air of 1.5 mg/m^3 is predicted, with a maximum dermal exposure of 5.49 mg/kg/day (calculated for PROC 10, no gloves).

7.12.1.1.2.6 Industrial and professional use in lubricants and metal working fluids

MDEA may be present in lubricants and metal working fluids at concentrations up to 10%. This use is described by the registrants with PROCs 2, 3, 8a, 8b, 9, 17 and 18. LEV and RPE are not required. Some registrants indicate the need to wear gloves with an efficiency of 90%. Others do not recommend the use of gloves for industrial or professional use. Eye protection will be required where there is the potential for incidental splashing.

The registrants have chosen to use the ECETOC TRA tool version 2 or the EASY TRA tool to assess exposure during aerosol forming processes (PROCs 17 and 18). The eMSCA identifies the same concerns here as it identified in relation to the use of the ECETOC TRA tool and the EASY TRA tool to assess exposure during activities covered by PROCs 7 and 11.

Note to registrants: As previously indicated it is important to use exposure modelling tools within their applicability domains. Registrants should take the same actions for these PROCs as were identified for the use of the ECETOC TRA tool and the EASY TRA tool to assess exposure during activities covered by PROCs 7 and 11.

For its assessment, the eMSCA is assuming that for non-aerosol forming processes (PROCs 2, 3, 8a, 8b and 9) airborne exposures will not exceed 1.5 mg/m^3 (8-hr TWA).

For aerosol forming proceses (PROCs 17 and 18), the eMSCA has used the Advanced REACH Tool (ART) version 1.5. In the absence of specific information about the products that are used and the machining activities that are performed, the eMSCA is relying on the information provided in registrations. Most registrants assume the concentration of MDEA in lubricants and metal working fluids will be 10% although one registrant assumed the concentration used for activities covered by PROCs 17 and 18 is only 5%. The eMSCA will assume the concentration of MDEA in products is up to 10% all industrial and professional use situations. For this assessment the eMSCA assumed that handling practices are adopted which reduce contact between the product and air since this reflects good occupational hygiene practices for metalworking fluids (the input parameters chosen by the eMSCA are listed in full in Appendix 1, table A2).

For its dermal exposure assessment, the eMSCA will not take account of the use of gloves since this reflects recommendations made by the majority of registrants.

Table 28: Exposure values for industrial and professional use in lubricants and metalworking fluids estimated by the eMSCA.

Contributing scenario	Assessment parameters*	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
Industrial			
PROC 2	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV and RPE and gloves are not used.	1.5	0.82
PROC 3			0.41
PROC 8a			8.23
PROC 8b			8.23
PROC 9			4.11
PROC 17		1.1	16.5
PROC 18			8.23
Professional			
PROC 2	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV and RPE and gloves are not used.	1.5	0.82
PROC 3			0.41
PROC 8a			8.23
PROC 8b			8.23
PROC 9			4.11
PROC 17		1.1	16.5
PROC 18			8.23

* A complete list of the assessment parameters used for the ART assessment is given in Appendix 1, table A2.

The maximum concentration in air that is expected to arise during use as in lubricants and metal working fluids is 1.5 mg/m³. The maximum dermal exposure that has been calculated is 16.5 mg/kg/day for PROC 17. High dermal exposures are also estimated for PROCs 8a and 8b.

7.12.1.1.2.7 Use in gas treatment

MDEA is widely used as a gas treatment agent. This is a predominantly closed process described by PROCs 1, 2, 3 and 8b. LEV and RPE are not required. Most registrants indicate workers are required to wear gloves although one registrant indicates that gloves are only mandatory for transfers covered by PROC 8b. For this reason, the eMSCA has assessed dermal exposure both with and without gloves. Eye protection may also be required if there is an opportunity for incidental splashing. It is assumed that all activities are performed for 8 hours per day.

Table 29: Exposure values for use in gas treatment estimated by the eMSCA.

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)	
			Glove efficiency 80%	No gloves
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), LEV and RPE are not	1.5	<0.01	0.03
PROC 2			0.27	1.37

PROC 3	used, glove efficiency is 80%.		0.14	0.69
PROC 8b			2.74	n/a

The maximum concentration in air that is expected to arise during the use of MDEA as a gas treatment agent is 1.5 mg/m^3. The maximum dermal exposure that has been calculated 2.74 mg/kg/day for PROC 8b (with gloves). The risk characterisation for use as a gas treatment agent will therefore be based on the values for PROC 8b.

