Ministry of Environment of Denmark
Environmental Protection Agency

Selected amines and amino alcohols

Evaluation of health hazards and proposal of health-based quality criteria and C-values for ambient air

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Preface

The Danish Environmental Protection Agency has requested health hazard assessments of a series of amine and amine alcohols used for the Carbon Capture (CC) technology. The use of these substances in this technology may result in airborne emissions from the plant where the technology is used. Therefore, in connection with the health hazard assessments of the substances, The Danish Environmental Protection Agency requested for the derivation of health-based quality criteria for the amine and amine alcohols, as well as the proposals of C-values (B-værdier).

The present report has been elaborated by DHI A/S by Astrid Skovmand and Poul Bo Larsen. The report has been subjected to review and discussion and has been endorsed by a steering committee with participation of The Danish Environmental Protection Agency and DHI A/S:

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Abbreviations

AMP	
CC	Carbon Capture
ECHA	European Chemicals Agency
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
N(L)OAEC	NOAEC or LOAEC
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
MAPA	N-methyl-1,3-propanediamine
MDEA	Methyldiethanolamine
MEA	Monoethanolamine
MIPA	Monoisopropanolamine
MMAD	Median mass aerodynamic diameter
MMEA	2-(methylamino)ethanol
OECD TG	OECD Technical Guidance
PZ	Piperazin
QC	Quality Criteria
TEA	Triethanolamine
UF	Uncertainty factor

Summary

The Danish Environmental Protection Agency has requested health hazard assessments of a series of amine and amine alcohols used for the Carbon Capture (CC) technology. The use of these substances in CC technology may result in airborne emissions from the plant where the technology is used. Therefore, in connection with the health hazard assessments of the substances, The Danish Environmental Protection Agency requested for the derivation of health-based quality criteria for the amine and amine alcohols, as well as the proposals of C-values (B-værdier).

Hazard assessments were conducted for eight relevant substances identified by Industry to the Danish EPA. Toxicological data was retrieved and reviewed for the identified substances and health-based quality criteria (QC) were derived according to current guidelines and proposals for C-values were given.

In the table below the substances are listed together with the proposals for health-based C-values:

	Critical effect	C-Value	Main group and class
Monoethanolamine **MEA** **CAS: 141-43-5**	Local respiratory tract irritation	0.07 mg/m^3	main group 2, class II
Methyldiethanolamine **MDEA** **CAS: 105-59-9**	Local respiratory tract irritation	0.01 mg/m^3	main group 2, class I
2-amino-2-methyl-1-propanol **AMP** **CAS: 124-68-5**	Systemic toxicity (organ toxicity liver)	0.07 mg/m^3	main group 2, class II
Piperazine **PZ** **CAS: 110-85-0**	Respiratory sensitisation	0.001 mg/m^3	main group 1, class I
N-methyl-1,3-propanediamine **MAPA** **CAS: 6291-84-5**	Local respiratory tract irritation	0.04 mg/m^3	main group 2, class II
Triethanolamine **TEA** **CAS: 102-71-6**	Local respiratory tract irritation	0.04 mg/m^3	main group 2, class II
Monoisopropanolamine **MIPA** **CAS: 78-96-6**	Local respiratory tract irritation	0.02 mg/m^3	main group 2, class II
2-(methylamino)ethanol **MMEA** **CAS: 109-83-1**	Systemic toxicity (organ toxicity kidney)	0.01 mg/m^3	main group 2, class I

1. Introduction

1.1 Background

In the CC technology, CO_2 is captured by a chemical process in which the CO_2 molecules are washed out of flue gas and bound in a liquid. Since amines chemically react with CO_2, liquid solutions containing amines are used in the CO_2 capturing process. Later the CO_2 is released, compressed, and transported away for storage, but the amines are re-circulated.

During these processes airborne emissions of the amines may take place. In order to protect human health from this emission there is a need to establish health-based quality criteria as well as C-values (B-værdier) for the substances.

1.2 Purpose

The Danish Environmental Protection Agency has requested assessment of the potential health hazards posed by eight amines used in the CC technology, as well as derivation of health-based quality criteria and proposals for C-values for the substances.

