SUBSTANCE EVALUATION REPORT

Public Name: **2-AMINOETHANOL**

EC Number(s): **205-483-3**

CAS Number(s): **141-43-5**

Submitting Member State Competent Authority: UK

Year of evaluation (as given in the CoRAP): **2014**

VERSION NUMBER: 2 **DATE: September 2016**

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	✓
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: [*please specify*]	

Executive summary

Grounds for concern

Initial concerns

The following initial concerns were identified in the justification document.

- Human health: suspected sensitiser. The substance is identified in the list of agents causing occupational asthma from the CSST (Commission de la santé et de la sécurité du travail) (updated April 2010). [The CSST is an organisation mandated by the Quebec government to oversee health and safety at work.] The justification document also noted that there was insufficient information regarding the carcinogenicity of 2-aminoethanol.
- Human exposure: wide dispersive use and aggregated tonnage (> 100,000 tpa). 2-Aminoethanol (MEA) is used in personal care products.

Additional concerns

During the evaluation of the human exposure the following additional concerns were identified:

1. IOELVs of 2.5 mg/m^3 (8-hour TWA) and 7.6 mg/m^3 (15-minute TWA) STEL have been established for MEA under the 2nd IOELV Directive (2006/15/EC). The worker long-term inhalation DNEL for local and systemic effects calculated by the lead Registrant is higher than the 8-hour TWA IOELV and the lead Registrant has not calculated worker or consumer DNELs for short-term local effects despite the harmonised classification that exists for acute toxicity by the inhalation route.

2. The evaluating MSCA identified worker scenarios where the 8-hour TWA exposure values that have been calculated exceed the 8-hour TWA IOELV. Taking into account the lack of quantitative exposure assessments for short-term peak exposures for workers and consumers, the evaluating MSCA was concerned that the measures that are being recommended in the exposure scenarios may not be sufficient to ensure safe use.

3. The evaluating MSCA also noted the limited information that is provided to help downstream users understand the scope of each exposure scenario and that limited justification has been provided for the parameters that have been used to model exposures, particularly in relation to the consumer exposure assessment.

Procedure

Initial assessment period: evaluation of existing information 26 March 2014 to 25March 2015

The evaluation focused on the information provided in the registration dossiers and additional information provided informally by the Registrants to support their proposed mode of action and human relevance for the human health effects of MEA. The evaluating member state competent authority (eMSCA) met with the Registrants in April 2014 to discuss the substance evaluation procedure. At various stages, the Registrants provided information following informal requests. The lead Registrant updated the lead CSR in June 2014 and the registration dossier in July 2015 to provide more information on the repeated-dose toxicity of MEA.

Chemistry

Analytical information provided in the dossiers was assessed to confirm substance identity and composition.

The physico-chemical data were 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 initial ground for concern was the main focus of the human health assessment. Respiratory sensitisation was listed as a concern because of MEA's inclusion on the CSST's (Commission de la Santé et de la Sécurité du Travail) list of agents causing occupational asthma (updated April 2010). The Registrants provided (publicly-available) information additional to that in the registration dossier to inform on the skin and respiratory sensitisation potential of MEA. An absence of carcinogenicity data was also noted in the justification document.

Additionally, a review of all the information in the registration dossier was undertaken to identify other potential areas of concern. To further support the evaluation, the Registrants provided the full study report for the two-generation reproduction study, following an informal request by the eMSCA.

A literature search conducted by the eMSCA in September 2014 did not identify any new information on the mammalian toxicology of MEA.

Environment and environmental exposure

As MEA was not prioritised for environmental concerns, only a brief review of all of the relevant environmental fate, behaviour and toxicity data was performed. The evaluation was based on information contained in the IUCLID 5 file and the Registrants' CSRs.

A literature search conducted in April 2014 did not identify any new information.

Human exposure

All of the human exposure information provided by the Registrants in their CSRs was assessed to determine whether the risks to human health were adequately controlled.

Conclusions

Initial assessment period: evaluation of existing information 26 March 2014 to 25 March 2015

Based on the evaluation of the information in the registration dossiers, supplemented with information provided informally by the Registrants, the following conclusions were reached.

Human health

The initial concern for sensitisation was clarified. Based on the available animal and human data, the eMSCA concluded that MEA did not meet the criteria for classification for skin or respiratory sensitisation. No further information is requested. The eMSCA notes that no reliable data on carcinogenicity of MEA are available for assessment. However, no effects of concern for systemic carcinogenicity (hyperplasia, pre-neoplastic changes) were observed in the available 28-day inhalation study or two-generation reproductive toxicity study. In addition MEA was clearly negative in the submitted genotoxicity studies. Although hyperplasia and metaplasia were observed

in repeat dose inhalation studies, these effects were considered of limited relevance to humans, considering the corrosive / irritant nature of MEA.

No further information is required on the carcinogenicity of MEA under this substance evaluation.

Human exposure

IOELVs of 2.5 mg/m^3 (8-hour TWA) and 7.6 mg/m^3 (15-minute TWA) STEL have been established for MEA under the 2nd IOELV Directive (2006/15/EC)[1]. During the evaluation, it became apparent that the worker long-term inhalation DNEL calculated by the lead Registrant is higher than the 8-hour TWA IOELV and the lead Registrant has not calculated worker or consumer DNELs for short-term local effects despite the harmonised classification that exists for acute toxicity by the inhalation route.

The eMSCA identified worker scenarios where the 8-hour TWA exposure values that have been calculated exceed the 8-hour TWA IOELV and consumer scenarios where "during event" inhalation exposures exceed the relevant consumer inhalation DNELs. The eMSCA was concerned that the measures that are being recommended in the exposure scenarios may not be sufficient to ensure safe use. These issues were raised in the Draft Decision which was sent to the Registrants on 7 May 2015 for 30 days commenting.

Environment and environmental exposure

The low environmental hazard profile of the substance was confirmed. MEA is rapidly degradable and does not bioaccumulate, although it does exhibit limited ecotoxicity. It is not considered to be vPvB or PBT. Given this profile, a review of the environmental exposure assessment was not undertaken.

Conclusion following Registrants commenting period and subsequent dossier updates – May 2015 to September 2016.

In May 2015 the eMSCA had a teleconference with the Lead Registrant to discuss the main points presented in the draft decision and to discuss the scope and timing of any planned dossier updates. The Lead Registrant agreed to the requests and whilst there had been no plan to submit a formal update at that point, it was agreed that it would be useful to have at least some of the relevant information in the dossiers. This would be provided in July 2015. In June 2015 the lead Registrant provided formal comments on the draft decision on behalf of the Ethanolamines consortium and other members of the SIEF. In these comments they agreed in writing to all relevant information requests. (One request related to a small number of Registrants relying on an old version of the Lead Registrant CSR – the Lead proposed to circulate the updated CSR to SIEF members). They accepted the recommendation to use the IOELV; agreeing to revise the exposure- and risk assessment accordingly and include the other information requested. A number of other Registrants confirmed that they would update their registrations to follow the approach taken by the lead Registrant. However, no responses were received from a group of 7 Registrants leading to some differences between Registrants in the scenarios which are supported and the PROC codes covered.

Subsequently updated dossiers were submitted by eleven Registrants, including the lead Registrant with some additional information which was reviewed by the eMSCA. As the information requests

[1]https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/commission-directive-2006-15-ec

in the draft decision had not been addressed the intention was to continue to request the information formally.

The substance evaluation is needed to decide whether sufficient information is available to clarify the initial concerns or further information is required for regulatory risk management, such as CLH, restriction or SVHC identification. It was concluded that MEA is not a sensitiser then the health effect of concern is respiratory tract irritation. The available evidence suggests that if effects arise at levels of exposure likely to be encountered in the workplace, these will be mild and unlikely to have lasting health consequences. Additionally it is likely that consumers will only occasionally perform the types of do-it-yourself (DIY) activities identified and no long-term health consequences are expected from transient mild respiratory tract irritation. The eMSCA therefore does not consider that the situation is of sufficient concern to trigger regulatory risk management activity for MEA.

Given these considerations and the expectation that the requested information will be provided in the revised CSRs the eMSCA decided to finish the substance evaluation process without issuing the Final Decision.

However, to ensure that accurate information is available in relation to the uses and the conditions of use that are supported, the Registrants should give particular attention to the "notes to Registrants" in this SEv report and update their dossiers without undue delay and communicate revised/new risk management measures to downstream users. In summary the Registrants are expected to:

For workers;

- provide clearer descriptions of the types of products and activities that are covered in each exposure scenario;
- confirm that exposures will not exceed the IOELVs when the operating conditions and risk management measures described in each exposure scenario are implemented correctly; and,
- provide the supporting evidence in their CSRs.

For consumers;

- provide clearer justifications for the parameters that have been used to model consumer exposure for each scenario;
- ensure that it is clear from the information provided in CSRs how local effects in the respiratory tract can be avoided during use.

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1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	2-Aminoethanol
EC number:	205-483-3
EC name:	2-Aminoethanol
CAS number (in the EC inventory):	141-43-5
CAS number:	141-43-5
CAS name:	Ethanol, 2-amino-
IUPAC name:	2-Aminoethanol
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	C_2H_7NO
Molecular weight range:	61.0831
Synonyms:	MEA

Structural formula:

Mono-constituent substance.

1.2 Composition of the substance

Name: 2-Aminoethanol

Description: 2-aminoethanol is both a primary amine and a primary alcohol (origin: organic).

Degree of purity: >80% w/w

Generally the information provided by the Registrants was sufficient to confirm the identity of the registered substance, although it is noted that UV-Vis is of limited use due to the chemical structure of MEA. However, it is recommended that Registrants consider the requirements of Annex VI 2.3.5 to ensure that they are compliant and have data specific to their registration. Further detail on the analysis is provided in the confidential annex.

Each Registrant provided some analytical information to support the composition reported in section 1.2 of their dossiers, but Registrants are reminded that they should include sufficient information for the analysis to be reproduced. GC and/or HPLC were used to determine concentration/purity of MEA and its associated impurities. However, one Registrant did not provide GC or HPLC data and therefore it is unclear as to how the concentration/purity of MEA and its impurities was determined.

No validation information such as recovery rates, limit of detection or quantitation were given for any method although one report included chromatograms of standards for some of the known impurities. Some of the analytical reports identified small amounts of impurities (<1%) which were not reported in section 1.2 and for some of the impurities the typical concentration reported was outside the range given. Registrants are reminded to check their dossiers to ensure compositional information reported in IUCLID (Section 1.2) is correct and supported by the analytical information provided (IUCLID section 1.4). Further detail on the specific analyses and compositions is given in the confidential annex.

Registrants are reminded that they should provide analytical data from each separate manufacturing source. In this instance it does not appear to be the case that each Registrant has provided information for their specific source. For example, companies with different manufacturing sites seem to have provided the same analysis data in all their registrations.

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
2-aminoethanol EC number: 205-483-3	>80%	>80 - ≤100	See confidential annex for individual compositions.

Table 3: Impurities

Impurities	Typical concentration (% w/w)	Concentration range (% w/w)	Remarks
See confidential annex for details	-	-	See confidential annex for individual compositions.

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
None	-	-	-

1.3 Physico-chemical properties

The physico-chemical properties reported in the registration dossiers are summarised in Table 5.

For most endpoints a number of endpoint records have been provided which includes information from various literature sources/industry databases and some measured data. Where a weight of evidence approach is taken the Registrants are reminded that the summary record should include some discussion regarding which is the key record and which is being taken forward, especially when there is a range of values presented.

Generally the results provided are sufficiently consistent between sources. However it is noted that the Registrants have provided a waiving argument for not measuring the surface tension. Following an internet search by the eMS an information sheet was found on the Dow website that indicates a surface tension of 48.3 dynes/cm at 25 °C. It is recommended that the Registrants provide information on surface tension.

Table 5: Overview of physicochemical properties

Property	Value	Remarks
Physical state	Clear liquid of aminic odour.	Value used for CSA: liquid at 20 °C and 101.3 kPa Registrants described the substance as: A viscous, colourless liquid with ammonia-like odour [experimental result/peer reviewed database/authoritative database; reliability 2 (reliable with restrictions)]. A MSDS on the Sigma-Aldrich website described the substance as a clear, colourless, viscous liquid.
Melting/freezing point	4 °C	Value used for CSA: 4 °C at 101.3 kPa Values from Registrants ranged between 9.96 - 10.6 °C [experimental result/peer reviewed database; reliability 2 (reliable with restrictions)].
Boiling point	167 °C at 1013.25 hPa	Value used for CSA: 167 °C at 101.3 kPa Values from Registrants ranged between 167 - 172 °C at 1013 hPa [experimental result/scientifically verified data/peer reviewed database; reliability 2 (reliable with restrictions)]. A MSDS on the Sigma-Aldrich website indicates a boiling range of 69 - 70 °C at 13 hPa.
Relative density	1.016 g/cm^3 at 20 °C	Value used for CSA: 1.016 g/cm^3 at 20 °C Values from Registrants ranged between 1.0157 g/cm^3 and 1.02 g/cm^3 at 20 °C. [Experimental result/scientifically verified data/peer reviewed database; reliability 2 (reliable with restrictions)]. A MSDS on the Sigma-Aldrich website indicates a relative density of 1.012 g/cm^3 at 25 °C.
Vapour pressure	0.5 hPa at 20 °C	Value used for CSA: 0.5 hPa at 20 °C Registrants reported values of 0.5 hPa at 20 °C, 4.1 hPa at 50 °C, 0.58 hPa at 26.9 °C, 2.43 mBar at 38 °C and 0.488 hPa at 25 °C [experimental result/scientifically verified data/peer reviewed database; reliability 2 (reliable with restrictions)]. A MSDS on the Sigma-Aldrich website indicates a vapour pressure of 0.3 hPa at 20 °C.
Surface tension	No data	Waiver - *'Based on chemical structure, no surface activity is predicted.'* An information sheet on the Dow website indicates a surface tension of 48.3 dynes/cm at 25 °C.
Water solubility	>1000 g/L at 20 °C (pH 12.1)	Value used for CSA: 1000 g/L at 20 °C. Miscible in any ratio. All Registrants support a water solubility ≥ 1000 g/L (i.e. miscible in any ratio) at 20 - 25 °C (pH 6.8 and 12.1) [experimental result/scientifically verified data/peer reviewed database; reliability 2 (reliable with restrictions)].
Partition coefficient n-octanol/water (log value)	-2.3 at 25 °C at pH 6.8 - 7.3	Value used for CSA: Log Kow (Pow): -2.3 at 25 °C Registrants reported values of -2.3 (pH 6.8 - 7.3), -1.91 (pH 7.3), -1.31 (pH not reported) and -1.622 (pH not reported) (all at 25 °C) [experimental result/peer reviewed database/software calculation; reliability 2 (reliable with restrictions)].
Flash point	91 °C at 1013.25 hPa	Value used for CSA: 91 °C at 1013 hPa Registrants reported values of 91 °C at 101.3 kPa, 92.5 °C at 1013.25 hPa, 86 °C at 1013 hPa, 94.5 °C at 1013 hPa and 85 °C at 1013 hPa [experimental result/peer reviewed database; reliability 2

		(reliable with restrictions)].
Flammability	Non flammable upon ignition. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.	Value used for CSA: Non flammable Combustible liquid. Flammability derived from flash point (and boiling point). Based on chemical structure pyrophoric properties and flammability in contact with water are not predicted. On the basis of its flash point MEA is not classified as flammable.
Explosive properties	No explosive properties	Value used for CSA: Non explosive There are no chemical groups associated with explosive properties present in the molecule. Furthermore an oxygen balance of -170% (as calculated by CRD), when considered in conjunction with the lack of structural triggers, is indicative of no explosive properties.
Self ignition temperature/ Auto flammability	424 °C at 1013.25 hPa	Value used for CSA: 424 °C at 1013 hPa Registrants reported values of 424 °C at 101.3 kPa, 410 °C at 993-1003 mBar and 410 °C at 1013 hPa [experimental result/peer reviewed database; reliability 2 (reliable with restrictions)].
Oxidising properties	No oxidising properties	Value used for CSA: Oxidising: No The substance is incapable of reacting exothermically with combustible materials on the basis of the chemical structure. An oxygen balance calculation made by eMS resulted in a value outside the region where there may be potential for the test substance to be an oxidiser (-170%), which along with the structural considerations of the chemical, supports the statement made by the Registrants that the substance is not an oxidiser.
Granulometry	Not applicable	These data are not required for liquid substances.
Stability in organic solvents and identity of relevant degradation products	Not applicable	Waiver - The Registrant has stated that: *'The stability of the substance is not considered as critical.'*
Dissociation constant	9.5 at 25 °C	Registrants reported pKa values of 9.5 at 25 °C and 9.21 at 35 °C [experimental result/peer reviewed database; reliability 2 (reliable with restrictions)].
Viscosity	23.86 mPa.s at 20 °C 23.5 mm^2/s at 20 °C 9.80 mm^2/s at 40 °C	Value used for CSA: Viscosity at 20 °C: 23.86 mPa.s (dynamic) Registrants provided the following viscosity measurements: 23.5 mm^2/s (static) at 20 °C (ISO 3104) 23.86 mPa.s (dynamic) at 20 °C (ISO 3104) 9.8 mm^2/s (static) at 40 °C (ISO 3104) 18.95 mPa.s (dynamic) at 25 °C (literature value) 19.35 mPa.s (dynamic) at 25 °C (literature value) On the basis of its chemical structure MEA is not considered to be an aspiration hazard.

2 MANUFACTURE AND USES

2.1 Quantities

Four registrations, 2 full and 2 for intermediate use, are listed on ECHA's dissemination site (http://echa.europa.eu/web/guest/information-on-chemicals/). The tonnage for the joint submission (25 joint registrants) is 100,000 – 1,000,000 tpa. The tonnage of the other full registration is 0-10tpa (1 registrant).

2.1.1 Manufacturing processes

See the confidential annex.

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

The following industrial uses have been identified:

1. Manufacture of MEA.
2. Formulation of products containing MEA.
3. Use in the manufacture of another substance (use as an intermediate).
4. Use in construction chemicals (e.g. cement and concrete)
5. Use for gas treatment
6. Use for water treatment
7. Use in metal working fluids
8. Use in electroplating/electronics
9. Use as an additive in PU systems
10. Use as a processing aid for paper, textiles and leather
11. Use in detergents, cleaners and ink removers
12. Use in biocidal products (e.g. wood protection)
13. Use in coatings including printing inks
14. Use in oilfield chemicals
15. Use in adhesives and sealants
16. Use as a laboratory chemical
17. Use as a processing aid (not becoming part of articles)
18. Use as an additive in plastic e.g. rubber
19. Use as an additive in fuel
20. Use of fuel

2.2.2 Use by professional workers

The following professional uses have been identified:

1. Use in formulation of mixtures

2. Use as an additive in construction chemicals (e.g. cement and concrete)
3. Use in metal working fluids
4. Use as an additive in PU systems
5. Use in detergents, cleaners and ink removers
6. Use in biocidal products (e.g. wood protection)
7. Use in coatings including printing inks
8. Use in oilfield chemicals
9. Use in adhesives and sealants
10. Use as a laboratory chemical
11. Use as an additive in plastic e.g. rubber
12. Use as an additive in fuel
13. Use of fuel
14. Use as a processing aid for paper, textiles and leather
15. Use in electroplating/electronics

2.2.3 Uses by consumers

The following consumer uses have been identified:

1. Use in detergents, cleaners and ink removers
2. Use in personal care products
3. Use in biocidal products (e.g. wood protection)
4. Use in coatings including printing inks
5. Use in adhesives and sealants
6. Use of fuel
7. Use of concrete and cement

2.3 Uses advised against

None reported.