7.12.1.1.2.8 Laboratory work in industrial settings and by professionals

Laboratory work, including quality control analyses is described by PROC 15. Gloves and eye protection are required, however registrants do not indicate the need for any risk management measures to limit inhalation exposure.

Table 30: Exposure values for laboratory work estimated by the eMSCA.

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m^3)	Dermal value (mg/kg/day)
PROC 15	Activity performed for up to 8 hours, substance used as such (100%), LEV and RPE are not used, glove efficiency is 80%.	1.5	0.07

The risk characterisation for laboratory use will based on the values for PROC 15.

7.12.1.1.2.9 Industrial and professional use as an additive in coatings

MDEA is a component in water based coatings which may be used in industrial settings or by professionals. The use is described by PROCs 7, 8a, 8b, 9, 10 and 13 for industrial settings and PROCs 8a, 8b, 10, 11 and 13 for professionals. Most registrants state the maximum concentration of MDEA in coatings is [redacted]% although one limits the maximum concentration to [redacted]%. LEV is only required for spray applications. Gloves with an assumed efficiency of 90% are recommended for all activities. Eye protection will also be required.

The registrants have chosen to use the ECETOC TRA tool version 2 or the EASY TRA tool to assess exposure during aerosol forming processes (PROCs 7 and 11). The eMSCA identifies the same concerns in this case as it identified previously where these tools have been used for these PROCs and expects the registrants to take the same actions to resolve this concern.

For its assessment, the eMSCA is assuming that for non-aerosol forming processes (PROCs 8a, 8b, 9, 10 and 13) airborne exposures will not exceed 1.5 mg/m^3 (8-hr TWA).

For aerosol forming proceses (PROCs 7 and 11), the eMSCA has used the Advanced REACH Tool (ART) version 1.5 (the input parameters chosen by the eMSCA are listed in full in Appendix 1, table A3). In the absence of specific information about the composition of coatings and the uses for specific products, the eMSCA is relying on the information provided in registrations and will assume that products contain up to 10% MDEA. It will assume that LEV is in operation for spraying, but in the absence of specific information about the type, it will select the most generic option available in the ART. The consequence

of this choice is that the ART calculations assume a lower effectiveness for LEV than would be assumed by the ECETOC TRA tool.

For its dermal exposure assessment, the eMSCA will take account of the use of gloves with 80% efficiency for all activities.

Table 31: Exposure values for industrial and professional use in coatings estimated by the eMSCA.

Contributing scenario	Assessment parameters*	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
Industrial			
PROC 7	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV is used. RPE is not used, glove efficiency is 80%.	5.7	5.14
PROC 8a	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV and RPE are not used, glove efficiency is 80%.	1.5	1.65
PROC 8b			1.65
PROC 9			0.82
PROC 10			3.29
PROC 13			1.65
Professional			
PROC 11	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV is used. RPE is not used, glove efficiency is 80%.	5.7	12.9
PROC 8a	Activity performed for up to 8 hours, substance used in a mixture (10%), LEV and RPE are not used, glove efficiency is 80%.	1.5	1.65
PROC 8b			1.65
PROC 10			3.29
PROC 13			1.65

* A complete list of the assessment parameters used for the ART assessment is given in Appendix 1, table A3.

The maximum concentration in air that is expected to arise during spraying is 5.7 mg/m³ and spraying is also associated with the highest potential dermal exposures. For other activities a maximum concentration in air of 1.5 mg/m³ is predicted, with a maximum dermal exposure of 3.29 mg/kg/day (calculated for PROC 10).

7.12.1.1.2.10 Professional use as an additive in concrete and cement

MDEA may be present in concrete and cement blends at concentrations of up to 10%. This use is described with PROCs 5, 8a, 10, 13, 19, 21 and 24c. PROCs 21 and 24c have been applied to describe processing of hardened concrete/cement. The eMSCA does not expect that there will be a significant opportunity for exposure to MDEA during processing of solidified materials. In this situation, the greater risk posed to workers will arise from process generated dusts and as such, the control measures that are applied to limit exposure to this dust will also manage any risks arising from residual MDEA. The eMSCA does not therefore consider it necessary to conduct an exposure and risk assessment for MDEA in solidified concrete.