1.3 Delimitation

The relevant substances for which hazard assessments were conducted, were identified by the Danish EPA and cover the following eight amines and amine alcohols:

MEA – monoethanolamine – CAS: 141-43-5

MDEA – methyldiethanolamine – CAS: 105-59-9

AMP – 2-amino-2-methyl-1-propanol – CAS: 124-68-5

PZ – piperazine – CAS: 110-85-0

MAPA – N-methyl-1,3-propanediamine – CAS: 6291-84-5

TEA -triethanolamine- CAS: 102-71-6

MIPA – monoisopropanolamine - CAS: 78-96-6

MMEA – 2-(methylamino)ethanol – CAS: 109-83-1

1.4 Methodology for the assessment

The methodology used for the toxicological assessments and the derivation of health-based quality criteria is described in the Danish EPA guidance document*: Danish EPA (2006). "Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer i jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5"* and in the ECHA guidance document in relation to REACH: *ECHA (2012) "Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health".*

The methodology used for the derivation of C-values is described in the Danish EPA guidance documents: *Danish EPA (2001). "Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2"* and *Danish EPA (2016). "Vejledning om B-værdier. Vejledning nr. 20".*

2. Toxicology

In this chapter an overview and short reviews of the information obtained for the substances are given together with a condensed description of the toxicological information and the derived quality criteria and C-values proposals.

For specific details and used references for each of the substance the reader is referred to the appendices.

2.1 General information

2.1.1 Uses

The eight amines / alcohol amines selected for this project are all used in the CC technology and emission to air may result from this use. However, as industrial chemicals they are used for a wide range of purposes of which some of the uses are described below:

Monoethanolamine (MEA) is a major industrial chemical, which may also be found in a very broad range of consumer products (Appendix A)

Methyldiethanolamine (MDEA) is widely used as a sweetening agent, in oil refinery, syngas production and natural gas. MDEA is found in consumers products such as in washing and cleaning products (Appendix B).

2-Amino-2-methyl-1-propanol (AMP) is mainly used to produce other chemicals (surface-active agents, vulcanization accelerators, and pharmaceuticals) and as an emulsifying agent for articles such as cosmetic creams and lotions, mineral oils, and paraffin wax emulsions (Appendix C).

Piperazine (PZ) is used as salts for different applications or as an intermediate in the chemical industry. In human and veterinary medicine, PZ is used as an anthelmintic to treat parasitic infections, as an antihistaminic and tranquillizer. It is also used as a corrosion inhibitor; as an additive in rubber production; and as a vulcanization accelerator (Appendix D).

N-methyl-1,3-propanediamine (MAPA) is used in formulation or re-packing and at industrial sites (Appendix E).

Triethanolamine (TEA) contains small amounts of diethanolamine and may act as an antioxidant against the auto-oxidation of animal and vegetable fats. It is commonly used as a pH adjuster and surfactant in industrial and cosmetic products (Appendix F).

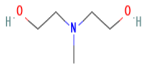
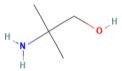
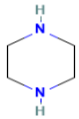
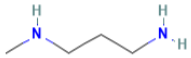
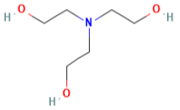
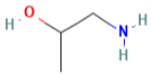
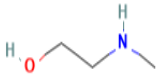
Monoisopropanolamine (MIPA) MIPA is a precursor of vitamin B12 and/or an intermediary in the production of propionaldehyde in many microbial genera. As an industrial chemical, MIPA is used in washing and cleaning products, biocides (e.g., disinfectants, pest control products), fuels and cosmetics and personal care products (Appendix G).

2-(methylamino)ethanol (MMEA) is used in formulation or re-packing, at industrial sites and in manufacturing (Appendix H).

2.1.2 Physicochemical properties

An overview of the physicochemical properties of all eight amines/ amino alcohols are shown in Table 1.