2.3.1 Uses by workers in industrial settings advised against

None reported.

2.3.2 Use by professional workers advised against

None reported.

2.3.3 Uses by consumers advised against

None reported.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Table 6 shows the harmonized classification given for MEA in Annex VI of the CLP Regulation (index number 603-030-00-8).

Table 6: Harmonised classification for MEA

Classification		***Labelling***		
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram Signal Word Code(s)	Hazard Statement Code(s)	Suppl. Hazard statement code(s)
Acute Tox. 4* Acute Tox. 4* Skin corr 1B Acute Tox. 4*	H302 H312 H314 H332	GHS07 GHS05 Dgr	H302 H312 H314 H332	
Specific Concentration Limits and M Factors				
Concentration	Classification			
C ≥ 5%	STOT SE 3; H335			

3.2 Self-classification

The Registrants apply the harmonised classification in accordance with Annex VI of the CLP regulation.

However, newly available data include chronic NOECs is the range 0.1 to 1.0 mg/l for invertebrates and algae. MEA is considered rapidly degradable. These data are reflected in the current REACH Registration self-classification of Aquatic Chronic 3, H412.

4 ENVIRONMENTAL FATE PROPERTIES

MEA is a high production chemical (100,000 to 1,000,000 tpa) with widespread industrial applications including consumer products (including laundry detergents and cleaning agents) and as a dispersing agent for agricultural chemicals. As such release to the environment is anticipated.

MEA has a measured dissociation constant of 9.5 at 25^{o}C (Perrin, 1964). It is anticipated MEA will exist as a cation at environmentally relevant pH.

Although it was not nominated as an environmental priority for the CoRAP, available environmental fate and hazard studies from the REACH registration have been reviewed. The data are summarised briefly with key studies highlighted.

A literature search was undertaken in May 2014, and relevant information from this is also included.

4.1 Degradation

A summary of key information in the dossiers on the fate of MEA is presented in Table 7. Full references are given in the confidential annex.

Table 7: Summary of relevant information on degradation

Method	Results	Remarks
Calculation using AOPWIN v1.92 Registrant Reliability: 2	DT_{50} 10.742 hours	
Ready biodegradation OECD Guideline 301A Registrant Reliability: 2	Readily biodegradable meeting 10 day window 9% degradation at day 1, 97% degradation by day 4 (DOC removal)	Not GLP
Ready biodegradation OECD Guideline 301B Registrant Reliability: 2	Readily biodegradable meeting 10 day window 14% degradation at day 2, 68% degradation at day 9, >70% degradation by day 28 (CO_2 evolution)	Not GLP
Ready biodegradation OECD Guideline 301F Registrant Reliability: 2	Readily biodegradable meeting 10 day window 14% degradation at day 2, 68% degradation by day 9 (O_2 consumption)	Not GLP
Ready biodegradation OECD Guideline 301F Registrant Reliability: 2	Readily biodegradable meeting 10 day window 10% degradation at day 2, 73% degradation by day 11 (O_2 consumption)	Not GLP
Ready biodegradation OECD Guideline 301C Registrant Reliability: 2	Readily biodegradable meeting 10 day window >90% degradation, 21d (DOC removal)	Not GLP Supporting evidence

4.1.1 Abiotic degradation

4.1.1.1 Hydrolysis

MEA does not contain any hydrolysable functional groups. Therefore hydrolysis is not anticipated. Furthermore, the substance is considered readily biodegradable. The Registrant has waived the end point. This is considered acceptable by the eMSCA.

4.1.1.2 Phototransformation/photolysis

4.1.1.2.1 Phototransformation in air

The Registrant has included a QSAR estimated half-life (DT_{50}) of 10.74 hours using AOPWIN v1.92. This value is based on the following changes:
(i) 24 hour timeframe from the default 12 hours
(ii) $5xE^5$ concentration of OH radicals from the default $1.5xE^6$

The Registrant considers that the QSAR is presumably within the applicability domain although neither a QSAR Prediction Reporting Format (QPRF) or QSAR Model Reporting Format (QMRF) are presented. The eMSCA recommends these are completed to fully validate the QSAR.

4.1.1.2.2 Phototransformation in water

No data available. As MEA is rapidly degradable on the basis of ready biodegradation testing, the endpoint has been waived by the Registrant. This is considered acceptable by the eMSCA.

4.1.1.2.3 Phototransformation in soil

No data available. As MEA is rapidly degradable on the basis of ready biodegradation testing, the endpoint has been waived by the Registrant. This is considered acceptable by the eMSCA.

4.1.2 Biodegradation

4.1.2.1 Biodegradation in water

4.1.2.1.1 Estimated data

No data available.

4.1.2.1.2 Screening tests

Four ready biodegradation studies are available in the MEA REACH Registration dossier following various OECD 301 methods (see table 7). The studies are not GLP compliant. All used domestic non-adapted sludge. In each study MEA achieved sufficient degradation to be considered readily biodegradable and the 10 day window was met for each method.

The OECD SIDS assessment (OECD, 1997) and CoCAM assessment (OECD, 2013) concluded that MEA was readily biodegradable.

4.1.2.1.3 Simulation tests (water and sediments)

No data available. As MEA is rapidly degradable on the basis of ready biodegradation testing, the endpoint has been data waived. This is considered acceptable by the eMSCA.

4.1.2.1.4 Summary and discussion of biodegradation in water and sediment

MEA is not anticipated to undergo hydrolysis due to the lack of relevant functional groups. In a series of ready biodegradation studies, significant biodegradation was observed with MEA meeting the readily biodegradable criteria and 10 day window assessment. Therefore MEA is considered by the Registrant to be rapidly degradable. The eMSCA agrees with this assessment.

4.1.2.2 Biodegradation in soil

No data available. As MEA is rapidly degradable on the basis of ready biodegradation testing, the endpoint has been data waived. This is considered acceptable by the eMSCA.

4.1.3 Summary and discussion on degradation

MEA is considered by the Registrant to be rapidly degradable on the basis of various ready biodegradation studies. On this basis, it is not anticipated to persist in the environment. The eMSCA agrees with this assessment.

Neither a QPRF nor QMRF were presented for degradation half-life in air estimate. The eMSCA recommends these are completed to fully validate the QSARs.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

Experimental data is not available.

The REACH Registration includes predicted adsorption coefficient values. The Registrant notes MEA has a pKa of 9.5 (Perrin, 1964) and will predominantly be present as a charged cation which in general adsorb more strongly than neutral forms.

Table 8 shows a summary of REACH Registration predicted values. The charged molecule prediction is based on a predicted log K_{ow} value of -1.61 and not the measured value of -2.3 (pH 6.8-7.3). Neither a QPRF nor QMRF were presented. The eMSCA recommends these are completed to fully validate the QSAR.

The US EPA KOCWIN method based on log K_{ow} is not within the model domain and not included.

The Registrant notes that predicted log K_{oc} values are below 3 l/kg and the substance is anticipated to have a limited adsorption potential. The eMSCA agrees with this assessment.

Table 8: Adsorption QSAR predictions

Model	K_{oc} l/kg	Log K_{oc}	Remarks
Calculation based on Franco A. and Trapp S. (2008, 2009 and 2010) Registrant Reliability: 2	15	1.16	Charged molecule Using log Kow -1.61 pH 5-8, 25ºC
US EPA KOCWIN v.2.00 MCI method Registrant Reliability: 2	1.167	0.067	Uncharged molecule 25ºC

4.2.2 Volatilisation

The REACH Registration includes predicted Henry's Law Constants from various models. The Registration key calculated endpoint range at 25ºC using REACH Guidance (ECHA, 2008) is: 1.18E-9 Pa*m^3/mol at pH5; 1.18E-7 Pa*m^3/mol at pH7; and 8.96E-6 Pa*m^3/mol at pH 9

Using US EPA EPI Suite HENRYWIN v.3.20 with experimental water solubility and vapour pressure, a supporting the Henry's Law Constant is 0.003054 Pa*m^3/mol at 25ºC Neither a QPRF nor QMRF were presented. The eMSCA recommends these are completed to fully validate the QSAR.

The Registrant notes MEA is not anticipated to partition from the aquatic environment to the atmosphere. The eMSCA agrees with this assessment.

4.2.3 Distribution modelling

The REACH Registration includes a distribution modelling study using experimental water solubility, vapour pressure, log K_{ow} and Mackay Level 1 v.3.00 calculation. The results predict MEA will largely partition to the aquatic environment (99.9%) with a small amount (0.11%) to the atmosphere.

4.2.4 Summary and discussion of environmental distribution

MEA is predicted to partition almost exclusively to the aquatic environment (99.9%) where it will remain and with little adsorption to suspended solids and sediment. In the aquatic environment, MEA is considered rapidly degradable.

This scenario is supported by the literature paper Davis and Carpenter, 1987 which reviewed information on the environmental fate of alkanolamines. It considered that alkanolamines would partition primarily to the aquatic environment where available data reflected rapid biodegradation.

Neither a QPRF nor QMRF were presented for adsorption coefficients or Henry's Law coefficients. The eMSCA recommends these are completed to fully validate the QSARs.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

MEA is considered miscible in water. Two experimental log Kow values are available as follows;
Key study: -2.3 at 25oC, pH 6.8-7.1 following OECD test guideline 107
Supporting study: -1.91 at 25oC, pH 7.3.

An experimental BCF is not available.

The joint REACH Registration includes calculated bioconcentration factors using two QSAR models. Based on molecular weight, MEA is outside of the model domain for the US EPA EPI Suite v.4.11 predictive model. Table 9 shows a summary of REACH Registration predicted values which suggest that the fish BCF is likely to be below 10 l/kg.

Table 9: Bioaccumulation QSAR predictions

Model	BCF l/kg wet wt	Log BCF	Remarks
Catalogic v5.11.9.8 Registrant Reliability: 2	2.3	0.36	All mitigating factors applied; within domain applicability
	9.2	0.96	Without mitigating factors; within domain applicability
T. E. S. T. v4.1 Registrant reliability: 2	0.75	-0.13	Average of applied models

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

MEA is considered hydrophilic with a low log K_{ow} value of -2.3. Predicted BCFs are significantly below bioaccumulation trigger values for classification (500 l/kg) and PBT (2,000 l/kg) assessment. Overall, MEA is considered by the Registrant to have low bioaccumulation potential. The eMSCA agrees with this assessment.

4.4 Secondary poisoning

MEA has a low bioaccumulation potential and is rapidly degradable. It is not considered to meet relevant human health classification criteria for carcinogenicity, mutagenicity or reproductive toxicity. Given the low potential for bioaccumulation, exposure of predators is considered low. On this basis, a secondary poisoning scenario is not considered necessary by the Registrant. The eMSCA agrees with this assessment.

5 HUMAN HEALTH HAZARD ASSESSMENT

The initial ground for concern for the human health evaluation of MEA was respiratory sensitisation (occupational asthma). An absence of carcinogenicity data was also noted in the justification document for the inclusion of MEA on the CoRAP; consequently, the available information on the repeated-dose toxicity of MEA was evaluated. In addition, an assessment of all the available information on MEA was conducted to identify any additional potential concerns, as none were identified those studies are not summarised in this report. References for summaries of unpublished studies are given in the confidential annex.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

MEA is a normal component of human food. It is part of the membrane-constituting class of glycerophospholipids and a degradation product of the amino acid serine.

5.1.1 Non-human information

The eMSCA identified the following information from the Committee for Medicinal Products for Veterinary Use on the metabolism of MEA that was not included in the registration dossier. The paper doesn't include the data underlying the Panel's conclusion (below), but is considered a reliable source of information. The metabolism and incorporation of MEA into phospholipids in animal tissue is via formation of phosphorylethanolamine (2-aminoethanol dihydrogenphosphate) and cytidine diphosphate ethanolamine (cytidine 5'-(trihydrogen diphosphate), mono(2-aminoethyl)ester) as intermediates to the cephalin phosphatidylethanolamine. Surplus amounts of MEA may be converted via acetaldyde to CO2. Phosphatidylethanolamine is one of the precursors of other phospholipids containing choline for example. Within 5 minutes after intraportal injection of (2-^{3}H)-aminoethanol a high percentage of the dose was reported to be incorporated into phosphorylethanolamine followed by incorporation into phosphatidylethanolamine. The metabolic pool for MEA-containing compounds in rat liver was calculated as 1.1 µmol MEA/liver, 3.8 µmol phosphorylethanolamine/liver, 0.239 µmol cytidine diphosphate ethanolamine/liver and 80.6 µmol phosphatidylethanolamine /liver. The available pharmacokinetic and metabolism data lead to the conclusion that MEA is rapidly metabolised and incorporated into lipids and other biomolecules (2-Aminoethanol: Summary Report – Committee for Veterinary Medicinal Products (EMEA/MRL/331/97-FINAL)).

No information is available on the toxicokinetics of MEA regarding the oral and inhalation route.

A dermal ADME study in the mouse was available (Klain GJ, et al., 1985). The results indicate that dermally-applied MEA penetrates the skin, is widely distributed and extensively metabolised. Extensive metabolism was indicated by the appearance of labelled carbon dioxide in skin and hepatic amino acids, proteins and incorporation into phospholipids, and by recovery of over 18% of radioactive dose as 14-CO_2. Urea, glycine, serine, choline, and uric acid were the urinary metabolites of MEA

Following intra-peritoneal administration of MEA to the rat, 11.5% of the dose was eliminated as carbon dioxide in eight hours. Approximately 50% of the injected radioactivity was found in the liver, with almost all the radiolabel associated with the lipid fraction. The spleen, kidneys and small intestine contained significant amounts of radioactivity whereas the heart, brain and diaphragm

contained only traces of radioactivity, amounting to approximately 1% of the injected dose (Taylor and Richardson (1967)).

Persistence of low levels of radioactivity in dog whole blood samples was obtained with [14C]ethanolamine ($t_{1/2}$:19 days). Route of administration not stated. Excretion of radioactivity as percentage of dose in dog urine was found to be 11 % for ethanolamine. The total blood radioactivity after 24 hours was only a small percentage of administered dose (ethanolamine, 1.69%). (Rhodes, C., and Case, D.E.,(1977))

The metabolism of radiolabelled ethanolamine was investigated in clonal human neuroblastoma cells *in vitro* up to 120 min. Neuroblastoma cells metabolized 2-aminoethanol to various phosphorylated and methylated choline derivatives when incubated *in vitro* for 12 hours with the compound. When 2-aminoethanol was injected intraventricular into the rat brain in vivo the same choline derivatives were identified as a function of time (Massarelli (1993)).

The eMSCA considers the *in vivo* dermal study of more value in deriving a quantitative figure for dermal absorption than the *in vitro* studies (see below), given that the latter was more of an inter-species comparative study. In the *in vivo* study (Klain, 1985) the potential absorbed dose amounted to about 75% after 24 hours' exposure to a dermal dose of 7.6 µg of MEA in ethanol (approx. 5.2 µg/cm^2), as shown below:

Sample	**Approx % of administered dose 24 hours following a dermal dose of 7.6 µg of MEA**
liver	24
skin administration site	24.3
exhaled CO_2	18
urine	4.6
faeces	1.8
kidneys	2.5
Lungs	0.55
brain	0.27
heart	0.15
Total	**76.17**

An *in vitro* study using mouse, rat, human and rabbit skin provided by the Registrant Sun, JD et al(1996)) gave values for dermal penetration values of:

rat skin	6%
mouse skin	17%
rabbit skin	9%
human skin	0.6%

These values were based on 6 hours' exposure, with continuous sampling, and didn't include the skin at the application site.

5.1.2 Human information

No information available.

5.1.3 Summary and discussion on toxicokinetics

MEA is a normal component of human food. It is part of the membrane-constituting class of glycerophospholipids and a degradation product of the amino acids serine.

A dermal ADME study in the mouse demonstrated that MEA was readily metabolised in the skin as well as in other organs and tissues in the mouse. Liver is a major site for metabolism of MEA. Extensive metabolism was indicated by appearance of radiolabelled carbon dioxide in skin and hepatic amino acids, proteins and incorporation into phospholipids, and by recovery of over 18% of radioactive dose as [14]-CO2. Urea, glycine, serine, choline, and uric acid were the urinary metabolites of 2-aminoethanol.

There are no data available on systemic availability via the oral and inhalation routes. The eMSCA considers that the available data on dermal absorption indicate that penetration of human skin could be low but are insufficient to make a definitive conclusion.

The *in vitro* human data indicate that dermal absorption in humans could be low but insufficient information was available to derive a more definitive value. Therefore 100% should be used in exposure calculations.

5.2 Acute toxicity

MEA has harmonised classifications of Acute Tox. 4* – H302, Acute Tox. 4* - H312, Acute Tox. 4* - H332. The information evaluated was consistent with these classifications.

5.3 Irritation

MEA has a harmonised classification of Corrosive Category 1B, H314 (causes severe skin burns and eye damage). The information evaluated is consistent with this classification.

5.4 Sensitisation

One of the grounds for concern for MEA was respiratory sensitisation, based on its listing as an occupational asthmagen by the CSST (Commission de la santé et de la sécurité du travail) (updated April 2010). The CSST document also lists MEA as a skin sensitiser.

5.4.1 Skin

Two animal studies were considered by the eMSCA a published guinea pig maximisation study (Wahlberg JE and Boman , A. 1996) and a LLNA conducted by the Registrant (see confidential annex for reference). These are summarised in table 10 below. Four additional studies were included in the registration dossier; however, none of these studies were considered reliable, as they did not follow any accepted guideline, the test material was of unknown purity or a mixture was tested.

Table 10: Summary of animal studies to investigate the skin sensitisation potential of MEA

Method	Doses	Results
Species: Guinea pig / Durkin Hartley Albino Group size: 15 animals used	*Induction* Intradermal= 0.6% v/v	**Group** | **MEA** | **Time after Challenge**

<table>
<tr><th>Method</th><th>Doses</th><th>Results</th></tr>
<tr>
<td>for the test substance (5 animals per concentration) 12 animals used for controls

Test Substance: MEA (Purity=not stated)

15/sex in test group

5/sex in positive and irritation controls

Vehicle= Water

No information on purity.