Table 32: Exposure values for professional use as an additive in concrete and cement estimated by the eMSCA.

Contributing scenario	Assessment parameters	Inhalation value (8-hr TWA, mg/m³)	Dermal value (mg/kg/day)
PROC 5	Activity performed for up to 8 hours, substance used as such (10%), LEV and RPE are not used, glove efficiency is 80%.	1.5	1.65
PROC 8a			1.65
PROC 10			3.29
PROC 13			1.65
PROC 19			17.0

The maximum concentration in air that is expected to arise during the the use of MDEA as an additive in concrete and cement is 1.5 mg/m^3. The maximum dermal exposure that has been calculated is 17.0 mg/kg/day for hand mixing where PPE is the only available risk management measure (PROC 19).

7.12.1.1.3 Conclusions about worker exposure

For MDEA, the eMSCA has performed its own exposure assessment. Instead of relying on Tier 1 modelling tools it has used the ART to estimate exposures for aerosol generating processes (PROCs 7, 11, 17 and 18). In order to generate predictions using this tool, several assumptions have been about the nature of the activities being performed and the nature of the workspaces. The eMSCA therefore considers there is uncertainty associated with its own exposure assessment. For all other processes where MDEA is present as a liquid, the eMSCA has set an upper limit of 1.5 mg/m^3 (10% of the SVC). This upper limit has not been modified to take account of any risk management measures e.g. LEV, and therefore represents a realistic worst case. The eMSCA does not consider that it is necessary to quantify exposure to residual MDEA in cured foams or solidified concrete. In these situations, the greater risk posed to workers will arise from process generated dusts and as such, the control measures that are applied to limit exposure to this dust will also manage any risks arising from residual MDEA.

For its dermal exposure assessment, the eMSCA has used estimates generated by the ECETOC TRA tool version 3 (a recently published validation study indicated that the performance of this tool was similar to the performance of other dermal exposure estimation tools). The eMSCA has applied the lowest glove efficiency in its calculations (80%) and has also estimated dermal exposure without gloves where one or more registrants indicates this option in their exposure scenarios. Previously, the eMSCA informed registrants that information should be provided about glove materials, thicknesses and breakthrough times. This information is still lacking in some registrations.

Note to registrants: The IR and CSA Guidance Chapter R14, section R.14.5.3 states that "It is an absolute requirement that the barrier properties of the glove material are known to be adequate to ensure the substance does not migrate through the material of the glove during the proposed use. It is important that gloves are sufficiently described in the IUCLID dossier and the CSR so that there is assurance that suppliers of substances and formulations, can effectively communicate (in section 8 of the Safety Data Sheet) the correct information to downstream users. Important information on gloves relates to those materials that are effective and over what duration they are effective. It is also useful to provide information on common glove materials that are known not to be

effective as a barrier" [10]. In accordance with the IR & CSA guidance, registrants should ensure that any PPE that is required is sufficiently described in their registrations.

Registrants were also asked to clarify how cleaning and maintenance activities are being addressed. This clarification is still required from the majority of registrants.

Note to registrants: REACH Annex 1 section 0.3 states that the chemical safety assessment shall consider all stages of the life cycle. The IR and CSA Guidance Chapter R14, section 14.5.1 indicates that this includes periodic cleaning and maintenance such as cleaning machinery and vessels between batches, changing filters or maintenance of reservoirs of processing fluids, etc. The guidance recommends that specific contributing scenairos should be provided for these activities but it is currently not possible for the eMSCA to identify these contributing scenarios in the majority of registrations. Registrants should ensure that contributing scenarios for perodic cleaning and maintenance are clearly identified in registrations and that sufficient descriptive information is provided to identify the specific activities (e.g. wiping vessels using hand tools, automated cleaning of pipes, manually changing filters, etc) that are covered.

7.12.1.2. Consumer

No consumer uses have been identified for MDEA

7.12.2. Environment

Not evaluated

7.12.3. Combined exposure assessment

A combined exposure assessment has not been peformed for MDEA.