TABLE 1. Physicochemical properties

Parameter	MEA CAS: 141-43-5 (Appendix A)	MDEA CAS: 105-59-9 (Appendix B)	AMP CAS: 124-68-5 (Appendix C)	PZ CAS: 110-85-0 (Appendix D)	MAPA CAS: 6291-84-5 (Appendix E)	TEA CAS: 102-71-6 (Appendix F)	MIPA CAS: 78-96-6 (Appendix G)	MMEA CAS: 109-83-1 (Appendix H)
Chemical structure								
Chemical formula	$H_2NCH_2CH_2OH$	$C_5H_{13}NO_2$	$C_4H_{11}NO$	$C_4H_{10}N_2$	$H_2NCH_2CH_2OH$	$C_6H_{15}NO_3$	C_3H_9NO	C_3H_9NO
Molecular weight	61.08	119.16	89.14	86.14	88.15	149.19	75.11	75.11
Physical state	Liquid	Liquid at 20°C	Solid at 20°C	Solid (at room temperature)	Liquid	Liquid (viscous)	Colourless liquid	Clear colourless liquid
Melting point	4°C	-21.3°C	30 - 31°C	106°C	-19.53°C	20.5°C	1.74°C	-3 °C - -5°C
Boiling point	167°C	243.3°C	165°C	147°C	140°C	336.1°C	159.5°C	160°C
Vapour pressure	0.5 hPa at 20 °C	0.003 hPa at 20°C	<1 hPa at 20°C	0.39 hPa at 23°C	1.333 kPa at 39.37°C	<0.0003 hPa at 21°C	0.63 hPa at 25°C	2.01 hPa at 30.6°C
Relative vapour density	2.1	1.04	3.0	3	Not identified	5.1	2.6	2.6
1 ppm = mg/m³	2.5 mg/m³	4.87 mg/m³	3.65 mg/m³	3.5 mg/m³	3.61 mg/m³	6.1 mg/m³	3.12 mg/m³	3.12 mg/m³
Water solubility	1000 g/L (miscible)	1000 g/L at 20°C	920 g/L at 20°C	150 g/L 20°C	1 000 g/L at 25°C	>1000 g/L at 20°C	miscible	1 000 g/L at 20°C
Partition coefficient log POW	-2.3 at 25°C	-1.16 at 23°C	-0.63 at 20°C	-1.24 at 25°C	-0.66	-2.3 at 25°C	-0.93 at 23°C	-0.91 at 25°C

Pka / pH	9.5 / pH: 12.05	8.52 / pH: 11.5	9.5 / pH: 11.3	9.73 / pH: 10.8 – 11.8	Not identified / pH: 13.5 at 20ºC and 100 g/L	7.76 / pH 10.5 (0.1 N solution)	9.62 at 20°C/ Ca. pH at 12 at 20 g/L and at 20°C	9.95 at 20°C / pH 13.6
Odour threshold	Ammonia like odour, 6.5 mg/m^3	Amine like odour, threshold not determined	Threshold not determined	Ammonia like odour, 0.1 ppm	Odourless	Mild ammonia like odour, 0.1 to 0.48 ppm	Mild ammonia like odour, threshold not determined	Fishy odour, threshold not determined

2.1.3 Regulation

An overview on the CLP-classification of all eight amines are shown in Table 2. Danish occupational exposure levels and current C-values are presented if available.