Similar to OECD 406-Magnusson and Kligman maximisation study, GLP

Wahlberg JE and Boman A (1996)</td>
<td>Epidermal= 10.3% v/v

Challenge
0.41, 2.05 and 4.1 % w/v

10% sodium lauryl sulphate in petrolatum was used prior to topical induction

The Experiment was repeated without controls</td>
<td>
<table>
<tr><th></th><th>conc %v/v</th><th colspan="2">Expt 1.</th><th colspan="2">Expt 2.</th></tr>
<tr><th></th><th></th><th>48h</th><th>72h</th><th>48h</th><th>72h</th></tr>
<tr><td rowspan="4">Test

N=15</td><td>0</td><td>0</td><td>0</td><td>-</td><td></td></tr>
<tr><td>0.41</td><td>2</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>2.05</td><td>1</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>4.1</td><td>2</td><td>3</td><td>1</td><td>1</td></tr>
<tr><td>Control

N=12</td><td>water</td><td>-</td><td>2</td><td>-</td><td>-</td></tr>
</table>
Based on the result of this study MEA is not classifiable as a skin sensitiser.
</td>
</tr>
<tr>
<td>Species: Mouse

LLNA conducted in July 2006 with ethanol.

Follows OECD guidance except for the positive control data.

Test substance: MEA hydrochloride</td>
<td>Concentrations- 10, 30 and 70%</td>
<td>Under the conditions of the experiment, 70% MEA caused an induction of cell counts (1.26) and increased thymidine incorporation (SI 2.03).
30% MEA only increased the SI index to 1.47 but was stat sig compared to control.
10% MEA could only increase ear weight but this is an indicator of irritation not sensitization. There was also no dose response.
In accordance with the OECD guideline, MEA was not a skin sensitiser as neither the cell counts nor stimulation index exceed those stated i.e. 1.5 and 3 respectively.
There is evidence of a dose related increase in SI however as both 30 and 70% ethanolamine were stat sig compared to the vehicle control.
A positive control not run concurrently and the most appropriate study given in the report of HCA in 1% pluronic is from April 2004 which is 2 years prior to the study. The study with HCA in acetone is from 2006 and shows a clear positive response which negates some of the concern but was not ideal.</td>
</tr>
</table>

Human data

No human data were provided by the Registrant on the skin sensitisation potential of MEA.

A published study was identified through a literature search conducted by the eMSCA (Lessmann H. et al, 2009). This study analysed patch test data (1992-2007) from patients who had been tested by the Information Network of Departments of Dermatology (IVDK) to identify particular exposures possibly associated with an elevated risk of sensitization. The study investigated MEA and the similar substances, 2,2',2"-Nitrilotriethanol (TEA) and 2,2'-iminodiethanol (DEA).

MEA - 3.8% of patients tested (n=9602) were positive, 3.5% questionable, 0.6% irritant. Metalworkers within this cohort were positive but at low percentage (15.2% with water-based metal working fluids (wbMWF), 7% in metal industry).

The study concluded that the chronic damage to the skin barrier in metal workers, the alkalinity of ethanolamines (increasing from TEA to MEA), and other cofactors may contribute to a notable sensitisation risk.

5.4.2 Respiratory system

Respiratory sensitisation (occupational asthma) was listed as a concern because of MEA's inclusion on the CSST's (Commission de la Santé et de la Sécurité du Travail) list of agents causing occupational asthma (updated April 2010). In contrast the UK's Health and Safety Executive produced a document 'Asthmagen? Critical assessments of the evidence for agents implicated in occupational asthma' (last updated 2001), which concluded the findings of the studies available did not provide good evidence that MEA can induce occupational asthma, such that there was insufficient evidence to conclude that MEA met the EU criteria (1996) for classification as a respiratory sensitiser and labelling with R42

The CSST and HSE documents reviewed 9 papers in total (two of which were considered in both the CSST and HSE documents; (Savonius *et al*., 1994) and (Gelfand HH, 1963). The reports are all relatively old dating between the 1960's and 1990's, however the eMSCA has conducted a literature review to update these reviews.

Reports considered in the CSST and HSE documents

CSST and HSE documents

A cleaner who was exposed over many years to several cleaning products developed cough and fever on using a particular type of detergent which contained ethanolamine amongst other ingredients (Savonius *et al*., 1994). She underwent bronchial challenge testing with the detergent, and gave a positive immediate response and subsequent fever. A control exposure and another detergent were negative at challenge. She was not challenged with ethanolamine, however these findings did not provide good evidence that ethanolamine was the cause of the response. As the subject had a fever this suggests some form of pneumonitis, therefore it wasn't clear that this subject had occupational asthma.

Gelfand (Gelfand, 1963) detailed reports of 14 users of 'beauty culture products' were described as having asthma, rhinitis or conjunctivitis. All were atopic and apparently had multiple allergies to chemicals. Ten of the patients with asthmatic symptoms relating to handling the products apparently gave positive bronchial challenge tests to both ethanolamine and ammonium thioglycolate. Asthmatic and non-asthmatic control subjects failed to react at challenge. However, the confusing and incomplete reporting of this study, in patients with apparently multiple allergies, makes it difficult to interpret the results and draw any conclusions regarding ethanolamine.

HSE Document

Two cases of occupational asthma attributed to ethanolamine were reported in the UK under the Surveillance of Work-related and Occupational Respiratory Disease scheme in 1993 (Sallie *et al*., 1994). Also, Butcher (1982) includes in a review unreferenced data indicating that ethanolamine

gas given a positive, immediate, bronchial challenge reaction but that the mechanism is uncertain. In the absence of more information regarding these cases, no conclusions can be drawn.

A study reported respiratory problems (coughing, tightness in the chest, runny nose, wheezing) in a worker using a detergent (containing 8% 2-aminoethanol) to remove wax. The worker mixed the detergent with hot water prior to use. A bronchial provocation test indicated an asthmatic reaction. It was noted that the worker had fever seven hours after the test.

The CSST report also cites the case of a worker in a beauty salon who developed asthma by using an aerosol product for nails and a hair lotion. The worker also developed hives on the hands. A challenge test and skin tests were positive to MEA.

Several isolated cases of skin sensitization are reported in workers using cutting oils. They developed eczema on the hands. Skin tests (closed) gave positive responses to the MEA.

CSST and HSE documents

Several isolated cases of skin sensitization are reported in workers using cutting oils. They developed eczema on the hands. Skin tests (closed) gave positive responses to the MEA (Bhushan, M. *et al* (1998), Koch, P. *et al* (1995)).

No information on respiratory sensitisation was provided in the registration dossier. Upon an informal request, the Registrants provided publically-available literature on the skin sensitisation potential of MEA. Additionally, the eMSCA conducted a Literature Search for papers on MEA and respiratory sensitisation (occupational asthma) on Medline in Web of Science published during the period 1980-2014. This search retrieved ca 750 papers, but of these only 4 were considered relevant to the current review (these papers had also been provided informally by the Registrants). One of these had already been CSST and HSE documents (Savonius *et al*., 1994). See section 11 for the search criteria used.

Table 11: Summary of the information available on the respiratory sensitisation potential of MEA

Reference	Overview	Methods	Findings	Comments	Conclusion
Savonious, B *et al.* 1994 This paper was considered in the HSE 'Asthmagens' Document and CSST documents.	Diagnosis of 3 cases of occupational asthma (OA) linked to exposure to ethanolamines. Two patients were confirmed only to have been exposed to triethanolamine (TEA), a third was exposed to a detergent product containing 8% ethanolamine (MEA) and 9% sodium metasilicate.	OA diagnosis was based on a provocation test in an inhalation challenge chamber with the suspected agent. Measurements of respiratory function (PEF/FEV_1).	Two patients diagnosed with OA, triggered by TEA. 1 patient diagnosed with OA triggered by a detergent containing 8% MEA and 9% sodium metasilicate. In this case exposure to the suspected detergent caused a decrease in FEV_1 of 27%. No response was observed following exposure to placebo, or a different detergent containing 9% TEA.	In the instance of the positive diagnosis of OA triggered by a detergent containing 8% MEA, the effects of MEA alone were not investigated. The author concluded that a reaction, other than an allergic one, or a reaction to something other than MEA could not be discounted. (ie. reaction to alkaline irritant (sodium metasilicate) in the product).	Some, inconclusive, evidence of a single case of OA, linked to MEA.
Makela, R *et al.* 2011	Diagnosis of occupational asthma (OA) in 20 female cleaners. 5 cases of OA were attributed to exposure to wax removing detergents (WRDs) containing ethanolamines.	OA diagnosis was based on patient history and lung function tests in response to specific challenge with the suspected products, and to pure TEA in one instance.	Of the 20 patients diagnosed with OA. 5 were attributed to WRDs containing ethanolamines. 1 case of OA was confirmed to be caused by TEA, in the single patient who was challenged with pure TEA. Exposure to pure MEA was not conducted. The author concluded that ethanolamines in the tested products were the likely cause of the reaction in all cases.	Significant lack of clarity regarding the formulation of the WRDs tested (defined solely as containing either MEA or TEA). Only 1 patient was challenged with pure TEA. No patients were challenged with pure MEA.	Limited evidence of OA triggered by exposure to MEA. Inconclusive as reaction to pure MEA was not examined.

Reference	Overview	Methods	Findings	Comments	Conclusion
Kamijo, Y *et al*. 2004	Case report of asthma-like symptoms and acute respiratory distress syndrome in a single patient following attempted suicide by oral ingestion of an MEA containing detergent, and subsequent choking/vomiting.	N/A	65 yo male admitted to hospital with asthma-like symptoms (no history of asthma) following oral ingestion of 600ml of a detergent product containing 3.3% MEA. Patient did not respond to treatment, and symptoms worsened to acute respiratory distress syndrome. Death occurred on day 4 following admission to hospital. Damage to the trachea, bronchi and alveoli were observed at post mortem.	N/A	Inconclusive. No evidence of respiratory sensitisation. Acute response in patient following oral ingestion (subsequent choking and vomiting) of an alkaline detergent (pH 11.7) containing 3.3% MEA.
Kamijo, Y *et al*. 2009	*In vivo/ex vivo* mechanistic studies of exposure to MEA. Performed following the case described by Kamijo, Y *et al*. 2004.	Measurement of bronchoconstriction (P_{ao}) and analysis of Histamine in Bronchoalveolar Lavage Fluid (BALF) in the guinea pig *in vivo*. Measurement of contraction of the guinea pig trachea *ex vivo*. Following exposure to MEA and MEA in combination with other agents known to affect respiratory function.	Exposure to MEA caused a significant increase in bronchoconstriction over control which was decreased by co administration of atropine and diphenhydramine hydrochloride. MEA did not cause an increase in histamine in BALF.	Purely mechanistic, no evidence for sensitisation.	Exposure to MEA causes significant bronchoconstriction in the guinea pig. A possible mechanism of action is via direct agonistic effects at histamine H_1 and muscarinic receptors. No evidence for respiratory sensitisation /OA.

MEA - Monoethanolamine MWF – Metal Working Fluid BALF – Bronchoalveolar Lavage Fluid ARDS – Acute Respiratory Distress Syndrome

PEF – Peak Expiratory Flow FEV_1 – Forced Expiratory Flow in 1 second DEA – Diethanolamine TEA – Triethanolamine OA – Occupational Asthma

P_{ao} – Airway opening pressure

5.4.3 Summary and discussion on sensitisation

Skin sensitisation

In the adjuvant type guinea pig maximisation study (Wahlberg and Boman, 1996), MEA induced a positive response in up to 20% of animals challenged with doses ranging from 0.41 to 4.1% v/v (no evidence of dose response relationship or any consistency in a second repeat experiment). No evidence of dermal response was observed in the irritation control group. The same study also investigated cross reactivity between MEA, DEA or TEA, and none was evident. A LLNA conducted by the Registrant (see confidential annex for reference) also gave a negative result for MEA.

A published study (Lessmann H *et al*, 2009) evaluated patch test data (1992-2007) from patients who had been tested by the Information Network of Departments of Dermatology (IVDK) to identify particular exposures possibly associated with an elevated risk of sensitisation. For MEA, 9602 patients were tested; 3.8% of these patients tested were positive, 3.5% a questionable response, and 0.6% an irritant response. In metal using workers 7% were positive and of those using water-based metal working fluids (wbMWF) 15.2% were positive. However, it should be noted that workers in this industry are likely to have compromised dermal barriers.

eMSCA Overall conclusion on Skin Sensitisation

The eMSCA considers that the negative animal studies and the lack of convincing human data support the Registrants view that MEA should not be classified for skin sensitisation, in-line with CLP guidance.

Respiratory sensitisation

Respiratory sensitisation (occupational asthma) was listed as a concern because of MEA's inclusion on the CSST's list of agents causing occupational asthma. However a contradictory conclusion was made by the UK's Health and Safety Executive document 'Asthmagen? This review was considered to be more comprehensive than the earlier CSST document and considered the widespread use of MEA compare to the limited number of reports of possible respiratory sensitisation.

eMSCA Overall conclusion on Respiratory Sensitisation

The review of available information indicated that there are no new data which would alter the conclusions made by the UK HSE ('Asthmagen? Critical assessments of the evidence for agents implicated in occupational asthma' (last updated 2001)). The concern has been clarified and no further information is requested.

5.5 Repeated dose toxicity

5.5.1 Non-human information

5.5.1.1 Repeated dose toxicity: oral

No conventional repeated dose oral toxicity studies with MEA were provided. An oral two generation reproduction toxicity study according to OECD 416 with MEA HCl was provided by the Registrant (see confidential annex for reference) to meet this requirement.

The pKa of ethanolamine is ca.9.5 and it is a weak base. The pKa of MEA HCl will be much lower than ethanolamine, and so under acidic conditions the presence of this as the salt will have no impact on the speciation. Therefore overall it is likely that whether rats are dosed with MEA HCl or MEA, and then come into the acidic environment in the stomach, the dominant species will be $HOCH_2CH_2NH_3^+$. Therefore there are no issues in reading across from MEA HCl to MEA.

The eMSCA notes that this study meets most of the requirements of a 90-day study, given its 10 week premating period and extensive histopathological examinations, although no measurements were made of haematological or clinical chemical parameters. The study included some toxicokinetic data (plasma levels of MEA, calculated as MEA HCl) which indicated that bioavailability of MEA HCl did not reach saturation at higher doses.

Table 12: Summary of information on oral repeated-dose toxicity

Method	Dose Levels	Remarks
Test Species : Rat/Cr:WI (Han) **Test Substance**: MEA hydrochloride (purity >99%) **Vehicle:** water **Group size**: 25/sex/dose **Route:** Oral (diet) **Method**: Similar to OECD Guideline 416 (food consumption not determined between days 14-21 after parturition), GLP At least 75 days after the beginning of treatment, F0 animals were mated to produce a litter (F1 generation). Mating pairs were taken from the same dose group and F1 animals selected for breeding were continued in the same dose group as their parents. Groups of 25 males and 25 females, selected from F1 pups to become F1 parental generation, were offered diets containing target dosages of	MEA hydrochloride was administered to groups of 25 male and 25 female Wistar rats (F0 parental generation) in the diet, adjusted obtain target dose levels of 0, 100, 300 and 1000 mg/kg bw/day.	**Reproductive data for this study are presented in section 5.9** **Organ Weight Tables are presented in Table 13 below;** There were effects on parental animals (F0 and F1; fertility/reproductive performance and systemic toxicity) at 1000 mg/kg bw/day. There were increased kidney weights seen at 300 mg/kg bw/day in both sexes in F1 parental animals however this no considered adverse given the magnitude of the change and lack of no histopathological correlates. There were no effects on pups at any dose level. **Summary of effects in parental animals at 1000 mg/kg bw/day;** **<u>1000 mg/kg bw/day</u>** **F0 parental animals** • Yellow discoloured urine (both sexes) • Significantly decreased body weight gain of the dams during gestation (bodyweight 8% below control on gestation day 20), probably secondary to an increased post-implantation loss in these animals.

Method	Dose Levels	Remarks
0, 100, 300 and 1000 mg/kg bw/d of the test substance post weaning, and the breeding program was repeated to produce a F2 litter. The study was terminated with the terminal sacrifice of the F2 weanlings and F1 parental animals. In addition to standard guideline parameter; i) Various sperm parameters (motility, sperm head count, morphology) were assessed in F0 and F1 generation males at scheduled sacrifice after appropriate staining; ii) Blood samples were taken from all F0 and F1 parental animals of each sex and test group during week 10 of premating treatment and the plasma was analyzed for the concentration of ethanolamine hydrochloride; iii) liver samples (lobus medialis) were taken from 10 female animals per test group during dissection of the animals. They were analyzed for their choline content in a separate study		• Significantly decreased food consumption in females during lactation • Statistically significantly decreased absolute and relative weight of epididymides, cauda epididymidis and prostate in males **F1 parental animals** • Yellow discoloured urine in both sexes • Significantly decreased bodyweight gain of the dams during gestation, secondary to an increased post-implantation loss in these animals. • Significantly increased kidney weights in males and females. As compared to control animals, the kidneys of low-, mid-, and top-dose male and female animals revealed a low incidence of basophilic tubules in a slightly higher number of animals. The severity (minimal to slight) was comparable between controls and treated animals and a clear dose-response relationship was missing, therefore this finding was considered to have no toxicological relevance. • Decreased food consumption in parental females during lactation • Significantly decreased absolute and relative weight of epididymides and cauda epididymidis in males **<u>300 mg/kg bw/day</u>** **F0 parental animals** No test substance related toxicity **F1 parental animals** Significantly increased kidney weights in males and females (see above for comments on histopathological findings) **Toxicokinetics** Toxicokinetic data on MEA (calculated as MEA HCl) from this two generation reproduction toxicity study showed a dose dependency in the plasma levels of MEA indicating that bioavailability of MEA HCl did not reach saturation at higher doses. **<u>eMSCA Conclusions</u>** The NOAEL (parental animals) was 300 mg/kg/d based on evidence of systemic toxicity: absolute and relative weights of epididymides and cauda epididymidis.

Method	Dose Levels	Remarks
2 year dog study **Test Species :** Beagle dog **Test Substance:** dye containing 22.42 % MEA (24 other substances) **Vehicle:** dietary study **Group size:** 18/sex/dose **Route:** Diet **Method:** no guideline followed. daily cage side observations, bodyweights weekly, food consumption and compound intake daily, ophthalmoscopic examination once (time point not stated), haematology baseline, 3, 6, 12, 18, and 24 month, clinical chemistry baseline, 3, 6, 12, 18, and 24 month, urinalysis time points not given, gross and histopathological examination on a wide range of tissues and included investigations using electron microscopy, **Wernick T, Lanmam BM and Fraux JL, 1975**	0, 19.5, 97.5 mg/kg bw/day	All animals in both test groups excreted blue-brown coloured urine on a daily basis. However, urine analyses showed no remarkable findings at any examination period. Colour was normal in the urines collected following overnight fasting and was probably an indication of rapid clearance. **eMSCA Conclusions** Overall no notable differences were seen in any of the parameters studied between the controls and the animals receiving 19.5 or 97.5 mg/kg bw/day of the dye/base composite (doses of MEA approximately equivalent to 4.4 or 21.9 mg/kg bw/day). Study is considered of limited value because of the complex test substance.

Table 13 gives the organ weight data from the 2 – generation study in rats summarised in table 12.