7.13. Risk characterisation

MDEA is not classified for adverse systemic effects following single exposure or repeated exposure. It is classified as an eye irritant and mild skin irritation was reported in several studies, but only following extreme exposure conditions (≥ 24 hours or repeated exposure, with occlusive conditions). It did not meet the criteria for classification as a skin irritant under conditions that more closely followed the OECD Test Guideline for skin irritation.

At high oral doses (1000 mg/kg/day), adverse reproductive effects have been seen. Reductions were reported in the numbers of implantation sites, there were increases in the numbers of resorptions, increases in post-implantation losses and fewer pups were delivered. Signs of general toxicity were also observed at these and lower dose levels (reduced body weight gain was seen starting at 300 mg/kg) suggesting that the reproductive effects may not be a specific effect of MDEA. No classification has been proposed for these effects. The health effect driving the value of the long-term inhalation and dermal DNELs is reduced body weight gain. The worker long-term inhalation DNEL of

[10] Version 3.0, accessed 12 October 2017.

1.2 mg/m^3 (8-hour TWA) and long-term dermal DNEL of 1.7 mg/kg/day are derived from a NOAEL of 100 mg/kg/day from an oral reproduction/developmental screening test.

7.13.1 Human health

Workers

Based on the registrants' exposure calculations and the DNELs proposed by the registrants, RCRs < 1 have been obtained for every exposure scenario.

The eMSCA has calculated its own DNELs for this substance and performed its own exposure assessment. This risk characterisation is based on the eMSCA's DNELs and exposure estimates. Table 33 focusses on the PROCs giving rise to RCRs > 1.

Table 33 Risk characterisation ratios calculated by the eMSCA using its own exposure values and DNELs.

Scenario	Activity giving rise to highest RCRs	RCR inhalation	RCR dermal*	RCR combined
Manufacture	PROC 8b	1.25	1.61	2.86
Use as an intermediate	PROC 8a/8b	1.25	1.61	2.86
Formulation of preparations	PROC 5/8a/8b	1.25	1.61	2.86
Distribution	PROC 4/9	1.25	0.81 (4.04)	2.06 (5.29)
	PROC 8a/8b	1.25	1.01	2.26
Use as a processing aid	PROC 7	3.83	1.01	4.84
	PROC 8a/8b/13	1.25	0.32 (1.16)	1.57 (2.41)
	PROC 11	3.83	2.52 (12.59)	6.35 (16.42)
	PROC 10	1.25	0.65 (3.23)	1.90 (4.48)
Use in lubricants	PROC 17	0.92	(9.71)	10.63
	PROC 18	0.92	(4.84)	5.76
	PROC 8a/8b	1.25	(4.84)	6.09
	PROC 9	1.25	(2.42)	3.67
Use in gas treatment	PROC 8b	1.25	1.61	2.86
Use in laboratories	PROC 15	1.25	0.04	1.29
Use in coatings	PROC 7	4.75	3.02	7.77
	PROC 8a/8b	1.25	0.97	2.22
	PROC 11	4.75	7.59	12.34
	PROC 10	1.25	1.94	3.19
Use in concrete/cement	PROC 5/8a/13	1.25	0.97	2.22

	PROC 10	1.25	1.94	3.19
	PROC 19	1.25	10	11.25

* values in brackets apply to situations where the use of gloves is not taken into account.

It can be seen from table 33 that the inhalation exposures estimated by the eMSCA marginally exceed the DNEL for the majority of uses. Spraying activities (PROCs 7 and 11) give rise to the highest inhalation RCRs. The assessment for use in coatings assumes LEV is in place, this risk management measure was not applied for use as a processing aid. The eMSCA acknowledges that there is uncertainty in the exposure estimates that lead to these high RCRs. The most likely consequence of this uncertainty is that potential inhalation exposure has been overestimated, therefore, the eMSCA does not identify a need to take further regulatory action. However, it would be useful for the reigstrants to provide more information about these spraying activities in their Chemical Safety Reports (CSRs) to help refine the exposure modelling calculations and obtain a more reliable estimation of risk.

RCRs > 1 are also obtained where it is assumed as a worst case that levels of MDEA in air will not exceed 10% of the SVC. The eMSCA expects that in reality, levels in air may be some way below this estimate but does not have any information that will enable it to refine this assmption.