TABLE 2. Regulatory overview, CLP-classification, Danish OEL and Danish C-value

	CLP-classification Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) + REACH reg. clsssification	Danish OEL AT (2022)	Danish C-value* 2016
MEA **CAS: 141-43-5** (Appendix A)	Acute tox. 4; H302 + H312 + H332 Harmful if swallowed, in contact with skin or if inhaled Skin Corr. 1B; H314 Causes severe skin burns and eye damage + STOT SE 3; H335 May cause respiratory irritation	2.5 mg/m^3 (value from 2022)	0.01 mg/m^3 (value from 1991)
MDEA **CAS: 105-59-9** (Appendix B)	Eye Irrit. 2; H319 Causes serious eye irritation	Not listed	Not listed
AMP **CAS: 124-68-5** (Appendix C)	Eye Irrit. 2; H319 Causes serious eye irritation Skin Irrit. 2; H315 Causes skin irritation Aquatic Chronic 3; H412 Harmful to aquatic life with long lasting effects)	Not listed	Not listed
PZ **CAS: 110-85-0** (Appendix D)	Skin Corr. 1B; H314 Causes severe skin burns and eye damage Resp. Sens. 1; H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled Skin Sens. 1; H317 May cause and allergic skin reaction Repr. 2; H361fd Suspected of damaging fertility	0,1 mg/m^3 (value from 2022)	Not listed
MAPA **CAS: 6291-84-5** (Appendix E)	No harmonized classification **+** Skin Corr. 1; H314 Causes severe skin burns and eye damage	Not listed	Not listed
TEA **CAS: 102-71-6** (Appendix F)	No harmonized classification	3,1 mg/m^3 (value from 1994)	0,01 mg/m^3 (value from 1991)
MIPA **CAS: 78-96-6** (Appendix G)	Skin Corr. 1B; H314 Causes severe skin burns and eye damage + Acute Tox 4 H312 Harmful in contact with skin	Not listed	Not listed
MMEA **CAS: 109-83-1** (Appendix H)	Acute tox. 4; H302 + H312 Harmful if swallowed, in contact with skin Skin Corr. 1B; H314 Causes severe skin burns and eye damage + Repr.. 2 H361 Suspected of damaging fertility or the unborn child + STOT SE 3 H335 May cause respiratory irritation + STOT RE 2 H373 May cause damage to organs through prolonged or repeated exposure) organs: kidney, testes, epididymides, ovaries, liver, and spleen	Not listed	Not listed

NB: Although no harmonised classification applies for a substance or specific end points, available data on the substance may justify classification for other hazard-endpoints and thus, should be included in the classification in the REACH-registration for the substance. “+” indicates the further, classification according to the REACH-registrations for the substances.

3. Toxicology

3.1 MEA – ethanolamine – CAS: 141-43-5 (Appendix A)

3.1.1 Derivation of QC

The critical effect of MEA is local respiratory tract irritation. In an OECD TG 412 inhalation study, Wistar rats were exposed nose-only to 2-aminoethanol aerosol for 28 days, for 6 hrs/day, 5 days/week. The test concentrations were 0, 10, 50 or 150 mg/m^3. The exposure resulted in adverse morphological changes to the epithelium in the larynx (metaplasia of the squamous epithelium, inflammation, and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with an increasing incidence and severity. The resulting local NOAEC for rats after 28-day exposure was 10 mg/m^3.

According to Danish EPA (2006) the health-based QC for MEA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III)
QC = 10 mg/m^3 / (2.5 x 10 x 6)
QC = 0.066 mg/m^3

3.1.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.07 mg/m^3** is proposed for MEA.

As a non-carcinogenic substance with a C-value in the range of 0.01-0.2 mg/m^3 the substances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class II.

3.2 MDEA – methyldiethanolamine – CAS: 105-59-9 (Appendix B)

3.2.1 Derivation of QC

It should be recognized that MDEA is an alkaline substance causing irritation to the mucous membranes of the eye. However, no inhalation data is available for assessing the potential for respiratory irritation.

MDEA as a tertiary amine is very similar to another tertiary amine: TEA, both in relation to chemical structure and the physicochemical properties. However, MDEA according to the classification and pKa value might be considered a slightly more potent irritant than TEA. There is substantial data including inhalation studies for the toxicological assessment of TEA, and thus it is considered relevant to perform a read-across from data on TEA to establishing a C-value for MDEA.

The QC for MDEA is based on read-across data from TEA.

The critical effect of TEA is local respiratory tract irritation. In a subacute inhalation toxicity study, conducted according to OECD TG 412, rats were exposed to the TEA at concentrations of 0.02, 0.1, and 0.5 mg/L, 6 hrs/day, 5 days/week. TEA was administered as a liquid aerosol during the 28-day period. A NOAEC of 0.5 mg/L and 0.02 mg/L was established for systemic effects and for local effects (fe-

male), respectively. Since slight local effects were observed in males, this concentration was determined to be the LOAEC for local effects in males (REACH 2022a). The LOAEC of 0.02 mg/L corresponds to 20 mg/m^3.