Table 13: Two-generation study with MEA: selected organ weight data

F0 Generation		Males				Females			
Parameter		**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
Terminal bodyweight		368.132	372.76 (101%)	373.604 (101%)	364.504 (99%)	223.26	219.916 (99%)	222.276 (100%)	221.876 (99%)
kidney	Absolute (g)	2.47	2.396 (97%)	2.544 (103%)	2.549 (103%)	1.688	1.707 (101%)	1.765 (105%)	1.875 (111%)
	Relative (%)	0.673	0.643 (96%)	0.681 (101%)	0.701 (104%)	0.756	0.776 (103%)	0.794* (105%)	0.816** (108%)
epididymides	Absolute (g)	1.134	1.13 (100%)	1.151 (101%)	1.041** (93%)	na	na	na	na
	Relative (%)	0.309	0.303 (98%)	0.309 (100%)	0.286** (93%)	na	na	na	na
cauda epididymidis	Absolute (g)	0.438	0.434 (99%)	0.445 (102%)	0.384** (88%)	na	na	na	na
	Relative (%)	0.119	0.116 (97%)	0.12 (101%)	0.106** (89%)	na	na	na	na
Prostate	Absolute (g)	1.194	1.103 (92%)	1.18 (99%)	1.021 (86%)	na	na	na	na
	Relative (%)	0.325	0.296*	0.317	0.281**	na	na	na	na

			(91%)	(98%)	(86%)				
F1 Generation		**Males**				**Females**			
Parameter		**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
Terminal bodyweight		393.668	392.608 (100%)	386.78 (98%)	383.764 (97%)	222.572	223.344 (100%)	223.556 (100%)	226.728 (102%)
kidney	Absolute (g)	2.393	2.372 (99%)	2.542* (106%)	2.659** (111%)	1.638	1.684 (103%)	1.74** (106%)	1.88** (115%)
	Relative (%)	0.608	0.605 (100%)	0.658** (108%)	0.694** (114%)	0.736	0.754 (102%)	0.77** (105%)	0.833** (113%)
epididymides	Absolute (g)	1.104	1.1 (100%)	1.113 (101%)	1.001** (91%)	na	na	na	na
	Relative (%)	0.281	0.281 (100%)	0.288 (102%)	0.261** (93%)	na	na	na	na
cauda epididymidis	Absolute (g)	0.426	0.41 (96%)	0.423 (99%)	0.375** (88%)	na	na	na	na
	Relative (%)	0.108	0.105 (97%)	0.109 (101%)	0.098** (91%)	na	na	na	na

(% of control value)
* :p≤0.05. ** :p≤0.01 Kruska-wallis and Wilcoxon test, two sided.

5.5.1.2 Repeated dose toxicity: inhalation

The Registrant has supplied a 28-day inhalation toxicity study performed according to OECD guideline 412 and GLP compliant see confidential annex for reference) and a supporting 5-day range-finding inhalation toxicity study.

Table 14: 28 days inhalation toxicity study in the rat with MEA (and range finding study)

Method	Dose Levels	Remarks
Species: Wistar rats, Crl:WI (Han)) **Group size**: 5/se/dose **Test Substance**: MEA (no vehicle) Purity=not stated **Exposure period**: 28 days 6 hours/day, 5 days/week (nose only) **Guideline**: OECD 412 , GLP complient	Target 0, 10, 50 and 150 mg/m^3 MEA Actual: 10.2±2.7, 49.1±8.3 and 155.9±23.4 mg/m^3 The concentrations of the inhalation atmospheres were analysed by GC. The vapour and liquid aerosol concentration were determined separately. Daily means were calculated based on two measured samples per concentration and exposure. Droplet size analysis was conducted twice in the high dose group only using a	**Range finding study** The dose levels used in this 28 day study were based on a 5 day (6/hours exposure/day) range-finding study. In this study animals 5 males/dose level were dosed at 20, 200 and 500 mg/m^3 nose only. Adverse morphological changes of epithelia in the nasal cavity and in the larynx, trachea and lung were seen at 200 and 500 mg/m^3. Findings included epithelial necrosis, inflammation, metaplasia, haemorrhage in the nasal cavity; necrosis, inflammation, metaplasia, cellular atypia and hyperplasia of the laryngeal epithelium; degeneration and hyperplasia of the respiratory epithelia in the trachea; and hyperplasia of the bronchiolar epithelium of the lungs. No adverse changes were seen at 20 mg/m^3. **Main study** No systemic effects were observed at any dose level. In the main study exposure to MEA at 150 mg/m^3 resulted in submucosal inflammation (levels I, II) in males and females, degeneration of submucosal glands (level I) in males and females, focal epithelial necrosis (level I) in males and females, focal squamous metaplasia, (level I) in males and females; (level II) in one male and 2 females and focal epithelial hyperplasia (level II) in males and females were observed in the larynx. In the trachea, focal squamous metaplasia (carina) accompanied by inflammation in males was

Method	Dose Levels	Remarks
	cascade impactor giving MMADs of 1.1 and 1.2 µm with a GSD of 5.3and 6.4. The calculated mass fractions of particles below 3 µm aerodynamic size were 70.0 and 70.3 %.	observed. At 50 mg/m³ submucosal inflammation (level I and II) in males and females and squamous metaplasia (level I and II) in few males and females in the larynx was reported. No treatment-related weight changes, gross lesions or microscopic findings at the low concentration (10 mg/m^3). **eMSCA Conclusions** No histopathological effects were seen in any other organ outside the respiratory tract. The NOAEC for systemic toxicity is the highest concentration of 150 mg/m^3 (equivalent to 215.6 mg/kg bw/day). The NOAEC for local effect was the lowest tested concentration of 10 mg/m^3 (equivalent to 14.4 mg/kg bw/day) under the test conditions of this study.

The Registrant has provided a number of other studies in their registration dossier; however these studies are very limited value because of, for example, limited animal numbers, very limited details of methodology and/or reliability of exposure measurements, and therefore have not been summarised in this Report.

Nevertheless the eMSCA has reviewed the studies and notes that they do not highlight any additional concerns. It is also noted that none of these studies are sufficiently reliable use in the derivation of DNEL values.

5.5.1.3 Repeated dose toxicity: dermal

The Registrant has provided one repeat dose dermal toxicity study in the rabbit. This study was confined to assessing site of contact effects.

Table 15: 2 week dermal toxicity study in the rabbit with MEA

Method	Dose Levels	Remarks
2 week repeat dose rabbit study		
Test Species : Rabbit (no other details given) **Test Substance:** monoethanolamine purity <99% **Vehicle:** Not stated **Group size:** 18/sex/dose **Route:** dermal **Method:** no guideline followed. 10 semi-occluded patches were applied for 24 hours to the shaved abdomen of	0.1 ml of 1-100% solutions	10 % or higher was corrosive to the skin, >1 % was extremely irritating to the skin and 1 % was irritating to the skin. No further data given.

Method	Dose Levels	Remarks
rabbits over a period of 14 day **Duration of dosing:** The test substance was repeatedly applied in a total of 10 exposures over a period of 14 days to the skin of rabbits **International Journal of Toxicology. Vol 2, Issue 7. 205 – 207 (1983)) original study (1944)**		

5.5.1.4 Repeated dose toxicity: other routes

Intraperitoneal dosing studies

The Registrant has provided two i.p. dosing studies in the rat and one in the mouse. These studies were not considered reliable because of lack of detail in the methodology and results. The i.p. route is also not a relevant route of exposure and therefore full details are not presented.

5.5.2 Human information

No relevant information available.

5.5.3 Summary and discussion of repeated dose toxicity

Inhalation exposure

The inhalational toxicity of MEA was studied in a 28-day GLP-compliant study performed according to OECD guideline 412. Findings included submucosal inflammation, degeneration of submucosal glands, focal epithelial necrosis, focal squamous metaplasia; and focal epithelial hyperplasia in the larynx. In the trachea, focal squamous metaplasia (carina) accompanied by inflammation in males were observed.

The NOAEC for systemic toxicity is the highest concentration of 150 mg/m^3 (equivalent to 43.5 mg/kg bw/day, based on 100% inhalation absorption and a standard 6-hour respiratory rate for rats of 0.29 m^3/kg bw). The NOAEC for local effect was the lowest tested concentration of 10 mg/m^3 under the test conditions of this study.

The Registrant has provided a number of other studies in their registration dossier; however, these are of limited value because of, for example, limited animal numbers, very limited details of methodology and/or reliability of exposure measurements. However, whilst not presented here, these studies provide findings which are consistent with the other studies in the registration dossier.

Oral exposure

No reliable conventional repeated dose toxicity studies with MEA are available. However, MEA HCl was tested in an oral two generation reproduction toxicity study according to OECD TG 416. The eMSCA notes that this does meet most of the requirements of a 90 day study, given its 10 week

premating period and extensive histopathological examinations, although no measurements were made of haematological or clinical chemical parameters.

Regarding general repeated dose toxicity, the dose level of 1000 mg/kg bw/day caused systemic toxicity in parental females, as was indicated by reduced food consumption and/or body weight gain during gestation and lactation. In the mid and high dose F1 animals the absolute and relative kidney weights were statistically significantly increased without histopathological correlate findings. In the top-dose F0 and F1 males the test substance administration led to a decrease of absolute and relative organ weights of cauda epididymidis and epididymides. Furthermore, prostate weight and the number of homogenization resistant caudal epididymal sperm was slightly, but significantly, decreased in the F0 males. These findings were considered to be treatment-related effects, whereas histomorphological correlates were missing. Based on this study, the NOAEL for general toxicity was set at 300 mg/kg bw/day.

A non-guideline two year dog study was considered of limited value given the complex nature of the test material; a dye containing 22.42 % MEA (and 24 other substances).

5.6 Mutagenicity

Mutagenicity was not identified as an area of concern for MEA. However, the available information was evaluated to inform on the carcinogenic potential of MEA.

5.6.1 Non-human information

5.6.1.1 In vitro data

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

Table 15: Summary of *in vitro* genotoxicity studies on MEA

***In vitro* data**			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
Bacterial reverse mutation assay Guideline: JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) **JETOC (1996)**	*S. typhimurium*,: TA98, TA 100, TA 102, TA 104, TA 1535, TA 1537 and TA1538 *E. coli*, WP2uvrA and WP2uvrA/pKM101	MEA (purity not stated) Test concentrations: 50 - 5000 µg/plate (Conducted with and without metabolic activivation)	**Conclusion: Negative** *S. typhimurium, E. coli*, WP2uvrA and WP2uvrA/pKM101: cytotoxicity at ≥2000 µg/plate Valid positive and negative controls.
Bacterial reverse mutation assay Guideline: equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) **Dean BJ, et al. (1985)**	*S. typhimurium*, other: TA 98, TA 100, TA 1535, TA 1537, TA 1538 *E. coli*, WP2 tyr- *E. coli* WP2 uvr A	MEA (purity not stated) Test concentrations: 0.2 - 2000 µg/plate (Conducted with and without metabolic activivation)	**Conclusion: Negative** Valid positive and negative controls

In vitro data			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
Mammalian cell gene mutation assay Guideline: OECD Guideline 476 (*In vitro* Mammalian Cell Gene Mutation Test)	Mouse lymphoma L5178Y cells	MEA (purity 99.83%) Test concentrations: 38.1, 76.3, 152.5, 305, 610 µg/ml (represents the limit dose of 10mM) (Conducted with and without metabolic activation)	**Conclusion: Negative** No cytotoxicity, but tested up to limit concentrations Valid positive and negative controls
Mammalian cell gene mutation assay Guideline: Method described in Trosko et al., 1984 (In Handbook of Carcinogen Testing) is based on metabolic cooperation between 6-thioguanine sensitive (HGPRT+) cells and 6-thioguanine resistant (HGPRT-) cells in vitro. **Chen TH, et al. (1984)**	Chinese hamster lung fibroblasts (V79)	MEA (purity not stated) Test concentrations: not indicated (Conducted without metabolic activation)	**Conclusion: Negative** Valid positive and negative controls
Bacterial reverse mutation assay Guideline: equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) **NTP (1982)**	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100	MEA (purity not stated) Test concentrations: 100, 333, 1000, 3333, 10000 µg/plate (Conducted with and without metabolic activation)	**Conclusion: Negative** No cytotoxicity. Valid positive and negative controls
In vitro mammalian chromosome aberration test Guideline: equivalent or similar to OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) **Dean DJ and Hodson-Walker G (1979)**	Rat hepatocytes (RL4) (met. act.: without)	MEA (purity not stated) Test concentrations: 100 – 400 µg/ml	**Conclusion: Negative** Valid positive and negative controls
In vitro mammalian chromosome aberration Guideline: none followed **Arutiunian RM, et al. (1987)**	human lymphocytes	MEA (purity not stated) Test concentrations: 0.61 - 61.08 µg/ml (0 (control), 0.01, 0.1, 0.2, 0.4, 0.6, 0.8 and 1 mM) (Conducted with and without metabolic activation)	**Conclusion: Weak positive** In studying the cytogenic effect of monoethanolamine in the human peripheral blood lymphocyte culture, the test substance was introduced on the 52nd hr of cultivation in the range of concentrations from 0.001 to 0.00001 M. The lymphocytes were cultured by the conventional method for 72 hr (Hugerford, Stain Technol 30:333-338, 1973). In this case the chromosomal aberrations

In vitro data			
Method	**Organism/Strain**	**Concentrations Tested**	**Result/Remarks**
			(CAs) in the cells of the I and II mitoses and SCEs were scored. For this purpose, the preparations were stained by the method of Chebotarev et al., Byull Eksperim Biologii i Meditsiny 85:242-243, 1977. No additional methodological information was provided. Valid positive and negative controls
Sister chromatid exchange assay in mammalian cells Guideline: none followed **Arutiunian RM, et al. (1987)**	human lymphocytes	MEA (purity not stated) Test concentrations: 0.61 - 61.08 µg/ml (Conducted with and without metabolic activation)	**Conclusion: Negative** Valid positive and negative controls
Cytogenetic assay in plants Guideline: none followed (Dry seeds of Crepis capillaris were treated with the test substance before germination) **Arutiunian RM, et al. (1987)**	Seeds of Crepis capillaris	MEA (purity not stated) Test concentrations: 0.001, 0.01, 0.1, 1, 2, 5 M (Conducted without metabolic activation)	**Conclusion: Weak positive** The dry seeds of Crepis capillaris were treated for one and four hours by six concentrations of the investigated compounds (including MEA). The effect of dimethyl sulfoxide (DMSO), in which Neozone-D was dissolved, was also investigated as a control (as well as a water control). After treatment with the investigated compounds the seeds were washed with running water and germinated. Sprouts at the G1 stage of the cell cycle were fixed with a mixture of acetic acid and ethanol. In each variant 500 metaphases were analysed on temporary squash preparations. Valid positive and negative controls
Cytogenetic assay in plants Guideline: none followed **Arutiunian RM, et al. (1987)**	*Salmonella typhimurium* TA 1534 and TA 153	MEA (purity not stated) Test concentrations: 1016 - 10150 µg/plate (Conducted without metabolic activation)	**Conclusion: Negative** Valid positive and negative controls

5.6.1.2 In vivo data

Table 16: Summary of *in vivo* studies on genotoxicity

In vivo data			
Method	**Species/Strain**	**Concentrations Tested**	**Result**
Mouse micronucleus assay oral (gavage) Guideline: OECD Guideline 474	mouse (NMRI) male/female	MEA (99.5%) 375, 750 and 1500 mg/kg bw (actual ingested)	**Conclusion: Negative** Dose levels selected based on a toxicity screen where mortalities were seen at 1750 mg/kg bw but all animals survived 1500 mg/kg bw In the main study 2 animals died 1500 mg/kg bw. Valid positive and negative controls.

5.6.2 Human information

No information available.

5.6.3 Summary and discussion of mutagenicity

The *in vitro* genotoxicity of MEA has been investigated in three bacterial reverse mutation assays, a chromosome aberration assay in rat hepatocytes and two mammalian cell gene mutation assays (mouse lymphoma (L5178Y) and Chinese hamster lung fibroblasts (V79).

Negative results were reported in all studies. Negative results were also obtained from an *in vivo* mouse micronucleus test where clear signs of substance related toxicity were observed at the top dose (mortalities).

The genotoxicity studies performed with MEA were consistently negative and give no cause for additional concerns.

5.7 Carcinogenicity

One of the grounds for concern stated under the justification for the selection of the candidate CoRAP substance was the lack of any carcinogenicity data on MEA.

5.7.1 Non-human information

5.7.1.1 Carcinogenicity: oral

An oral carcinogenicity study is not available. An oral two-generation study and several repeated-dose studies are available and have been evaluated to inform on the carcinogenicity end-point (see section 5.5).

5.7.1.2 Carcinogenicity: inhalation

An inhalational carcinogenicity study is not available. Several repeated-dose studies are available and have been evaluated to inform on the carcinogenicity end-point (see section 5.5).

5.7.1.3 Carcinogenicity: dermal

The Registrant has provided a published non-guideline tumour promotion study in mouse skin which is summarised in Table 17.

Table 17: Summary of mouse tumour promotion study

Method	Dose Levels	Remarks
Tumour promotion in mouse skin **Test species**: Mouse (strain S) **Route**: Dermal **Group Sizes**: 20 males/group **Test material:** Name of test material (as cited in study report): 33% aqueous 2-aminoethanol-Oleate-solution. Composition of test material,: 0.91 g ethanolamine, 4.23 g oleic acid, 2.0 ml benzylalcohol in 100 ml water containing 0.1 % chlorcrestol. **Duration of exposure**: 24 weeks **Frequency of treatment**: once a week **Guideline**: None **Salaman MH and Glendenning OM, (1957)**	ca. 15 mg/kg bw/application	**Method** Test group 1: DMBA was applied in acetone to the skin of the back. After an interval of 3 weeks, 0.1 ml 33 % ethanolamine oleate in water was injected intradermally weekly for 24 weeks. Test group 2: DMBA was applied in acetone to the skin of the back. After an interval of 3 weeks, 0.1 ml of phenol in water was injected intradermally weekly for 24 weeks (0.5% for the first 12 weeks and 1% for the second 12 weeks). Test groups 3 and 4: The treatment was comparable to Test group 1 and 2 without DMBA pre-treatment. 9,10-dimethyl-1 : 2-benzanthracene (DMBA- a known tumour initiator) **Result** Group 1: a tumour appeared during the 11th week of exposure at a site which had received 2 injections of ethanolamine oleate. A few other tumours appeared from week 15 onwards and at week 33 there were 6 tumor-bearing mice out of 18 survivors Group 2: 5 tumours appeared on 2 out of 20 mice at the 23rd week at the time of 22nd phenol injection. No tumours were observed in a control group receiving DMBA alone. **eMS Conclusion** The eMS concludes that although this study may provide some evidence for tumour promotion, since a mixture was tested no firm conclusions can be drawn on the influence of MEA on these results.

5.7.2 Human information

No relevant information available.