Use in lubricants/greases (PROC 17/18) at high energy conditions gives rise to inhalation RCRs < 1. For this assessment the eMSCA assumed that handling practices are adopted which reduce contact between the product and air because this is consistent with good occupational hygiene practices. It would be useful for registrants to provide more information about the types of lubricants and metalworking fluids that may contain MDEA and their uses to help clarify the likely conditions of use.

For dermal exposure, many RCRs are above 1, particularly for professional spraying, hand mixing of concrete and cement and situations where gloves are not used. In this case, the dermal DNEL value has been derived from an oral study which the eMSCA acknowledges is likely to be a conservative approach. The eMSCA has also assumed gloves have an effectiveness of only 80%. If gloves are used properly and glove management programmes are in place, it is possible to achieve higher levels of protection. For these reasons, the eMSCA has a low concern that skin contact will resut in systemic toxicity. To minimise the potential for skin irritation, it would be useful for the registrants to stress to downstream users the importance of good housekeeping practices and effective glove management programmes. It would also be useful to revisit the risk management approaches, particulary for tasks where gloves are not currently recommended, to see if additional measures can be implemented to reduce dermal exposure.

Consumers

Not applicable

Indirect exposure of humans via the environment

Not applicable

7.13.2 Environment

Not evaluated

7.13.3 Overall risk characterization

In conclusion, although RCRs > 1 have been obtained for several scenarios, these RCRs are mainly driven by conservative DNELs, particularly for the dermal route and conservative assumptions about the effectiveness of gloves at limiting dermal exposure.

For these reasons, the RCRs > 1 are not considered to signify a serious risk to health under the working conditions described in exposure scenarios. However, there is a possibility that mild skin irritation may arise if sufficint attention is not paid to managing dermal exposure, particularly for situations where gloves are currently not recommended. Taking into account the remaining unfulfilled information requests in the draft decision, it will be helpful if the registrants update registrations with the following:

- To help limit dermal exposure it is important that registrants emphasise the need to implement effective glove management programmes and adopt good housekeeping practices in their exposure scenarios. It would also be useful to revisit situations where gloves are not currently worn to see (in discussion with downstream users) if tasks can be modified and additional risk management measures implemented to reduce opportunities for skin contact.

- Where gloves are required, all registrants must provide the information about suitable glove materials, thicknesses and breakthrough times described in the IR and CSA Guidance Chapter R14, section R.14.5.3.

- To help reduce the uncertainties in the exposure assessment registrants should seek more information from downstream users about the conditions of use and risk management measures that are typically applied. This is particularly important for spraying activities. The information should be presented transparently in their CSRs.

- Registrants should also transparently describe how cleaning and maintenance activities have been covered in each scenario.

- Given the likelihood that the Tier 1 exposure modelling tools that registrants are using will overestimate potential inhalation exposure, it would be useful if registrants can give further thought to the way they assess potential airborne concentrations associated with each use.

7.14. References

Title	Author	Publication/source details	Date
Acute Toxicity and Primary Irritancy of Alkylalkanolamines.	Ballantyne B. and Leung H-W.	Vet. Human Toxicol. 38, 422-426.	1996
Aliphatic and Alicyclic Amines.	Benya et al.	Patty´s Industrial Hygiene and Toxicol. fourth edition, Vol II p.1112.	1994
2, 2"-methyliminodiethanol.	GESTIS - Substance database	GESTIS - Substance database of 'Berufsgenossenschaftlichen Instituts für Arbeitsschutz' (BGIA), query date 13 Jun 2007.	2007
Evaluation of the genotoxic potential of alkylalkanolamines.	Leung HW and Ballantyne B	Mutat. Res. 393, 7-15. Testing laboratory: Union Carbide Corporation.	1997
Developmental toxicity study with N-methyldiethanolamine by	Leung HW and Ballantyne B	J. Toxicol. -Cut. & Ocular Toxicol., 17(4), 179-190.	1998