According to Danish EPA (2006) the health-based QC for MDEA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV x UF V)
QC = 20 mg/m^3 / (2.5 x 10 x 6 x 3 x 3)
QC = 0.014 mg/m^3 or 0.01 mg/m^3

3.2.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure. Thus, a **C-value of 0.01 mg/m^3** is proposed for MDEA.

As a non-carcinogenic substance with a C-value in the range of ≤ 0.01 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class I.

3.3 AMP–2-amino-2-methyl-1-propanol –CAS: 124-68-5 (Appendix C)

3.3.1 Derivation of QC

The critical effect for AMP was identified as potential toxicity in the liver in relation to repeated exposure. Oral dose levels of 0, 70, 210 and 700 mg/kg bw/day were used in a study, according to OECD TG 421. The NOEL for general toxicity in males was 210 mg/kg bw/day, while the general toxicity NOEL for females could not be determined. A LOAEL of 70 mg/kg bw/day for females is selected based on the presence of very slight microscopic liver effects (REACH 2022b)

According to Danish EPA (2006) a health-based quality criteria for systemic effects of AMP can be derived from a LOAEL of 70 mg/kg bw/day for systemic exposure. This point of departure is used as the basis for the calculation.

The first step to derive the quality criteria in air is to convert an oral LOAEL (in mg/kg bw/day) to an inhalation concentration (in mg/m^3). As a default the ECHA guideline uses a daily inhalation rate for rats of 1.15 m^3/ kg bw/day. Also, when no specific data on the oral absorption rate and the inhalation absorption rate, the inhalation rate by default is considered to be twice as high as the oral inhalation rate (ECHA 2012). Thus, a LOAEC can be calculated according to:

LOAEC = LOAEL/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 70 mg/kg bw/day/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 30 mg/m^3

The quality criterion can then be calculated:

QC = N(L)OAEC/ (UF I x UF II x UF III x UF IV)
QC = 30 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.066 mg/m^3 or 0.07 mg/m^3

This level is also considered to protect against local effects in relation to the respiratory tract as the substance has a chemical structure closely related to MEA having a QC value of 0.07 mg/m^3.

3.3.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.07 mg/m^3** is proposed for AMP.

As a non-carcinogenic substance with a C-value in the range of 0.01-0.2 mg/m^3 the substances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class II.

3.4 PZ – Piperazine – CAS: 110-85-0 (Appendix D)

3.4.1 Derivation of QC

The critical effect for PZ is respiratory sensitisation as observed from occupational exposure. No specific health-based quality criteria value can be calculated for this effect as no threshold can be set for respiratory sensitisation. By default, piperazine is assigned a C-values of 0.001 mg/m^3.

3.4.2 Proposal for C-value

As a respiratory sensitizing substance with a **C-value of 0.001 mg/m^3** the substance should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 1. Furthermore, the C-value of 0.001 mg/m^3 ensures low emission as a class 1 substance.

3.5 MAPA – N-methyl-1,3-propanediamine – CAS: 6291-84-5 (Appendix E)

3.5.1 Derivation of QC

MAPA is a strong base, and therefore irritation may occur when in contact with the skin, eyes or the airways. In a repeated dose study in rats by inhalation, animals were exposed to MAPA at concentrations of 0, 61, and 189.3 mg/m^3 for 6 hrs/day for 13 days. No statically significant effects were observed for clinical sign, gross pathology, and histopathology in the treated animal. Although a NOAEC of 189.3 mg/m^3 was reported for systemic effects, no NOAEC for severe nasal irritation was reported, even though irritation was noted at all doses. As the substance is considered as a severe irritant a LOAEC of 61 mg/m^3 is considered for the local effects (REACH 2022c).

According to Danish EPA (2006) the health-based QC for MAPA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV)
QC = 61 mg/m^3 / (2.5 x 10 x 6 x 10)
QC = 0.04 mg/m^3

3.5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.04 mg/m^3** is proposed for MAPA.

As a non-carcinogenic substance with a C-value in the range of 0.01 -0.2 mg/m^3 the substances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class II.