5.7.3 Summary and discussion of carcinogenicity

A carcinogenicity study was not available for MEA.

MEA was clearly negative in the submitted genotoxicity studies.

Although no conventional repeated-dose oral toxicity studies with MEA were available, an oral two generation reproduction toxicity study with MEA HCl was submitted. This study meets most of the requirements of a 90 day study, given its 10 week premating period and extensive histopathological examinations, although no measurements were made of haematological or clinical chemical parameters. In this oral study there was no evidence of any hyperplasia and/or pre-neoplastic lesions during histopathological investigations.

In a 28-day inhalation study, hyperplasia and metaplasia were observed, indicating irritation/inflammation of the respiratory tract following repeated inhalational exposure. A number of other studies provided by the Registrant in their registration dossier which were considered of limited value because of, for example, limited animal numbers, very limited details of methodology and/or reliability of exposure measurements also showed clear evidence of irritation/inflammation following exposures to MEA vapour.

Overall, given that MEA is a corrosive substance, the relevance of these respiratory tract lesions to humans is questionable.

A non-guideline tumour promotion study in mouse skin provided some evidence that MEA is a tumour promotor, however since a mixture was tested no firm conclusions can be drawn on the influence of MEA on these results. The available data do not indicate there is a specific concern with respect to carcinogenicity, apart from the lack of any lifetime studies in animals. In the absence of a specific concern such data are not considered necessary.

No further information on carcinogenicity is requested under this substance evaluation.

5.8 Toxicity for reproduction

The available information on reproductive toxicity has been evaluated. No additional concerns were identified.

5.9 Endocrine disrupting properties

The available data give no indication that ED is a potential concern.

5.10 Other effects

5.10.1 Non-human information

5.10.1.1 Neurotoxicity

No information available.

5.10.1.2 Immunotoxicity

No information available.

5.10.1.3 Specific investigations: other studies

5.10.2 Human information

No information available.

5.10.3 Summary and discussion of specific investigations

5.11 Combined effects

No specific studies are available. There was no evidence found in the literature accessed to indicate that MEA can cause additional toxicity as part of a mixture. No additional concerns are identified.

5.12 Derivation of DNEL(s) / DMEL(s)

The Registrant has derived long-term DNELs for worker exposure via the dermal and inhalation routes. The long-term DNEL – inhalation is based on the 28 days inhalation study in rats, the long-term DNEL – dermal has also been based on the same study. The Registrant has proposed use of the 28 days inhalation study in rats in setting long-term DNEL – inhalation as no systemic effects were observed after inhalation exposure up to the highest concentration tested, 150 mg/m^3, for 28 days, therefore derivation of a dermal long-term DNEL for systemic effects based on the inhalation study would be a conservative approach.

5.12.1 Overview of typical dose descriptors for all endpoints

Table 18: Available dose-descriptor(s) per endpoint for MEA as a result of its hazard assessment

Endpoint	Study	NOAEL(C)	LOAEL(C)	Associated effect and remarks
Acute toxicity	Acute oral			Published data LD_{50} 1000-2500 mg/kg bw. Two reliable studies give LD_{50} values of ca 1515 and 1089 mg/kg bw MEA has a harmonised classification of Acute Tox. 4 - H302
	Acute Dermal			Published data LD_{50} 600 to 3374 mg/kg bw. One reliable study gave LD_{50} values of 2504 mg/kg bw (males) and 2881 mg/kg bw (females). MEA has a harmonised classification of Acute Tox. 4 - H312
	Acute inhalation			Three acute inhalation toxicity studies were available for MEA, all exposures were to saturated vapours, the calculated levels of MEA in the test atmospheres were questionable (no measurements were taken). MEA has a harmonised classification of Acute Tox. 4 - H332
	Skin irritation	Corrosive		In a number of studies dermal application MEA resulted in severe irritation, necrosis and 'chemical burns'.
	Eye irritation	Corrosive		Available animal data demonstrated that MEA caused severe damage to eyes, including severe corneal injury, iritis, bloody discharge, severe conjunctival irritation and necrosis.
	Respiratory irritation	No Information	No Information	MEA is severely irritating to the eye indicating that it will also irritating to the respiratory tract. Acute exposures to vapours gave no indication of irritation, however it is considered highly likely that exposure to aerosols would result respiratory tract irritation.

	Skin sensitisation	Not sensitising		A guinea pig maximisation study was included in the registration dossier
	Respiratory sensitisation	Not sensitising		The eMSCA considers that based on available published papers there is insufficient evidence when compared to current criteria to conclude that MEA is a respiratory sensitiser.
Repeated dose toxicity	two-generation study	NOAEL for general toxicity was considered to be 300 mg/kg bw/day	Reduced epididymal and prostate weight	No conventional repeated dose toxicity studies with MEA were provided. An oral two generation reproduction toxicity study according to OECD 416 with MEA HCl was provided to meet this requirement.
	28 day inhalation toxicity study in the rat with MEA	The NOAEC for systemic toxicity is the highest concentration of 150 mg/m^3. The NOAEC for local effect was the lowest tested concentration of 10 mg/m^3 under the test conditions of this study	50 mg/m³ for local effects	Local effects on larynx, trachea and lung including inflammation, hyperplasia and necrosis.
Mutagenicity		N/A	N/A	Not mutagenic *in vitro* or *in vivo*
Carcinogenicity	No information			
Reproductive toxicity	two-generation study	NOAEL (parental animals):300 mg/kg bw/day. NOAEL (Reproduction): 300 mg/kg bw/day. NOAEL (Offspring): 1000 mg/kg bw/day.	LOAEL (parental animals):1000 mg/kg bw/day based systemic toxicity; absolute and relative weights of epididymides and cauda epididymidis. LOAEL (Reproduction): 1000 mg/kg bw/day based on reduced number of implantation sites (resulting in increased number of smaller litters). There was also some evidence decreased sperm head count in cauda epididymidis. NOAEL (Offspring): 1000 mg/kg bw/day based on the absence of adverse effects at the top dose.	No reproductive data with MEA were provided. An oral two generation reproduction toxicity study according to OECD 416 with MEA HCl was provided to meet this requirement.
Reproductive toxicity	two-generation study	NOAEL (development): 300 mg/kg bw/day.	LOAEL (development): 1000 mg/kg bw/day based on increased post-implantation loss.	As above
Developmental toxicity	Oral study in rats	maternal NOAEL of 120 mg/kg bw/day a developmental toxicity NOAEL	Maternal LOAEL of 450 mg/kg bw/day based on reduced food consumption, lower mean bodyweights and impaired bodyweight	No evidence of an adverse effect on development

		of 450 mg/kg bw/day	gain Developmental toxicity no LOAEL as no effect at the top dose tested 450 mg/kg bw/day	
Developmental toxicity	Oral study in rats	maternal NOAEL of 120 mg/kg bw/day a developmental toxicity NOAEL of 500 mg/kg bw/day	Maternal LOAEL of 300 mg/kg bw/day based on reduced food consumption, lower mean bodyweights and impaired bodyweight gain Developmental toxicity no LOAEL as no effect at the top dose tested 500 mg/kg bw/day	No evidence of an adverse effect on development
Developmental toxicity	Dermal study in rats	maternal NOAEL of 75 mg/kg bw/day a developmental toxicity NOAEL of 225 mg/kg bw/day	Maternal LOAEL of 225 mg/kg bw/day based on Systemic effects: significantly reduced body weight gain. Local effects: dermal irritation followed a progression, beginning with erythema and leading to necrosis, scabs, and scar formation Developmental toxicity no LOAEL as no effect at the top dose tested 225 mg/kg bw/day	No evidence of an adverse effect on development
Developmental toxicity	Dermal study in rabbits	maternal NOAEL of 10 mg/kg bw/day a developmental toxicity NOAEL of 225 mg/kg bw/day	Maternal LOAEL of 25 mg/kg bw/day based on Systemic effects reduced body weight gain (↓38.3% during gestation days 0-29). Local effects: erythema, oedema, ecchymosis, necrosis, exfoliation, crusting. NOAEL for developmental toxicity was set at the highest dose level of 75 mg/kg bw/day Developmental toxicity no LOAEL as no effect at the top dose tested 225 mg/kg bw/day	No evidence of an adverse effect on development

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

A number of studies could be considered in setting the DNELs, including a two-generation study with MEA-HCl, and with MEA, a 28-day inhalation study in rats, oral and dermal developmental toxicity studies in rats and a dermal developmental toxicity study in rabbits.

Systemic dermal DNELs. Long-term systemic DNELs for the dermal route will be derived by route-to-route extrapolation.

As adverse effects on fertility and development were observed, DNELs for these end-points will also be calculated for the dermal, inhalation and oral routes and compared with the respective systemic DNELs.

The following DNELs were derived for workers and the general population:

- acute inhalation exposure (15 minutes);
- long-term inhalation local / systemic exposure;
- long-term dermal systemic exposure;
- long-term oral systemic exposure (general population only).

In the absence of good quality data to inform on dermal absorption in rats and humans, default values of 100% for both species will be used. As there was no information to inform on oral and inhalation absorption values, the default values of 100% for both will be used, except for extrapolation from the oral route to the inhalation route, in which case the worst-case scenario of 50% oral absorption and 100% inhalation absorption will be assumed.

5.12.2.1 Workers

Worker long-term local/systemic inhalation

In a 28-day inhalation study in rats, the critical effect for inhalation exposure was local irritation of the respiratory tract.

An indicative occupational exposure limit (IOELV) is in place for MEA (Directive 2006/15/EC). This IOELV is based on a recommendation for an OEL made by SCOEL in 1996. SCOEL used a LOAEC of 5 ppm (13 mg/m^3) from an inhalation study in rats, dogs and guinea pigs. Irritation and behavioural changes (lethargy after two to three weeks of exposure) were the critical effect. This LOAEC was very close to the NOAEC of 10 mg/m^3 from the 28-day inhalation study included in the registration dossier. SCOEL then applied an uncertainty factor of 5 to account for the extrapolation from animals to humans, resulting in an 8-hour time-weighted average of 1 ppm (2.5mg/m^3). Given the minimal nature of the adverse effects at the LOAEL of 50 mg/m^3 in the 28-day inhalation study (level I and II sub-mucosal inflammation and level I and II squamous metaplasia in a few animals), the eMSCA considers that the IOELV is an appropriate value to use for workers in the risk characterisation.

DNEL derived by Registrants

The starting point used by the Registrants was the NOAEC of 10 mg/m^3 from the 28-day inhalation study. The DNEL was 3.3 mg/m^3.

Worker acute inhalation

The use pattern of MEA (section 9.1) indicates that peak inhalation exposures are possible. The Registrants did not derive a DNEL for acute inhalation exposure, on the basis that the acute inhalation toxicity studies included in the registration dossier did not show a hazard for acute inhalation toxicity. However, MEA has a harmonised classification for acute toxicity by the inhalation route based on weight-of-evidence from additional studies that were not included in the registration dossier. Therefore, the eMSCA considers that a DNEL for acute inhalation exposure should be given.

The acute inhalation studies employed single doses and the exposure levels were not always accurately determined; therefore, they are not suitable for the setting of a DNEL.

SCOEL recommended a short-term exposure limit (15 minutes) of 3 ppm (7.6 mg/m^3) when considering an OEL. Given the minimal nature of the adverse effects at the LOAEC of 50 mg/m^3 in the 28-day inhalation study (level I and II sub-mucosal inflammation and level I and II squamous metaplasia in a few animals), the eMSCA considers that the IOELV is an appropriate value to use for workers in the risk characterisation.

Worker long-term dermal systemic

Calculated from oral two-generation reproduction study (NOAEL 300 mg/kg/d)

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

= 300 mg/kg/d x 100/100 = 300 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	2	Adjustment for sub-chronic to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

Worker DNEL long-term dermal - systemic = 300/ 100 = **3 mg/kg/d**

Calculated from oral developmental toxicity study in rats (NOAEL 120 mg/kg/d)

Two oral developmental toxicity studies in rats are available, each giving NOAEL values for systemic (maternal) toxicity of 120 mg/kg/d and with LOAELs of 450 mg/kg/d and 300 mg/kg/d.

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

= 120 mg/kg/d x 100/100 = 120 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for

		remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	6	Adjustment for sub-acute to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*300*	

Worker DNEL long-term dermal - systemic = 120/ 300 = **0.4 mg/kg/d**

The LOAEL from this developmental toxicity study was 300 mg/kg/d (reduced food consumption, lower mean bodyweights and impaired body weight gain). Another oral developmental study in rats was available, also with a NOAEL of 120 mg/kg/d but a LOAEL of 450 mg/kg/d (reduced food consumption, lower mean bodyweights and impaired body weight gain). Given the dose spacing in these studies and the absence of adverse effects at 300 mg/kg/d in a study of longer duration (the two-generation study), the DNEL of 3 mg/kg/d is considered to be the most appropriate.

DNEL derived by Registrants

The Registrants extrapolated from the 28-day inhalation study to the dermal exposure route. The DNEL derived was 0.38 mg/kg/d.

Worker fertility, inhalation exposure

A NOAEL for fertility effects of 300 mg/kg/d was obtained from the oral two-generation study in rats.

NOAEC = 300 x (1/0.38) x (50/100) x (6.7/10)

= 264.47 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that might occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*12.5*	

Worker DNEL inhalation – fertility = 264.47 /12.5 = **21.2 mg/m^3**

Worker fertility, dermal exposure

The NOAEL of 300 mg/kg/d for fertility effects from the oral two-generation study in rats will be used as the starting point (no modification of the dose descriptor necessary).

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*50*	

Worker DNEL dermal – fertility = 300/50 = **6 mg/kg/d**

Worker developmental toxicity, inhalation exposure

Taking into account dose spacing, the highest NOAEL for developmental effects was 500 mg/kg/d from an oral developmental toxicity study in rats.

NOAEC = 500 x (1/0.38) x (50/100) x (6.7/10)

= 440 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*12.5*	

Worker DNEL inhalation – developmental toxicity = 440 /12.5 = **35.2 mg/m^3**

Worker developmental toxicity, dermal exposure

Taking into account dose spacing, the highest NOAEL for developmental effects was 500 mg/kg/d from an oral developmental toxicity study in rats. No modification of the starting dose is required.

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	5	Default value for workers
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*50*	

Worker DNEL dermal – developmental toxicity = 500 / 50 = **10 mg/kg/d**

5.12.2.2 General population

General population long-term local / systemic inhalation

In a 28-day inhalation study in rats, the critical effect for inhalation exposure was local irritation of the respiratory tract.

An indicative occupational exposure limit (IOELV) is in place for MEA (Directive 2006/15/EC). This IOELV is based on a recommendation for an OEL made by SCOEL in 1996. SCOEL used a LOAEC of 5 ppm (13 mg/m^3) from an inhalation study in rats, dogs and guinea pigs. Irritation and behavioural changes (lethargy after two to three weeks of exposure) were the critical effect. This LOAEC was very close to the NOAEC of 10 mg/m^3 from the 28-day inhalation study included in the registration dossier. SCOEL then applied an uncertainty factor of 5 to account for the extrapolation from animals to humans, resulting in an 8-hour time-weighted average of 1 ppm (2.5mg/m^3) for occupational exposures. Given the minimal nature of the adverse effects at the LOAEC of 50 mg/m^3 in the 28-day inhalation study (level I and II sub-mucosal inflammation and level I and II squamous metaplasia in a few animals), the eMSCA considers that the IOELV is an appropriate value to use in the risk characterisation.

To take account of the greater intra-species variability of the general population compared with workers, an additional factor of 2 will be applied to the 8-hour TWA of 2.5 mg/m^3, giving a value of 1.25 mg/m^3 (0.5 ppm). Adjustment of the 8-hour TWA to 24 hours (0.5 ppm x 8 hours / 24 hours = 0.2 ppm) gives a value of 0.5 mg/m^3. This value will be used by the eMSCA.

DNEL derived by Registrants

The starting point used by the Registrants was the NOAEC of 10 mg/m^3 from the 28-day inhalation study. The DNEL was 2 mg/m^3.

General population acute inhalation

The use pattern of MEA (section 9.1) indicates that general population peak inhalation exposures might be possible.

The eMSCA notes an indicative occupational exposure limit (IOELV) is in place for MEA (Directive 2006/15/EC). This IOELV is based on a recommendation for an OEL made by SCOEL in 1996. SCOEL used a LOAEC of 5 ppm (13 mg/m^3) from an inhalation study in rats, dogs and guinea pigs. Irritation and behavioural changes (lethargy after two to three weeks of exposure) were

the critical effect. This LOAEC was very close to the NOAEC of 10 mg/m^3 from the 28-day inhalation study included in the registration dossier. SCOEL then applied an uncertainty factor of 5 to account for the extrapolation from animals to humans, resulting in an 8-hour time-weighted average of 1 ppm (2.5 mg/m^3). A short-term exposure limit (15 minutes) of 3 ppm (7.6 mg/m^3) was recommended. Given the minimal nature of the adverse effects at the LOAEC of 50 mg/m^3 in the 28-day inhalation study (level I and II sub-mucosal inflammation and level I and II squamous metaplasia in a few animals), the eMSCA considers that the IOELV is an appropriate value to use in the risk characterisation.

To take account of the greater intra-species variability of the general population compared with workers, an additional assessment factor of 2 will be applied to the STEL (15 minutes) of 7.6 mg/m^3, giving a value of 3.8 mg/m^3.

General population long-term dermal systemic

Calculated from oral two-generation reproduction study (NOAEL 300 mg/kg/d)

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

= 300 mg/kg/d x 100/100 = 300 mg/kg/d

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	2	Adjustment for sub-chronic to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*200*	

General population DNEL long-term dermal - systemic= 300 / 200 = **1.5 mg/kg/d**

DNEL derived by Registrants

The Registrants extrapolated from the 28-day inhalation study to the dermal exposure route. The DNEL calculated by the Registrants was 0.24 mg/kg/d.

General population long-term oral systemic

Calculated from oral two-generation reproduction study in rats (NOAEL for systemic toxicity 300 mg/kg/d)

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	2	Adjustment for sub-chronic to chronic

Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*200*	

General population DNEL long-term oral = 300/200 = **1.5 mg/kg/d**

Calculated from oral developmental toxicity study in rats (NOAEL for systemic effects 120 mg/kg/d)

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	6	Adjustment for sub-acute to chronic
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*600*	

General population DNEL long-term oral = 120/600 = **0.2 mg/kg/d**

The LOAEL from this developmental toxicity study was 300 mg/kg/d (reduced food consumption, lower mean bodyweights and impaired body weight gain). Another oral developmental study in rats was available, also with a NOAEL of 120 mg/kg/d but a LOAEL of 450 mg/kg/d (reduced food consumption, lower mean bodyweights and impaired body weight gain). Given the dose spacing in these studies and the absence of adverse effects at 300 mg/kg/d in a study of longer duration (the two-generation study), the DNEL of 1.5 mg/kg/d from this study will be taken forward.

DNEL derived by the Registrants

The Registrants use the NOAEL of 300 mg/kg/d from the two-generation reproduction study as the starting point. The DNEL derived by the Registrants was 3.75 mg/kg/d.