repeated cutaneous application to CD rats.			
Pharmacokinetics of N-Methyldiethanolamine following acute cutaneous and intravenous dosing in the rat.	Leung HW et al.	J. Toxicol-Cut. & Ocular Toxicol., 15, 343-353.	1996
The Skin Sensitization Potential of Four Alkylalkanolamines.	Leung HW et al.	Vet Human Toxicol, 40 (2), 65-67.	1998
Validation of the dermal exposure model in ECETOC TRA.	Marquart H, et al.	Annals of Work Exposures and Health, 61(7), 854-871.	2017
SIDS INITIAL ASSESSMENT PROFILE and SIDS Initial Assessment Report For CoCAM 2 Paris, France April 22-25, 2012 OECD eChemPortal.	OECD	The Global Portal to Information on Chemical Substances. http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=600DD4DF-294C-4CC0-B3C4-3ECEEF33D658.	2012
Investigation of relationship between saturated vapour concentration and real exposure to vapour.	Pengelly and Johnson	HSE report number RR923: http://www.hse.gov.uk/research/rrhtm/rr923.htm	2012
RANGE-FINDING TOXICITY DATA List	Smyth H. et al.	V. Arch. Ind. Hyg. and Occ. Health, 10, 61.	1954
Acute and subchronic repeated cutaneous application of N-methyl diethanolamine in the Fischer 344 rat.	Werley, M. S. et al	J. Toxicol. Cut. Ocular Toxicol., 16, 157-171.	1997
Salmonella Mutagenicity Tests: III. Results From the Testing of 255 Chemicals.	Zeiger E et al.	Env. Mutag. 9 (Suppl. 9), 1-110, 1987.	1987

7.15. Abbreviations

%	Percentage
B	Bioaccumulative
BCF	Bioconcentration factor
CLP	Classification, labelling and packaging (of substances and mixtures)
Cm	Centimetre
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
D	Day
DEA	2,2'-iminodiethanol, CAS No 111-42-2 (EC No 203-868-0)
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment tool
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
ES	Exposure Scenario
ERC	Environmental release category
EU	European Union
g	Gramme
GC	Gas chromatography
GC/FID	Gas chromatography – Flame Ionisation Detection
GC/MS	Gas chromatography – mass spectrometry
GLP	Good laboratory practice
hPa	Hectopascal
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
kJ	Kilojoule
km	Kilometre
kPa	Kilopascal
K_{oa}	Octanol-air partition coefficient
K_{oc}	Organic carbon-water partition coefficient
K_{ow}	Octanol-water partition coefficient
L	Litre
LEV	Local Exhaust Ventillation

Log	Logarithmic value
LOD	Limit of detection
LOQ	Limit of quantitation
M	Molar
m	Metre(s)
µg	Microgram
mg	Milligram
MEA	2-aminoethanol, CAS No 141-43-5 (EC No 205-483-3)
MDEA	2,2'-methyliminodiethanol
min	Minute
mL	Millilitre
mol	Mole
MS	Mass spectrometry
MSCA	Member State Competent Authority
m/z	Mass to charge ratio
n/a	not assessed
nm	Nanometre
NOEC	No-observed effect concentration
OC	Operational condition
OECD	Organisation for Economic Co-operation and Development
p	Statistical probability
P	Persistent
Pa	Pascal
PBT	Persistent, Bioaccumulative and Toxic
PC	Product category
pg	Picogramme
pKa	Acid dissociation constant
PNEC	Predicted no effect concentration
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
PROC	Process Category
QSAR	Quantitative structure-activity relationship
r^2	Correlation coefficient
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU Regulation No. 1907/2006)
RCR	Risk characterisation ratio
RMM	Risk Management Measures
RPE	Respiratory protective equipment

t	Tonne
T	Toxic (hazard classification)
TEA	2,2′,2″-nitrilotriethanol, CAS No 102-71-6 (EC No 203-049-8)
TG	Test Guideline
UK	United Kingdom
UV	Ultraviolet
vB	Very bioaccumulative
vP	Very persistent
vPvB	Very persistent and very bioaccumulative
wt.	Weight

7.16. Appendix 1 – Input parameters for ART calculations

The eMSCA has used the ART to generate exposure estimates for aerosol generating activities for three scenarios. In doing this, it has been necessary for the eMSCA to make several assumptions about the nature of the work activities and of the workplaces where these activities take place. In the interests of transparency, the following text identifies where assumptions have been made and the reasons why particular input parameters have been chosen. The eMSCA recommends that if the registrants are considering using the ART to refine their own exposure estimates, they obtain additional information from their downstream users from which to identify appropriate input parameters.