3.6 TEA -triethanolamine- CAS: 102-71-6 (Appendix F)

3.6.1 Derivation of QC

In a Subacute inhalation toxicity study, conducted according to OECD TG 412, rats were exposed to TEA at concentrations of 0.02, 0.1, and 0.5 mg/L, 6 hrs/day, 5 days/week. TEA was administered as a liquid aerosol during a 28-day period. A NOAEC of 0.5 mg/L and 0.02 mg/L was established for systemic effects and for local effects (female), respectively. Local effects were characterized histopathologically by focal inflammatory changes in the submucosa of the larynx region with a tendency to concentration dependent increase in incidence and severity of the lesion from mid to high concentration in both sexes. Since slight local effects were observed in males, this concentration was determined to be the LOAEC for local effects. The LOAEC of 0.02 mg/L corresponds to 20 mg/m^3.

According to Danish EPA (2006) the health-based quality criteria for TEA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV)
QC = 20 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.044 mg/m^3

3.6.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.04 mg/m^3** is proposed for TEA.

As a non-carcinogenic substance with a C-value in the range of 0.01 -0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

3.7 MIPA – monoisopropanolamine - CAS: 78-96-6 (Appendix G)

3.7.1 Derivation of QC

As no specific data is available from which to estimate the quality criterion it is considered justified to read-across from the data on monoethanolamine (MEA) that is a very closely related substance with respect to chemical structure, physicochemical data and toxicological profile

The critical effect of MEA is local respiratory tract irritation. In an OECD TG 412 inhalation study, Wistar rats were exposed nose-only to 2-aminoethanol aerosol (with a vapour fraction; purity of the test substance: 99.93%) for 28 days, for 6 hrs/day, 5 days/week. The test concentrations were 0, 10, 50 or 150 mg/m^3. The exposure resulted in adverse morphological changes to the epithelium in the larynx (metaplasia of the squamous epithelium, inflammation, and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with an increasing incidence and severity. The resulting local NOAEC for rats after 28-day exposure was 10 mg/m^3.

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV))
QC = 10 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.02 mg/m^3

Compared to MEA a further assessment factor of 3 was used to consider uncertainties using read-across.

Based on a read across from MEA data, a QC of 0.02 mg/m^3 can be set for MIPA.

3.7.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.02 mg/m^3** is proposed for MIPA.

As a non-carcinogenic substance with a C-value in the range of 0.01 – 0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

3.8 MMEA – 2-(methylamino)ethanol – CAS: 109-83-1 (Appendix H)

3.8.1 Derivation of QC

Considering the physical-chemical properties of MMEA (i.e., a pH of 13.6), there is sufficient reason to suppose that the test substance may be a strong irritant to the airways and to the mucous membranes of the eye. However, no adequate data is available for deriving a QC for local effect.
For systemic toxicity an oral LOAEL of 50 mg/kg bw/day was set based on adverse effects in the kidneys of male rats. This was identified in a combined repeated dose and reproductive/developmental toxicity testing, conducted according to OECD TG 422 (REACH 2022d).

The first step to derive the quality criteria in air is to convert an oral LOAEL (in mg/kg bw/day) to an inhalation concentration (in mg/m^3). As a default the ECHA guideline uses a daily inhalation rate for rats of 1.15 m^3/ kg bw/day. Also, when no specific data on the oral absorption rate and the inhalation absorption rate, the inhalation rate by default is considered to be twice as high as the oral inhalation rate (ECHA 2012). Thus, a LOAEC can be calculated according to:

LOAEC = LOAEL/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 50 mg/kg bw/day/ (1.15 m3/ kg bw/day x 2)
LOAEC = 22 mg/m^3

The quality criterion can then be calculated:

QC = N(L)OAEC/ (UF I x UF II x UF III x UF IV)
QC = 22 mg/m^3 / (2.5 x 10 x 6 x 10)
QC = 0.014 mg/m^3 or 0.01 mg/m^3

This level is also considered to protect against local effects in relation to the respiratory tract as the substance has a chemical structure closely related to MEA having a QC value of 0.07 mg/m^3. However, as MMEA has a methyl group attached to the nitrogen atom compared to MEA, the substance is more alkaline as indicated by the higher pH value, which again justify the lower QC value of 0.01 mg/m^3.