General population fertility, inhalation exposure

A NOAEL for fertility effects of 300 mg/kg/d was obtained from the oral two-generation study in rats.

NOAEC = 300 x (1/1.15) x (50/100)

= 130.4 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	10	Default value for general population

Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*25*	

General population DNEL inhalation – fertility = 130.4 / 25 = **5.2 mg/m^3**

General population fertility, dermal exposure

The NOAEL of 300 mg/kg/d for fertility effects from the oral two-generation study in rats will be used as the starting point (no modification of the dose descriptor necessary).

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL dermal – fertility = 300/100 = **3 mg/kg/d**

General population fertility, oral exposure

The NOAEL of 300 mg/kg/d for fertility effects from the oral two-generation study in rats will be used as the starting point (no modification of the dose descriptor necessary).

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL oral – fertility = 300 / 100 = **3 mg/kg/d**

General population developmental toxicity, inhalation exposure

Taking into account dose spacing, the highest NOAEL for developmental effects was 500 mg/kg/d from an oral developmental toxicity study in rats.

NOAEC = 500 x (1/1.15) x (50/100)

= 217.4 mg/m^3

Assessment factors:

Inter-species differences	2.5	No allometric scaling for inhalation exposure, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*25*	

General population DNEL inhalation – developmental toxicity = 217.4 / 25 = **8.7 mg/m^3**

General population developmental toxicity, dermal exposure

Taking into account dose spacing, the highest NOAEL for developmental effects was 500 mg/kg/d from an oral developmental toxicity study in rats. No modification of the starting dose is required.

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL dermal – developmental toxicity = 500 / 100 = **5 mg/kg/d**

General population developmental toxicity, oral exposure

Taking into account dose spacing, the highest NOAEL for developmental effects was 500 mg/kg/d from an oral developmental toxicity study in rats. No modification of the starting dose is required.

Assessment factors:

Inter-species differences	10	4 for allometric scaling rat to human, 2.5 for remaining differences
Intra-species differences	10	Default value for general population
Duration of exposure	1	No adjustment for effects that may occur after a single exposure
Dose-response	1	Clear NOAEL identified
Quality of the database	1	Quality of the database is adequate
Overall assessment factor	*100*	

General population DNEL oral – developmental toxicity = 500 / 100 = **5 mg/kg/d**

5.12.2.3 Summary of lowest DNELs for each exposure pattern calculated by eMSCA

The eMSCA identified the following DNELS as the lowest for each exposure pattern.

Table 19. Summary of the lowest DNELS for each exposure pattern

Exposure pattern	**Study**	**Modified NOAEL / NOAEC**	**AF**	**DNEL**
Worker DNEL long-term inhalation – local/systemic	IOELV: 8-hour TWA	13 mg/m^3	5	2.5 mg/m^3
Worker DNEL acute inhalation	IOELV: STEL	13 mg/m^3	5	7.6 mg/m^3
Worker DNEL long-term dermal - systemic	Two-generation reproduction study in rats	300 mg/kg/d	100	3 mg/kg/d
Worker DNEL inhalation – fertility	Two-generation reproduction study in rats	264.47mg/m^3	12.5	21.2 mg/m^3
Worker DNEL dermal – fertility	Two-generation reproduction study in rats	300 mg/kg/d	50	6 mg/kg/d
Worker DNEL inhalation – developmental toxicity	Oral developmental toxicity study in rats	440.47mg/m^3	12.5	35.2 mg/m^3
Worker DNEL dermal – developmental toxicity	Oral developmental toxicity study in rats	500 mg/kg/d	50	10 mg/kg/d

General population DNEL long-term inhalation – local / systemic	IOELV: 8-hour TWA adjusted to 24 hours	13 mg/m^3	10	0.5 mg/m^3
General population DNEL acute inhalation	IOELV: STEL	13 mg/m^3	10	3.8 mg/m^3
General population DNEL long-term dermal - systemic	Two-generation reproduction study toxicity study in rats	300	200	1.5 mg/kg/d
General population DNEL long-term oral	Two-generation reproduction study in rats	300 mg/kg/d	200	1.5mg/kg/d
General population DNEL inhalation – fertility	Two-generation reproduction study in rats	130.4 mg/m^3	25	5.2 mg/m^3
General population DNEL dermal – fertility	Two-generation reproduction study in rats	300 mg/kg/d	100	3 mg/kg/d
General population DNEL oral – fertility	Two-generation reproduction study in rats	300 mg/kg/d	100	3mg/kg/d
General population DNEL inhalation – developmental toxicity	Oral developmental toxicity study in rats	217.4 mg/m^3	25	8.7 mg/m^3
General population DNEL dermal – developmental toxicity	Oral developmental toxicity study in rats	500 mg/kg/d	100	5 mg/kg/d
General population DNEL oral – developmental toxicity	Oral developmental toxicity study in rats	500 mg/kg/d	100	5 mg/kg/d

As the DNEL for local inhalation effects is protective of systemic effects and the long-term systemic DNELs are protective for fertility and developmental effects, the following DNELs will be used by the eMSCA in the risk characterisation.

Worker DNEL acute inhalation	7.6 mg/m^3
Worker DNEL long-term inhalation – local/systemic	2.5 mg/m^3
Worker DNEL long-term dermal – systemic	3 mg/kg/d
General population DNEL acute inhalation	3.8 mg/m^3

General population DNEL long-term inhalation – local/systemic	0.5 mg/m^3
General population DNEL long-term dermal – systemic	1.5 mg/kg/d
General population DNEL long-term oral	1.5 mg/kg/d

A qualitative approach to the risk management of eye and skin corrosivity is recommended.

The Registrants used the following DNELs in their risk characterisation.

Registrants' DNELs	**Value**
Worker long term inhalation local effects DNEL	3.3 mg/m^3
Worker long-term systemic dermal NOAEL	1 mg/kg bw/day
General population long term oral systemic DNEL	3.75 mg/kg bw/day
General population long term inhalation local/systemic DNEL	2 mg/m^3
General population long-term systemic dermal NOAEL	0.24 mg/kg bw/day

5.13 Conclusions of the human health hazard assessment and related classification and labelling

With the exception of respiratory sensitisation, the only information available to address the potential human health risks of MEA comes from studies in animals. MEA has already been classified under Annex I of Directive 67/548/EEC as Xn R 20/21/22. The data evaluated by the eMSCA are consistent with this classification, which is equivalent to CLP Acute tox category 4; H302, CLP Acute tox category 4; H332 and CLP Acute Tox. 4 - H331.

The initial ground for concern for MEA was the potential for it to induce occupational asthma, based on its listing by the CSST (Commission de la santé et de la sécurité du travail) (updated April 2010). The CSST document also lists MEA as a skin sensitiser.

The UK's Health and Safety Executive produced a document 'Asthmagen? Critical assessments of the evidence for agents implicated in occupational asthma' (last updated 2001). This document contains the assessments of various substances including MEA. It concludes that in contrast to the widespread use of MEA, the number of reports of occupational asthma was small, and the findings of the studies available do not provide good evidence that ethanolamine can induce occupational asthma, so that there was insufficient evidence to conclude that MEA meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma). The eMSCA finds no additional data to alter the conclusion made in this document.

No conventional repeated dose toxicity studies with MEA were provided. An oral two-generation reproduction toxicity study according to OECD 416 with MEA HCl was provided to meet this requirement. The epididymis was a clear target organ, accompanied by reduced kidney and prostate weights. The Registrant supplied a modern 28 days' inhalation toxicity study performed according to OECD guideline 412. There was no evidence of systemic toxicity in this study at the top dose of 150 mg/m^3 MEA however there were a range of adverse morphological changes of epithelia in the nasal cavity and in the larynx, trachea and lung (including epithelial necrosis, inflammation, metaplasia, haemorrhage in the nasal cavity; necrosis, inflammation, metaplasia, cellular atypia and hyperplasia of the laryngeal epithelium; degeneration and hyperplasia of the respiratory epithelia in

the trachea; and hyperplasia of the bronchiolar epithelium of the lungs). There was no evidence from the repeat dose toxicity studies that classification is required.

The *in vitro* genotoxicity of MEA has been investigated in three bacterial reverse mutation assays, a chromosome aberration assay in rat hepatocytes and two mammalian cell gene mutation assays (mouse lymphoma (L5178Y) and Chinese hamster lung fibroblasts (V79). Negative results were reported in all studies. Negative results were also obtained from an *in vivo* mouse micronucleus test where clear signs of substance related toxicity were observed at the top dose (mortalities). Based on the available data, the evaluating Member State agrees with the Registrants that no classification is required in accordance with CLP and no further testing is required.

No reliable data on carcinogenicity of MEA are available for assessment. The eMSCA notes that no effects of concern for systemic carcinogenicity (hyperplasia, pre-neoplastic changes) were observed in the available 28-day inhalation study or two-generation reproductive toxicity study, and MEA was clearly negative in the submitted genotoxicity studies. Hyperplasia and metaplasia, observed in repeat dose inhalation studies, were considered of limited relevance to humans, considering the corrosive / irritant nature of MEA.

No further information on carcinogenicity is requested under this substance evaluation.

No concerns for reproductive toxicity were identified.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

MEA is a clear, viscous liquid of aminic odour with a boiling point of 167 °C. It is non-flammable with a flashpoint of 91 °C, and does not possess explosive or oxidising properties. On the basis of its chemical structure (i.e. non-hydrocarbon) MEA is not considered to be an aspiration hazard, and partition coefficient n-octanol/water (log value) data demonstrates that there is no potential for accumulation in fat/bioaccumulation. Based on the available data, MEA does not meet the criteria for classification for any physico-chemical properties/endpoints.

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

Reliable key aquatic toxicity information from the REACH Registration is presented in Table 20 below. As MEA is not an environmental priority for evaluation, only a brief review is provided. The eMSCA is aware that the Registrant has identified additional aquatic and terrestrial ecotoxicity and fate studies. These are not considered to affect PNECs and have not been reviewed at this time.

Table 20: Summary of relevant information on aquatic toxicity

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	End-point	Toxicity (mg/l)	
Acute toxicity to fish Equivalent to OECD Guideline 203, GLP Registrant reliability: 1	Common Carp (*Cyprinus carpio*)	Mortality	Semi-static, pH 7.8-10.3	96 hours	LC_{50}	349 (measured) 95% CI 280-500 mg/l	See confidential annex
Fish, Early-Life Stage Toxicity Test, OECD Guideline 210 Registrant reliability: 2	Japanese Rice Fish (*Oryzias latipes*)	Body length and weight	Flow-through	41 days	NOEC	1.24 (mm)	NITE, 2008 NITE, 2013a See confidential annex
Daphnia sp Acute Immobilisation Equivalent to OECD Guideline, 202 GLP Registrant reliability: 2	*Daphnia magna*	Acute immobilisation	Static	48 hours	EC_{50}	65 (n)	See confidential annex
Daphnia sp Acute Immobilisation OECD Guideline, 202, GLP Registrant reliability: 2	*Daphnia magna*	Acute immobilisation	Semi-static	48 hours	EC_{50}	97.26 (n)	NITE, 1997c NITE, 2013c US EPA 2013d
Daphnia sp Acute Immobilisation In house method Registrant reliability: 2	*Daphnia magna*	Acute immobilisation	Static	48 hours	EC_{50}	36.2 (n)	PCA Services, Inc., 2008 See confidential annex
Daphnia magna Reproduction OECD Guideline 202 (1984), GLP Registrant reliability: 2	*Daphnia magna*	Survival; reproduction; growth	Semi-static, pH 7.4-10	21 days	NOEC	0.85 (twa)	NITE, 1997d NITE, 2013d See confidential annex
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP Registrant reliability: 2	*Pseudo-kirchneriella subcapitata* (formerly *Selenastrum capricornutum*)	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	2.8 (n) 1 (n)	NITE, 1997e NITE, 2013e US EPA 2013f
Freshwater Algal Growth Inhibition OECD Guideline 201 Registrant reliability: 1	*Desmodesmus subspicatus* (formerly *Scenedesmus subspicatus*)	Cell multiplication inhibition	Static	72 hours	ErC_{50} EC_{10}	22 (n) 8.5 (n)	See confidential annex

n refers to nominal
mm refers to mean measured
twa refers to time weighted average

Additional unpublished references given in the confidential annex.

7.1.1 Toxicity data

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

The Registrant uses an Assessment Factor of 10 as chronic data are available for three trophic levels, and the 21-d *Daphnia* NOEC of 0.85 mg/l to derive the freshwater aquatic PNEC as 0.085 mg/l.

Assuming an additional factor of 10, the marine aquatic PNEC is 0.0085 mg/l

7.1.2.2 PNEC sediment

The Registrant uses the Equilibrium Partitioning Method (EPM) to derive the freshwater sediment PNEC as 0.0942 mg/kg wet weight (0.4342 mg/kg dry weight), and the marine sediment PNEC as 0.00942 mg/kg wet weight (0.0434 mg/kg dry weight).

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

No data available.

7.2.1.2 Toxicity to terrestrial plants

Two publications are available and included in the Registration (Bergmann and Eckert, 1990; and Bergmann *et al*, 1991) considering the effect of MEA on barley and rye. In each study a positive effect was observed and adverse effects were not noted. As MEA is rapidly degradable, studies have not been evaluated by the eMSCA.

7.2.1.3 Toxicity to soil micro-organisms

No data available.

7.2.1.4 Toxicity to other terrestrial organisms

No further data available.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC soil)

The Registrant uses the Equilibrium Partitioning Method (EPM) to derive the soil PNEC as 0.0325 mg/kg wet weight (0.0367 mg/kg dry weight).

7.3 Atmospheric compartment

MEA is not considered to be an ozone depleting or greenhouse gas so the eMS has not considered this compartment further.

7.4 Endocrine disrupting properties

Endocrine disrupting properties are not considered in the Registration or CSRs. Therefore this endpoint has not been evaluated further by the eMSCA.

7.5 Microbiological activity in sewage treatment systems

7.5.1 Toxicity to aquatic micro-organisms

From the REACH Registration, a 3 hour IC_{50} of >1,000 mg/l is available for domestic activated sludge following OECD Test Guideline 209 (Klecka *et al,* 1984).

7.5.2 PNEC for sewage treatment plant

Using as Assessment Factor of 10, the STP PNEC is 100 mg/l.

7.6 Non compartment specific effects relevant for the food chain (secondary poisoning)

Not relevant.

7.6.1 Toxicity to birds

No data available.

7.6.2 Toxicity to mammals

No data available.

7.6.3 Calculation of PNECoral (secondary poisoning)

MEA has a low bioaccumulation potential and is rapidly degradable. It is not considered to meet relevant human health classification criteria for carcinogenicity, mutagenicity or reproduction. Given the low potential for bioaccumulation, exposure of predators is considered low. On this basis a secondary poisoning scenario is not considered necessary by the Registrant. The eMSCA agrees with this assessment.

7.7 Conclusion on the environmental hazard assessment and on classification and labelling

MEA has a harmonised classification (603-030-00-8) as not classified for the environment.

Newly available data include chronic NOECs is the range 0.1 to 1.0 mg/l for invertebrates and algae. MEA is considered rapidly degradable. These data are reflected in the current REACH Registration self-classification of Aquatic Chronic 3.

8 PBT AND VPVB ASSESSMENT

8.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

8.1.1 Persistence assessment

MEA is considered rapidly degradable and therefore is not considered persistent.

8.1.2 Bioaccumulation assessment

MEA has a low measured logK_{ow} below 4.5 and predicted BCFs below 2000. Therefore it is not considered bioaccumulative.

8.1.3 Toxicity assessment

Acute and chronic ecotoxicity data are available for MEA for three trophic levels. The lowest NOEC is 0.85 mg/l which is does not meet the screening criteria of ≤ 0.01 mg/l.

MEA is not classified for human health as carcinogenic, mutagenic or reprotoxic.

Therefore MEA is not considered toxic.

8.1.4 Summary and overall conclusions on PBT and vPvB Properties

MEA is not considered by the Registrant to be PBT or vP/vB. The eMSCA agrees with this assessment.

9 EXPOSURE ASSESSMENT

9.1 Human Health

MEA is an amino alcohol. In addition to its use as an intermediate in the manufacture of other substances, it has surfactant properties, it can be used as an emulsifier and functions as a weak base. These properties mean that it is used in a wide range of applications including washing and cleaning products, inks and toners, biocides, fuels, cosmetics and personal care products, metal working fluids, coating products and polymers. The ability of MEA to function as a weak base is exploited in gas scrubbing systems where it is used to remove carbon dioxide (CO_2) and hydrogen sulphide (H_2S) from mixed gas streams. This property also means that it is used as a buffering agent and a corrosion inhibitor. MEA is not supplied to consumers as the substance itself, but products containing MEA are available to consumers.

In July 2016, when this report was finalised, ECHA had received one joint submission covering 100,000 – 1,000,000 tonnes per annum (tpa) and three opt out submissions. Of these, two are reduced data packages submitted for use as an intermediate under strictly controlled conditions and one covers supply at 1-10 tpa. Of these dossiers, only the exposure and use information from the 22 registrations that were active during the initial assessment period was evaluated. New Registrants first submitting registrations after 7th May 2015 (the date the draft decision was sent to active Registrants for comment – see the Executive Summary, Procedure for more details) have not been included in the evaluation because their dossiers had not been submitted to ECHA by the time of the initial assessment and they were not part of the decision making process that was initiated in May 2015.

The 22 Registrants from the joint submission can be divided into two groups according to the timeliness with which they have updated their registrations. A group of 15 Registrants have updated their dossiers since the initial assessment period. All CSRs in this group follow the approach being taken by the lead Registrant. A separate group of 7 Registrants who's CSRs follow an early version of the lead Registrant's CSR which was submitted before the evaluation began, did not update their registrations in response to the evaluation and have not given any information to the eMSCA about their intentions to update their dossier. To distinguish between the two groups, this group of 7 will be referred to as non-updating Registrants in this report.

As a consequence of the different approaches to updates, there are differences between Registrants in the scenarios that are covered and, for some uses covered by all Registrants, differences in the PROC codes that have been assigned. The Information Requirements and Chemical Safety Assessment (IR&CSA) Guidance Part D, section D.1.3 indicates that registrations should clearly identify which uses are covered by the joint submission and which uses are covered separately to ensure accurate information is available.

9.1.1 Exposure assessment for worker

9.1.1.1 Overview of uses and exposure scenarios

Tables 21 and 22 identify the scenarios listed on ECHA's dissemination site for the joint and opt out submissions respectively. Table 21 also identifies the differences in the scenarios and PROC codes covered by the two groups of Registrants that are part of the joint submission.

Table 21: Scenarios and PROC codes covering workplace uses assessed in the joint submission.