The following assumptions have been made by the eMSCA:

The parameters covering activity duration and substance emission potentials are derived from information contained in registrations.

The parameters covering activity emission potentials are intended to reflect working practices that will lead to higher rather than lower exposure estimates but which seem relevant for titles of each scenario.

It has been assumed that effective housekeeping practices are in place because this would be expected in workplaces that are complying with workplace health and safety legislation.

If registrations indicate that LEV is in use, a generic option has been selected since the exposure scenarios do not provide information about the specific type of LEV that should be used. If no LEV is indicated in registrations, the assumption is made that no localised controls are in place.

No information is provided in registrations about general room ventilation so a generic input parameter has been adopted.

It is assumed that each activity takes place in a busy workroom where the activity is being performed by more than one worker at a time, hence there is the potential for exposure from both near- and far-field sources.

The input parameters that have been used to generate exposure estimates for this evaluation are listed in tables A1-A3.

Use as a catalyst in polymerisation reactions

Table A1: Input parameters used by the eMSCA to assess worker exposure to MDEA during spraying activities covered by PROCs 7 and 11.

Activity duration	480 minutes
Near field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	In any direction (including upwards)
Spray technique	Spraying with high compressed air use
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	Any size workroom
Risk management measures	
Localised controls	
Primary	No localised controls (0% reduction)
Secondary	No localised controls (0% reduction)
Dispersion	
Ventilation rate	No restriction on general ventilation characteristics
Far field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	In any direction (including upwards)
Spray technique	Spraying with high compressed air use
Risk management measures	
Localised controls	
Primary	No localised controls (0% reduction)
Secondary	No localised controls (0% reduction)
Segregation	No segregation (0% reduction)
Predicted exposure levels	
Mecanistic model results	
75th percentile full-shift exposure	4.6 mg/m^3
Interquartile confidence interval	2.2 - 9.8 mg/m^3

Use in lubricants and metal working fluids

Table A2: Imput parameters used by the eMSCA to assess worker exposure to MDEA during its use for activities covered by PROCs 17 and 18.

Activity duration	480 minutes
Near field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Minor (5-10%)
Viscosity	Medium
Activity emission potential	
Activity class	Application of liquids in high speed processes (e.g. rotating tools)
Situation	Large-scale activities involving high speed movements
Containment level	Handling that reduces contact between product and adjacent air. Note: this does not include processes that are fully contained by localised controls (see next questions).
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	Any size workroom
Risk management measures	
Localised controls	
Primary	No localised controls (0% reduction)
Secondary	No localised controls (0% reduction)
Dispersion	
Ventilation rate	No restriction on general ventilation characteristics
Far field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Minor (5-10%)
Viscosity	Medium
Activity emission potential	
Activity class	Application of liquids in high speed processes (e.g. rotating tools)
Situation	Large-scale activities involving high speed movements
Containment level	Handling that reduces contact between product and adjacent air. Note: this does not include processes that are fully contained by localised controls (see next questions).
Risk management measures	
Localised controls	

Primary	No localised controls (0% reduction)
Secondary	No localised controls (0% reduction)
Segregation	No segregation (0% reduction)
Predicted exposure levels	
Mechanistic model results	
75th percentile full-shift exposure	1.1 mg/m^3
Interquartile confidence interval	0.54 – 2.5 mg/m^3

Use in coatings

Table A3: Input parameters used by the eMSCA to assess worker exposure to MDEA during spraying activities covered by PROCs 7 and 11.

Activity duration	480 minutes
Near field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Minor (5-10%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	In any direction (including upwards)
Spray technique	Spraying with high compressed air use
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	Any size workroom
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Dispersion	
Ventilation rate	No restriction on general ventilation characteristics
Far field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Minor (5-10%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	In any direction (including upwards)
Spray technique	Spraying with high compressed air use
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Segregation	No segregation (0% reduction)
Predicted exposure levels	
Mecanistic model results	
75th percentile full-shift exposure	5.7 mg/m^3
Interquartile confidence interval	2.7 - 12 mg/m^3