3.8.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, a **C-value of 0.01 mg/m^3** is proposed for MMEA.

As a non-carcinogenic substance with a C-value in the range of ≤ 0.01 mg/m^3 the sub-stances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class I.

4. Overall evaluation and conclusion

The findings of this project in relation to the potential health hazards posed by the eight amines/ amino alcohols used in the CC technology, as well as the proposals of C-values for the substances are presented in Table 3.

TABLE 3. Critical health hazards and proposed C-values

	Critical effect	C-Value	Main group, class	
MEA CAS: 141-43-5	Local respiratory tract irritation	0.07 mg/m^3	main group 2, class II	Appendix A
MDEA CAS: 105-59-9	Local respiratory tract irritation	0.01 mg/m^3	main group 2, class I	Appendix B
AMP CAS: 124-68-5	Systemic toxicity (organ toxicity liver)	0.07 mg/m^3	main group 2, class II	Appendix C
PZ CAS: 110-85-0	Respiratory sensitisation	0.001 mg/m^3	main group 1, class I	Appendix D
MAPA CAS: 6291-84-5	Local respiratory tract irritation	0.04 mg/m^3	main group 2, class II	Appendix E
TEA CAS: 102-71-6	Local respiratory tract irritation	0.04 mg/m^3	main group 2, class II	Appendix F
MIPA CAS: 78-96-6	Local respiratory tract irritation	0.02 mg/m^3	main group 2, class II	Appendix G
MMEA CAS: 109-83-1	Systemic toxicity (organ toxicity kidney)	0.01 mg/m^3	main group 2, class I	Appendix H

For MEA, MDEA, MAPA, TEA and MIPA effects in relation to local irritation of the respiratory tract were identified as the most critical effect. All of these substances were placed in main group 2 with C-values in the range of 0.1 – 0.07 mg/m^3.

AMP and MMEA as alkaline substances were also considered having irritative properties, however, no specific data were available from which a C-value could be derived based on such effects. However, data on systemic toxicity indicated rather low effect-levels for liver and kidney toxicity, respectively. Both of these substances were allocated to main group 2 with C-values of 0.07 mg/m^3 and 0.01 mg/m^3, respectively.

Piperazine having respiratory sensitisation as the most critical effect was placed in main group 1. As no lower threshold level can be determined for this effect a C-value of 0.001 mg/m^3 was allocated to the substance.

5. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. Link: https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.
ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health.

6. Appendices

Appendix A

November 2022

Monoethanolamine (MEA) – CAS: 141-43-5

Synonyms: 2-aminoethanol; 2-hydroxyerthylamine; ethanolamine

C-value (2022): 0.07 mg/m^3, main group 2, class II.

1. General information

1.1 Occurrence and use

Monoethanolamine (MEA) is used and is found in a very broad range of consumer products. It is a major industrial chemical used at a tonnage level in the range up to 1 billion tonnes per year in EU (ECHA 2022). MEA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

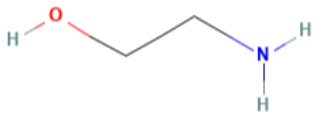
Table A.1 Regulatory overview, MEA

Regulation	Specification	Reference
CLP-classification	Acute tox. 4; H302 + H312 + H332 (Harmful if swallowed, in contact with skin or if inhaled) Skin Corr. 1B; H314 (Causes severe skin burns and eye damage) STOT SE 3; H335 (May cause respiratory irritation), at a concentration ≥ 5%	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Acute tox. 4; H302 + H312 + H332 (Harmful if swallowed, in contact with skin or if inhaled) Skin Corr. 1B; H314 (Causes severe skin burns and eye damage) Eye Damage 1 H318 (Causes serious eye damage) STOT SE 3; H335 (May cause respiratory irritation)	REACH-reg
REACH **Restriction** **SVHC**	Registered at the tonnage level of 100 000 – 1 000 000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	2.5 mg/m^3 (value from 2022)	AT 2022
Danish C-value* 2016	0.01 mg/m^3 (value from 1991)	Danish EPA 2016 (listed 1991)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, MEA