Description	Process (PROC) code	
	Group of 15 Registrants	Additional PROC codes supported by the group of 7 non-updating Registrants
Manufacture of MEA.	1, 2, 3, 4, 8a, 8b, 9, 15	
Formulation of products containing MEA.	1, 2, 3, 4, 5, 8a, 8b, 9	
Professional use in formulation of mixtures	3, 4, 5, 8a, 8b, 9	
Industrial use in the manufacture of another substance (use as an intermediate).	1, 2, 3, 8a, 8b, 9	15
Industrial use in construction chemicals (e.g. cement and concrete)	7, 8a, 8b, 10, 13, 14, 15	
Professional use as an additive in construction chemicals (e.g. cement and concrete)	5, 8a, 10, 11, 13	19, 21, 24
Industrial use for gas treatment	1, 2, 3, 8a, 8b	5, 22, 23
Industrial use for water treatment	1, 2, 3, 4, 8a, 8b, 13	5, 22, 23
Industrial use in metal working fluids	2, 5, 8a, 8b, 10, 13, 17, 18	3, 7,
Professional use in metal working fluids	5, 8a, 8b, 10, 13, 17, 18, 20	2, 3
Industrial use in electroplating/electronics	2, 3, 5, 8b, 9, 13	7, 8a, 10, 17, 18
Industrial use as an additive in PU systems	5, 7, 8a, 8b, 9, 10, 13, 14, 15	
Professional use as an additive in PU systems	5, 8a, 8b, 10, 11, 13, 14, 15	
Industrial use as a processing aid for paper, textiles and leather	2, 4, 7, 8a, 8b, 9, 10, 13	
Industrial use in detergents, cleaners and ink removers	3, 4, 8a, 8b	7, 10, 13,19

Professional use in detergents, cleaners and ink removers	3, 8a, 10, 11, 13, 19	
Industrial use in biocidal products (e.g. wood protection)	1, 3, 5, 8a, 8b, 9, 13, 15	
Professional use in biocidal products (e.g. wood protection)	1, 3, 4, 5, 8a, 10, 11, 13	
Industrial use in coatings including printing inks	1, 2, 3, 4, 5, 7, 8a, 8b, 10, 13, 15	
Professional use in coatings including printing inks	1, 2, 3, 4, 5, 8a, 8b, 9, 10, 11, 13, 15, 19	
Industrial use in oilfield chemicals	1, 2, 3, 4, 8a, 8b	
Professional use in oilfield chemicals	1, 2, 3, 4, 8a	
Industrial use in adhesives and sealants	1, 2, 4, 5, 7, 8b, 9, 10, 13, 15, 17, 19	
Professional use in adhesives and sealants	2, 8b, 9, 10, 11, 13, 15, 17, 19	
Industrial use as a laboratory chemical	15	
Professional use as a laboratory chemical	15	
Industrial use as a processing aid (not becoming part of articles)	1, 2, 3, 4, 5, 8a, 8b, 9, 15	
Industrial use as an additive in plastic e.g. rubber	Uses not covered in CSRs	14
Professional use as an additive in plastic e.g. rubber		14
Industrial use as an additive in fuel		2, 3, 4, 8a, 8b, 16, 19,
Professional use as an additive in fuel		2, 3, 4, 8a, 8b, 16, 19,
Industrial use of fuel		8a, 8b, 16, 19
Professional use of fuel		8a, 8b, 16, 19
Professional use as a processing aid for paper, textiles and leather		10, 13
Professional use in electroplating/electronics		8a, 8b, 10, 13, 17, 18

Table 22: Scenarios and PROC codes covered in the two opt-out submissions which were included in the evaluation

Description	Process (PROC) code
Submission covering 1 - 10 tpa	
Formulation of preparations	2, 3, 4, 8b
Professional use as a laboratory chemical	8a, 8b, 9, 15
Professional use in the manufacture of other reagents (small volume)	8a
Submission covering use as an intermediate only	
Manufacture under strictly controlled conditions	1, 2
Industrial use resulting in the manufacture of another substance under strictly controlled conditions	1

9.1.1.2 Scope and type of exposure

The worker exposure assessment and risk characterisation are based on modelled data. For workers, the Registrants have derived a long-term local/systemic DNEL covering the inhalation route and a long-term systemic DNEL covering the dermal route. A qualitative assessment has been provided to address the hazards of skin corrosivity and eye damage.

However, although the substance has harmonised classifications for acute toxicity (Acute Tox. 4; H302, H312, H332) and respiratory tract irritation (STOT SE 3; H335), these hazards do not appear to have been covered either quantitatively or qualitatively in the Registrants' assessments.

Note to Registrants: It is important that registrations are transparent about the way identified hazards have been taken into account in the risk assessment because information from registrations is used by authorities to make decisions on the need for regulatory action. All registrants should ensure that their assessments cover all identified hazards. Further advice on the scope of the exposure assessment is available in the IR & CSA Guidance part D, section D.2.3.

9.1.1.2.1 Monitoring data

No worker exposure monitoring data were provided.

9.1.1.2.2 Modelled data

The Registrants carried out and summarised worker exposure estimates for the individual process categories (PROC) within each exposure scenario using the models described below.

Table 23: Overview of modelling tools used by the Registrants and the eMSCA

Process	Model used by Registrants	Model used by eMSCA to verify calculations
All worker exposure scenarios assessed by the group of 15 Registrants	Easy TRA version 4.0.0 using the Registrant's proposed exact	ECETOC TRA version 3 modified to replicate the Registrant's calculations by

other than contributing scenarios involving aerosol-forming activities	substance concentrations for each use (rather than the ECETOC category approach) and non-standard glove protection factors	using: • the exact substance concentrations proposed by the Registrants for each use (rather than the standard category approach in the model)[a] • the glove protection factors proposed by the Registrants where these exceed the standard upper value (90%) in the model for professional situations
Contributing scenarios for aerosol-forming activities (PROC codes 7, 11, 17 and 18) assessed by the group of 15 Registrants.	Advanced REACH Tool (ART) version 1.5 As ART only predicts inhalation exposure, it is unclear how the Registrants predicted dermal exposure for these activities.	Advanced REACH Tool (ART) version 1.5 for inhalation exposure. ECETOC TRA version 3 for dermal exposure modified to replicate the Registrant's calculations by using: • the exact substance concentrations proposed by the Registrants for each use (rather than the standard category approach in the model)[a] • the glove protection factors proposed by the Registrants where these exceed the standard upper value (90%) in the model for professional situations
All worker exposure scenarios assessed by the group of 7 non-updating Registrants.	ECETOC TRA version 2	ECETOC TRA version 2 modified to replicate the Registrant's calculations by using: • the exact substance concentrations proposed by the Registrants for each use (rather than the standard category approach in the model)[a] • the glove protection factors proposed by the Registrants (ECETOC TRA version 2 does not include a standard option for the use of protective gloves)[b]

[a] For those scenarios which were predicted to result in a Risk Characterisation Ratio ≥ 1, the eMSCA has presented additional calculations using the default concentration ranges in the tool.

[b] To make this modification the eMSCA has assumed that all dermal exposure will occur on the hands / wrists.

The eMSCA confirmed that the modelling approaches and input parameters used by individual members of the joint submission in their CSRs matched the calculations presented in versions of the lead Registrant's CSR.

The eMSCA attempted to replicate the worker exposure calculations provided by the Registrants using the same tools used by each Registrant. Since the eMSCA does not have access to the Easy TRA tool, which is an adaptation of the ECETOC TRA tool, the eMSCA used the ECETOC TRA tool version 3 to replicate calculations performed with the Easy TRA tool. The eMSCA confirmed that the scenarios for which the ECETOC TRA tool version 3 and ART version 1.5 have been used are within the stated range of applicability for these tools.

Using the information provided by the Registrants on model inputs, the eMSCA tried to replicate the Registrants' estimates. Of the 211 worker exposure calculations presented in the updated CSR, the eMSCA has been able to fully reproduce both the Registrants' inhalation and dermal exposure values for 208 contributing scenarios. Of the 52 worker exposure calculations presented exclusively CSRs from non-updating Registrants, the eMSCA has been able to fully reproduce both the Registrants' inhalation and dermal exposure values for only 36 contributing scenarios.

Although the eMSCA was not able to replicate the values being used by the Registrants in every case, in many cases the eMSCA's calculations resulted in smaller values implying that the Registrants are taking a precautionary approach. There were only three instances where the eMSCA calculated higher exposure values. These included: (1) a contributing scenario (PROC 19) relating to professional use in construction chemicals covered only by non-updating Registrants, (2) a contributing scenario (PROC 17) relating to industrial use in adhesives and sealants and (3) a contributing scenario (PROC 10) relating to professional use in adhesives and sealants. It was unclear why the Registrants' calculations in these situations deviated from those of the eMSCA.

Most of the scenarios covered in MEA registrations are for activities using mixtures containing MEA. The Registrants have chosen to take concentration into account by applying a linear reduction to the starting assessment rather than apply the tool defaults. This approach will produce lower exposure estimates than would be obtained using the tool defaults and is therefore less precautionary. For example, for scenarios covering use in mixtures containing up to 5%, the default concentration band adopted within the ECETOC TRA tool (1-5%) reduces the starting exposure prediction by 80% whereas using 5% concentration directly in calculations reduces the starting exposure prediction by 95%, using 2% directly reduces the starting exposure prediction by 98% and using 1% reduces the starting exposure prediction 100 fold. Tier 1 tools such as the ECETOC TRA tool use a small number of parameters to estimate exposure and because this introduces several sources of uncertainty into exposure calculations, the tool defaults are intended to produce conservative exposure estimates. To ensure the ECETOC TRA tool retains this conservatism, the developers of the ECETOC TRA tool (on which the Easy TRA is based) do not support the use of linear concentration modifiers. The eMSCA will take this deviation into account when it considers the picture presented by RCR values using the Registrants and its own exposure values.

The eMSCA also notes the Registrants' statement that ART version 1.5 has been used to calculate levels of both inhalation and dermal exposure resulting from aerosol-forming activities. This is likely to be inaccurate as ART considers only inhalation exposure. Since the exposure values could be replicated using the ECETOC TRA tool version 3 for the dermal exposure component, the eMSCA assumes that this tool was used in combination with ART version 1.5.

Note to Registrants: Modelling tools are intended to generate conservative exposure estimates providing they are used in accordance with the guidance issued by the tool developers. Applying modifiers that are not supported by the tool developers could reduce the level of conservatism in the exposure predictions. Registrants are free to choose alternative tools if necessary to refine their exposure assessments.

Looking at the duration of use assumed in the Registrant's calculations, the majority of contributing scenarios have been assessed on the basis that the activity is performed for the full shift. However, shorter durations of activity have been used for some contributing scenarios. Where this modifier is applied, the TRA tool provides an estimate of full shift exposure assuming that the only opportunity for exposure to MEA arises during this task. If this is not the case then, depending on the types of tasks and potential for exposure, additional measures may need to be implemented to protect the worker.

Note to Registrants: To ensure that companies receiving exposure scenarios including tasks assessed on a reduced duration basis implement sufficient measures to protect their workers, clarification should be provided with the scenario that the RMMs identified apply where the worker does not have further exposure to MEA during the day.

In relation to the use of the ECETOC TRA tool version 2, all worker exposure scenarios considered were within the stated range of applicability for this version of the tool other than those involving aerosol-forming processes (PROC codes 7, 11, 17 and 18). Levels of inhalation exposure resulting from these aerosol-forming processes should have been quantified using a tool that includes these processes within its applicability domain or measured data.

Note to Registrants: The IR & CSA Guidance Chapter R14, section R.14.4.6 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. Non-updating Registrants should update their CSRs with an appropriate assessment and, if necessary, amend the conditions of use described in their exposure scenarios.

All of the worker exposure estimates rely on the use of protective gloves. For industrial situations covered in the updated CSR, most of the contributing scenarios (124 out of 133) assume a glove protection of 95% with the remaining 9 contributing scenarios assuming 90% protection. For professional situations covered in the updated CSR, most of the contributing scenarios (73 out of 78) assume a glove protection of 95% with the remaining 5 contributing scenarios assuming 90% protection. For industrial situations covered only by non-updating Registrants, glove protection was assumed to be either 90% (17 out of the 27 contributing scenarios) or 98% (10 out of the 27 contributing scenarios). For professional situations covered only in the earlier (non-updated) CSR, glove protection was assumed to be either 90% (19 out of the 25 contributing scenarios), 95% (1 of the 25 contributing scenarios) or 98% (5 out of the 25 contributing scenarios). It is noted that the higher proposed levels of glove protection (>90%) for professional situations exceed the standard protection factor assumed in ECETOC TRA version 3 for professional workers. Although there is no information in the CSR to explain why varying levels of glove protection have been assumed, it is noted that the Registrants have provided the appropriate standard statements to describe the training and supervision requirements when higher levels of protection are assumed.

Note to Registrants: The IR and CSA Guidance Chapter R14, section R.14.15.3 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". In relation to the use of non-standard protection factors for gloves, Registrants should note the earlier comment about the application of non-standard modifiers to tool outputs. In accordance with the IR & CSA guidance, Registrants should ensure that any PPE that is required is sufficiently described in their registrations.

The Registrants' qualitative worker risk assessment has identified the different levels/frequencies of exposure likely to be associated with each PROC code. To avoid local, skin and eye effects the Registrants have proposed, depending on the process, the use of protective clothing, gloves and eye/face protection. The Registrants have also highlighted the need for good working practices, training and supervision. Noting the earlier comment about the need to provide sufficient information on the types of PPE that are required, the Registrants' qualitative risk assessment for local skin and eye effects is considered to be appropriate and acceptable. As previously indicated, CSRs need to be transparent about the way potential respiratory tract irritation and acute toxic effects have been addressed.

9.1.1.2.3 Comparison of monitoring and modelled data

Not relevant.

9.1.2 Exposure assessment for consumer

9.1.2.1 Overview of uses and exposure scenarios

Table 24 identifies the scenarios listed on ECHA's dissemination site for consumer use and differences between the two groups of Registrants. Consumer uses are not covered by the non-intermediate opt-out submission.

Table 24: Consumer uses assessed in the joint submission.

Description	**Product Category (PC)**	
	Group of 15 Registrants	**Group of 7 non-updating Registrants**
Consumer use in detergents, cleaners and ink removers	35	35
Consumer use in personal care products	39*	39*
Consumer use in biocidal products (e.g. wood protection)	8	8
Article service life: use in biocidal products (e.g. wood protection)	Environmental exposure assessment only	
Consumer use in coatings including printing inks	9a, 18	9a, 18
Consumer use in adhesives and sealants	1	1
Consumer use of fuel	Uses not covered in CSRs	13
Consumer use of concrete and cement		9b

* Exposure not calculated. In accordance with Article 14 (5b) of the REACH Regulation (EC) No 1907/2006, exposure estimation and risk characterisation does not need to be performed for the end use of a substance in cosmetic products within the scope of Directive 76/768/EEC.

9.1.2.2 Scope and type of exposure

The exposure assessment and risk characterisation are based on modelled data. For consumers, the Registrants have derived long-term local/systemic DNEL covering the inhalation route and long-term systemic DNELs covering the oral and dermal routes. A qualitative assessment has been provided to address the hazards of skin corrosivity and eye damage.

However, although the substance has harmonised classifications for acute toxicity (Acute Tox. 4; H302, H312, H332) and respiratory tract irritation (STOT SE 3; H335), these hazards do not appear to have been covered either quantitatively or qualitatively in the Registrants' assessments.

Note to Registrants: It is important that registrations are transparent about the way identified hazards have been taken into account in the risk assessment because information from registrations is used by authorities to make decisions on the need for regulatory action. All Registrants should ensure that their assessments cover all identified hazards. Further advice on the scope of the exposure assessment is available in the IR & CSA Guidance part D, section D.2.3.

9.1.2.2.1 Monitoring data

No exposure monitoring data were provided.

9.1.2.2.2 Modelled data

The Registrants have provided exposure estimates for each consumer exposure scenario using the model described below.

Table 25: Overview of modelling tools used by the Registrants and the eMSCA

Process	Model used by Registrants	Model used by eMSCA to verify calculations
Consumer exposure scenarios	Easy TRA version 4.0.0 (referring to ConsExpo version 4.1)	ConsExpo version 4.1

The eMSCA confirmed that the modelling approaches and input parameters used by individual members of the joint submission in their CSRs matched the calculations presented in versions of the lead Registrant's CSR.

All of the consumer exposure scenarios that have been assessed are within the stated range of applicability for the ConsExpo model.

The eMSCA has attempted to replicate the consumer exposure calculations provided by the Registrants using ConsExpo version 4.1. Although the Registrants have provided information on model inputs, the eMSCA has not been able to replicate all of the Registrant's estimates. It was also noted that several of the Registrants' estimates were based on assumptions for frequency of use,

duration of application, duration of exposure, room volume and ventilation rate which differed (generally to provide a less precautionary calculation) from the standard values proposed by the relevant ConsExpo Fact Sheets and Specific Consumer Exposure Determinants (SCEDs). Of the 14 consumer exposure calculations presented in the updated CSR, the eMSCA has been able to reproduce (but not always exactly) the Registrants' inhalation, dermal and oral exposure values for 9 contributing scenarios. Of the 4 consumer exposure calculations presented exclusively in the earlier (non-updated) CSR, the MSCA has been able to reproduce (but not exactly) the Registrants' inhalation, dermal and oral exposure values for only 1 contributing scenario.

Note to Registrants: Modelling tools are intended to generate conservative exposure estimates providing they are used in accordance with the guidance issued by the tool developers. Applying modifiers that are not supported by the tool developers could reduce the level of conservatism in the exposure predictions. Registrants are free to choose alternative tools if this is necessary to refine their exposure assessments.

A key concern that the eMSCA has identified is the fact that the Registrants have not reported 'during event' inhalation exposure values, only the 'per day' values calculated by ConsExpo. This is not the most precautionary approach for a substance such as MEA where the effect driving the risk assessment is site of contact irritation. The likelihood that adverse effects will occur depends on the concentration of MEA attained at the target site at any point in time. If exposures from short duration activities (e.g. lasting for less than one hour) are averaged over the whole day, this could result in potentially harmful exposures being assessed as safe. For this reason, the eMSCA has calculated a short-term inhalation DNEL (15-minute TWA) for consumers and has compared during event exposures with this short-term DNEL for short duration activities.

Note to Registrants: The eMSCA is concerned that the Registrants assessment is not adequate to assess the likelihood that respiratory tract irritation will be avoided in consumers using products containing MEA since this effect does not seem to be covered by either the quantitative or qualitative assessments. If there is insufficient information for authorities to conclude that safe use has been demonstrated, this could result in actions being triggered. All Registrants should ensure that their assessments cover all identified hazards. Further advice on the scope of the exposure assessment is available in the IR & CSA Guidance part D, section D.2.3.

The Registrants' qualitative consumer risk assessment has identified the uses likely to involve MEA concentrations capable of resulting in acute eye and skin effects. For these uses, the Registrants have considered the scale/frequency of use, the likelihood of splashes and aerosol formation, the level of consumer awareness of the hazards associated with the products and the likelihood that reasonable precautions will be taken by consumers to avoid skin and eye contamination. The Registrants qualitative risk assessment for skin and eye irritation is considered to be appropriate and acceptable.

9.1.2.2.3 Comparison of monitoring and modelled data

Not relevant for this evaluation.

9.1.3 Conclusion of exposure assessment – human health

The Registrants have relied on exposure modelling tools to quantify worker and consumer exposure to MEA. The eMSCA found several areas where these exposure assessments should be improved to ensure that the assessment covers all of the identified hazards. The draft decision communicated to

the Registrants on 7th May 2015 contained a number of requests to address the quality and accuracy issues with the worker and consumer exposure assessments which the Registrant's agreed to take into account in future updates. The specific issues have been highlighted in the *"Notes to Registrants"* in this chapter.

On the basis that the eMSCA has sufficient information to (i) understand the uses of MEA and (ii) carry out its own exposure assessment, it does not intend to take any further action at this time.

However, to ensure accurate information is available 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. It is therefore expected that all Registrants, including those submitting registrations for the first time after 7th May 2015, will pay particular attention to the issues noted in this report and will ensure that the findings from this substance evaluation are taken into account in their own Chemical Safety Assessments.

9.2 Environmental exposure assessment

MEA is rapidly degradable, not bioaccumulative and exhibits limited ecotoxicity. It is not considered vP/vB or PBT. Given MEA was a not an environmental CoRAP priority, a review of the environmental exposure assessment has not be undertaken by the eMSCA.

9.3 Combined exposure assessment

Combined exposure has not been addressed by the Registrants. Given that the health effects driving the risk assessment are concentration-dependent rather than dose-dependent, sequential exposures to MEA and products containing MEA are not expected to result in any increased risk compared with the "per event" risks. For this reason, the evaluating MSCA does not consider that a combined exposure assessment is relevant for MEA.

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

The eMSCA position differs in some respects from that of the Registrants. The Registrants' exposure calculations and the DNELs proposed by the Registrants, resulted in all of the exposure scenarios / contributing scenarios having risk characterisation ratios (RCR) < 1 for inhalation, dermal and total exposure. The worker long-term inhalation DNEL calculated by the Registrants of 3.3 mg/m^3 is intended to prevent local effects in the respiratory tract. However, it is slightly higher than the 8-hour TWA IOELV of 2.5 mg/m^3 (8-h TWA) listed in the 2nd IOELV directive (2006/15/EC). A 15 minute TWA IOELV of 7.6 mg/m^3 is also listed because SCOEL considered there is a need to limit peak exposures. The Registrants have not calculated a short term inhalation DNEL for MEA.

The eMSCA has not identified any information that suggests these IOELVs are insufficient to protect worker health. Since these values will have been set at levels that SCOEL considers to be protective of health the eMSCA has chosen to adopt the IOELVs as its worker long- and short-term inhalation DNELs. It has compared the exposures expected under the operating conditions (OCs) and risk management measures (RMMs) recommended by the Registrants with these occupational exposure limits.

Based on the eMSCA's exposure estimates (where these differ from those presented in the CSRs), the following exposure scenarios / contributing scenarios are predicted to result in RCRs ≥ 1.

Table 26: Worker exposure scenarios resulting in RCRs ≥1

Description	PROC code	RCR (based on evaluating MSCA's exposure estimates and DNELs)		
		Inhalation	Dermal	Total
Industrial manufacturing of the substance	2 (Use in closed, continuous process with occasional controlled exposure)	1.02 Short term[a] 1.34	0.02	1.04
Industrial formulation of mixtures	2 (Use in closed, continuous process with occasional controlled exposure)	1.02 Short term[a] 1.34	0.02	1.04
Industrial use as an intermediate	2 (Use in closed, continuous process with occasional controlled exposure)	1.01 Short term[a] 1.34	0.02	1.04
Industrial use in construction chemicals	7 (Industrial spraying): indoors, 'option A'	1.00	0.001	1.00

Industrial use in construction chemicals	7 (Industrial spraying): indoors, 'option B'	1.00	0.004	1.00
Professional use in construction chemicals	19 (Hand mixing with intimate contact)	1.27 Default[b] 5.09	0.12	1.39
Industrial use as a gas treatment	2 (Use in closed, continuous process with occasional controlled exposure)	1.02 Short term[a] 1.34	0.02	1.04
Industrial use as a water treatment	2 (Use in closed, continuous process with occasional controlled exposure)	1.02 Short term[a] 1.34	0.02	1.04
Industrial use in metal working fluids	8a (Transfer of substance or preparation…at non-dedicated facilities)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Industrial use in metal working fluids	13 (Treatment of articles by dipping and pouring)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Professional use in metal working fluids	8b (Transfer of substance or preparation…at dedicated facilities)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Professional use in metal working fluids	13 (Treatment of articles by dipping and pouring)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Professional use in metal working fluids	17 (Lubrication at high energy conditions and in partly open process)	1.08	0.01	1.09
Professional use in metal working fluids	18 (Greasing at high energy conditions)	1.08	0.004	1.08
Professional use in electroplating and electronics	18 (Greasing at high energy conditions)	1.27 Default[b] 10.18	0.01	1.28
Industrial use as an additive or processing aid in textile, leather or paper	8a (Transfer of substance or preparation…at non-dedicated facilities)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04

Industrial use as an additive or processing aid in textile, leather or paper	13 (Treatment of articles by dipping and pouring)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Industrial use in detergents and cleaners	8a (Transfer of substance or preparation…at non-dedicated facilities)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Professional use in detergents and cleaners	13 (Treatment of articles by dipping and pouring)	1.02 Short term[a] 1.34 Default[b] 6.11	0.02	1.04
Industrial use in adhesives and sealants	17 (Lubrication at high energy conditions)	1.72	0.05	1.77
Professional use in adhesives and sealants	17 (Lubrication at high energy conditions)	1.08	0.01	1.09
Professional use as a laboratory chemical	15 (Use as laboratory reagent)	1.02 Short term[a] 1.34	0.01	1.02
Industrial formulation and processing	2 (Use in closed, continuous process with occasional controlled exposure)	1.02 Short term[a] 1.34	0.02	1.04
Professional use as an additive in plastic (e.g. rubber)	14 (Production or preparation of articles)	1.22	0.002	1.22

[a] Inhalation RCRs have been calculated with reference to the 8-hour TWA IOELV. For contributing scenarios where inhalation exposure has been estimated using ECETOC TRA v. 3, it has been possible to also derive a short term inhalation RCR based on the predicted short term exposure levels and the STEL.

[b] In attempting to replicate the Registrants' exposure modelling, the eMSCA's calculations have used a linear modification to reflect the Registrants' specified in-use concentration for each contributing scenario, as appropriate. Where this approach has been used, the inhalation exposure RCR based on the tool default options has also been reported when ECETOC TRA v. 2 or v. 3 has been used.

The eMSCA does not have any concerns where the operating conditions and risk management measures that are being used maintain exposures below the IOELVs. However, the eMSCA's comparisons between the exposure estimates it has calculated for MEA and the limit values established in the 2nd IOELV directive suggest that the measures described in some exposure scenarios for MEA may not be sufficient to maintain exposures at or below these levels in all cases.

The provision of more descriptive information about the types of products/activities that are being covered by each scenario would help to place the modelling parameters that have been chosen in the context of the actual conditions in the workplace. This allows decisions to be made about whether

or not the exposure assessments represent a reasonable worst case. As noted in section 9, the use of linear concentration modifiers rather than the tool defaults will tend to move calculations away from the reasonable worst case as will the use of modifiers reducing task duration.

While the eMSCA has not found positive evidence that there is a risk to workers health, there is not enough information for it to conclude that the operating conditions and risk management measures that are currently described in exposure scenarios will be sufficient in all cases.

The draft decision communicated to the Registrants on 7th May 2015 contained a request that the Registrants shall confirm that the operating conditions and risk management measures communicated via exposure scenarios are sufficient to comply with the IOELVs. In their comments the Registrants accepted the recommendation and stated that the exposure- and risk assessment would be revised accordingly.

Noting that the Registrants will provide this confirmation, that the health effect of concern is respiratory tract irritation and that the available evidence suggests that if effects arise at levels of exposure likely to be encountered in the workplace, these will be mild and unlikely to have lasting health consequences, the eMSCA does not consider that the situation is of sufficient concern to trigger regulatory risk management activity for MEA.

However, to ensure that accurate information is available in relation to the uses and the conditions of use that are supported, it is expected that the Registrants will update their dossiers with the following information without undue delay:

- **provide clearer descriptions of the types of products and activities that are covered in each exposure scenario;**
- **confirm that exposures will not exceed the IOELVs when the operating conditions and risk management measures described in each exposure scenario are implemented correctly; and,**
- **provide the supporting evidence in their CSRs.**

10.1.2 Consumers

There are also differences between the position of the eMSCA and the Registrants in relation to the consumer assessment.

The Registrants' exposure calculations and the DNELs proposed by the Registrants resulted in all of the exposure scenarios / contributing scenarios having risk characterisation ratios (RCR) < 1. However, the Registrants in their calculations averaged the inhalation exposure values for each activity over the day and compared these values with the long-term inhalation DNEL. Although the Registrants' approach follows the Information Requirements and Chemical Safety Assessment Guidance Chapter R15, section 15.2.5, for MEA, the lead effect driving the risk assessment is site-of-contact irritation. The likelihood that effects will occur depends on the concentration of MEA attained at the target site at any point in time, rather than the dose (concentration x time, or total amount). If exposures from short duration activities (e.g. lasting for less than one hour) are averaged over the whole day, this could result in missing the potential for "during event" spikes in the exposure profile causing site-of-contact irritation.

To investigate the potential scale of the problem with short term peak exposure, the eMSCA has proposed a DNEL for consumers (general population) for short-term inhalation exposure by applying a factor of 2 to the IOELV for short-term exposure in the workplace (see Workers section above). The factor of 2 was chosen since this represents the difference in the interspecies variability factors that are normally applied for workers (factor of 5 applied) and consumers respectively (factor of 10 applied) in DNEL calculations starting from a NOAEL. The eMSCA's general population short-term inhalation DNEL is therefore 3.8 mg/m^3. This has been compared with 'during event' (short-term) inhalation exposure values calculated using ConsExpo 4.1. Scenarios resulting in RCRs > 1 are presented in table 27.

Table 27: Consumer exposure scenarios resulting in RCRs > 1 when the short-term inhalation DNEL is compared with 'during event' exposure values.

Scenario	Inhalation RCR (based on eMSCA's exposure estimates and DNELs)
Consumer use of coatings - application of paint remover.	5.95
Consumer use of adhesives - application of parquet glue (gluing on surface)	2.01
Consumer use of adhesives - application of carpet glue	8.58
Consumer use of adhesives - application of two component glue	2.19
Consumer use of concrete - contact with concrete wall	25.53
Consumer use of concrete - mixing and loading cement	5.47

Since the long-term inhalation DNEL for consumers calculated by the eMSCA is lower than that proposed by the Registrants, for completeness the eMSCA has also recalculated the RCRs for 'per day' exposure. Scenarios resulting in RCRs > 1 are presented in table 28.

Table 28: Consumer exposure scenarios resulting in RCRs > 1 when the long-term inhalation DNEL is compared with 'per day' exposure values.

Description	RCR (based on eMSCA's exposure estimates and DNELs)			
	Inhalation	Dermal	Oral	Total
Consumer use of coatings - application of paint remover.	1.88	0.02	-	1.9
Consumer use of adhesives - application of parquet glue (gluing on surface)	1.02	0.08	-	1.1
Consumer use of adhesives - application of parquet glue (floating parquet)	2.56	0.03	-	2.59
Consumer use of adhesives - application of carpet glue	3.4	0.06	-	3.46

Consumer use of adhesives - application of two component glue	1.39	0.06	-	1.45
Consumer use of concrete - contact with concrete wall	194.00	>>1	-	>>1
Consumer use of concrete - mixing and loading cement	5.47	0.13	0.007	5.61
Consumer use of concrete –application of concrete	1.98	0.006	0.00003	1.99

Based on this assessment, the scenario of greatest concern appears to be the contact with concrete wall scenario. Although the eMSCA's calculations for this situation predict a RCR greatly in excess of acceptable levels, in reality it is considered likely that contact with already built concrete structures will result in a negligible exposure to MEA and that the high exposure values and RCRs estimated for this situation are a consequence of the available modelling tools being unsuitable to assess this situation. For this reason, the eMSCA does not intend to take further action in relation to this scenario. It is also noted that in the updated registrations this use of MEA (consumer use in concrete and cement) is no longer listed.

For the remaining scenarios, no RCR value is greater than 9. In deciding how to react to these RCRs, the eMSCA took note of the following:

- the health effect of concern is respiratory tract irritation. The available evidence suggests that the effects are likely to be mild and unlikely to have lasting health consequences, particularly since these activities are likely to be performed only occasionally by consumers.
- these are strenuous DIY activities which would only be undertaken by adults in reasonably good health and not exhibiting the types of health characteristics that justify the use of higher assessment factors for interspecies variability among consumers. It could therefore be argued that the higher DNELs calculated for workers would also be applicable for consumers for certain types of activities.

As a separate observation, the eMSCA notes that several of the Registrants' consumer exposure estimates have relied on assumptions for frequency of use, duration of application, duration of exposure, room volume and ventilation rate which differed (generally to provide a less precautionary calculation) from the standard values proposed by the relevant ConsExpo Fact Sheets and Specific Consumer Exposure Determinants (SCEDs). Taken together the precautionary aspects of the DNEL calculations and the less precautionary aspects of the exposure calculations introduce a high degree of uncertainty into the consumer risk characterisation. While there is no positive evidence that consumers long-term health is at risk from the use of products containing MEA, it is not possible to conclude that transient irritation will never occur under all foreseeable conditions of use, which may include use in small, poorly ventilated spaces.

The draft decision communicated to the Registrants on 7th May 2015 contained requests that the Registrants provide further information on the scope of each consumer ES, justify their choice of modelling parameters and calculate "during event" inhalation exposure values for consumers to be used in their risk characterisation. In their comments the Registrants agreed to revise their CSR accordingly.

Given that there is uncertainty about whether or not consumers will experience adverse effects (local effects on the respiratory tract) during these activities and that no long-term health

consequences are expected from transient mild respiratory tract irritation, the eMSCA does not propose to initiate further action.

However, to ensure that accurate information is available in relation to the uses and the conditions of use that are supported, it is expected that the Registrants update their dossiers with the following information without undue delay and communicate revised/new risk management measures to downstream users:

- **provide clearer justifications for the parameters that have been used to model consumer exposure for each scenario;**
- **ensure that it is clear from the information provided in CSRs how local effects in the respiratory tract can be avoided during use.**

10.1.3 Indirect exposure of humans via the environment

10.2 Environment

10.2.1 Risk characterisation for PBT

10.2.2 Aquatic compartment (incl. sediment)

10.2.3 Terrestrial compartment

10.2.4 Atmospheric compartment

10.2.5 Microbiological activity in sewage treatment systems

10.3 Overall risk characterisation

10.3.1 Human health (combined for all exposure routes)

For the reasons outlined in section 9.3, a risk characterisation for combined human exposure is not relevant for MEA.

10.3.2 Environment (combined for all exposure routes)

11 OTHER INFORMATION

Literature Search criteria used:

Search criteria for the Environment (April 2014)	**Search criteria for respiratory sensitisation - Medline from 1/1/2000 – 1/7/2014**
monoethanolamine (MEA): CAS 141-43-5, EC 205-483-3	2-aminoethanol (syn. Ethanolamine) EC Number 205-483-3
2-aminoethanol	Respiratory Symptoms
Alkanolamines	Respiratory Ill Health
Bioaccumulation	Respiratory Illness
Bioconcentration	Respiratory Effects
Persistence	Respiratory Function
Degradation	Respiratory Disease
Biodegradation	Respiratory Tract Diseases
Ecotoxicity	Respiratory Function Tests
Fish	Respiratory outcomes
Invertebrate	Dyspnea
Algae	Shortness of breath
Monitoring	Breathlessness
Sewage treatment plant / works	Spirometry
	Cough
	Wheeze
	Sputum
	Phlegm
	Asthma
	Asthma Exacerbation
	Allergic Asthma
	Occupational Asthma
	Bronchitis
	Chronic bronchitis
	COPD
	Pulmonary disease, chronic obstructive
	Long-term respiratory symptoms
	RADS
	Emphysema
	Alveolitis, Extrinsic allergic
	Respiratory sensitisation
	Chronic respiratory symptoms
	Respiratory hypersensitivity
	Pulmonary function
	Work related respiratory symptoms
	Irritant induced asthma
	Chronic obstructive airways disease
	Hypersensitivity pneumonitis.

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13 ABBREVIATIONS

AAF	acetylaminofluorene
ADI	acceptable daily intake
ai	active ingredient
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
bw	bodyweight
CHO	Chinese hamster ovary
CI	confidence interval
CLV	ceiling value
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CSR	Chemical safety report
cv	coefficient of variation
DEA	2, 2’-iminodiethanol
DMSO	dimethyl sulfoxide
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECG	electrocardiogram
EHC	Environmental Health Criteria
eMSCA	Evaluating member state competent authority
FAO	Food and Agriculture Organization
FCAT	Freund's complete adjuvant test
FEF	forced expiratory flow
FEV	forced expiratory volume
FOB	functional observational battery
GDH	glutamate dehydrogenase
GEMS	Global Environmental Monitoring System
GI	gastrointestinal
GLC	gas-liquid chromatography
GLDH	glutamate dehydrogenase

GLP	good laboratory practice
cGMP	cyclic guanosine monophosphate
GOT	glutamic-oxaloacetic transaminase
GPMT	guinea-pig maximization test
GPT	glutamic-pyruvic transaminase
GST	glutathione-S-transferase
h	hour(s)
Hb	haemoglobin
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HPLC	high-performance liquid chromatography
HSE	Health and Safety Executive (UK)
IC	ion chromatography
Ig	immunoglobulin
im	intramuscular
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
IU	International unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LI	labelling index
LOAEL	lowest-observed-adverse-effect level
LOD	limit of determination
LOEL	lowest-observed-effect level
LSC	liquid scintillation counter
MAC	maximum allowable concentration
MAK	maximum workplace concentration (Maximale Arbeitsplatzkonzentration)
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
mCi	millicurie
MCV	mean cell volume
mg/kg bw/day	milligram per kilogram bodyweight per day.
MRL	maximum residue limit

MS	mass spectrometry
ND	not detectable
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOLC	no-observed lethal concentration
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration (USA)
PCE	polychromatic erythrocytes
PCV	packed-cell volume
PEF	peak expiratory flow
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PT	prothrombin time
QA	quality assurance
QAP	quality assurance programme
QC	quality control
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RCR	Risk characterisation ratio
SC	suspension concentrate
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SEM	standard error of the mean; scanning electron microscopy
SPF	specific pathogen free
TEA	2,2’,2”-Nitrilotriethanol
TLC	thin-layer chromatography
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TWA	time-weighted average

UDS	unscheduled DNA synthesis
v/v	volume per volume
WBC	white blood cell
WG	water-dispersible granule
WHO	World Health Organization
WP	wettable powder
w/v	weight per volume