Parameter	CAS No. 141-43-5	Reference
Structural formula		PubChem database
Chemical formula	H2NCH2CH2OH	PubChem database
Molecular weight	61.08	PubChem database
Physical state	Liquid	REACH-reg
Melting point	4°C	REACH-reg
Boiling point	167°C	REACH-reg
Vapour pressure	0.5 hPa at 20 °C	REACH-reg
Relative vapour density	2.1	PubChem database
1 ppm = mg/m^3	2.5 mg/m^3	US-NRCCT (1987)
Water solubility	1000 g/L (miscible)	REACH-reg
Partition coefficient log POW	-2.3 at 25°C	REACH-reg
Pka / pH	9.5 / pH: 12.05	PubChem database
Odour threshold	Ammonia like odour, 6.5 mg/m^3	US-NRCCT (1987)

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *The REACH-registration dossier (registered at the tonnage level of 100 000 – 1 000 000 tonnes per year), last modified in 18-Nov-2022*
- *MAK (2018). 2-Aminoethanol / monoethanolamine. MAK value documentation.*
- *HSE (2021). Appendix C: summary of toxicological evidence for MEA and NDMA*

The toxicological properties of MEA are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination
There is no quantitative information on the systemic uptake of MEA through oral or inhalation routes, but it is assumed that MEA is absorbed through the skin, lungs, and gastrointestinal tract.

MEA is rapidly metabolized in the liver and incorporated into phospholipids in cellular membranes. Excess MEA is converted through acetaldehyde to carbon dioxide and exhaled. In a study of dermal uptake MEA was widely distributed and extensively metabolized HSE (2021).

3.2 Human toxicity

Respiratory irritation
In asthma patients, the inhalation of aerosols generated from up to 10% solutions did not cause irritation but was considered an odour nuisance. The actual concentrations in the air were not reported (MAK 2016).

Respiratory sensitisation
Symptoms of respiratory sensitisation have been reported, but there are difficulties in interpretating the results due to concomitant exposures, uncertainties in the concentration and duration of exposure, and other factors such as the sensitivity of those studied to multiple allergies. However, symptoms of occupational asthma had been identified in a limited number of case reports despite the widespread use of MEA (HSE 2021).

3.3 Animal toxicity

Single dose toxicity
MEA has a moderate acute toxic potential by inhalation, oral exposure, and dermal exposure resulting in the classification as Acute tox. 4.

Inhalation
The LC50 value for acute inhalation toxicity for 6 hours exposure duration was established to exceed 1300 mg/m^3 (REACH-reg.).

Oral intake
The LD50 value for acute oral toxicity is 1089 mg/kg bw in rats (REACH-reg.).

Dermal contact
The LD50 value for acute dermal toxicity is 2504 mg/kg bw in rats (REACH-reg.).

Irritation
MEA is corrosive to skin and mucous membranes including the eyes resulting in the classification as Skin Corr. 1B; Eye dam. 1 and STOT SE 3.

Skin irritation
The available skin irritation studies with rabbits, performed according to methods similar to OECD TGs, indicate clearly that MEA is corrosive to the skin (REACH-reg).

Eye irritation
The available eye irritation studies with rabbits, performed according to methods similar to OECD guidelines, indicate that MEA leads to irreversible eye damage (REACH-reg).

Respiratory irritation

Respiratory irritation including submucosal inflammation and squamous metaplasia in the larynx and trachea were observed at 50 and 150 mg/m^3 in a sub-acute OECD TG 412 inhalation study where Wistar rats were exposed to a respirable MEA aerosol at 10, 50 and 150 mg/m^3 for 6 hours a day, 5 days a week. The NOAEC for local effects of the respiratory system was reported to 10 mg/m^3 (REACH-reg., data from anonymous study report, 2010).

Skin sensitisation

MEA is not considered to be a skin sensitiser based on animal experiments.
2-monoethanolamin was tested negative for skin sensitisation in a guinea pig maximisation test. Also, the hydrochloride of the substance: 2-hydroxyethylammonium chloride was tested negative for skin sensitisation in an OECD TG 429 mouse local lymph node assay (LLNA) study (REACH-reg.).

Repeated dose toxicity

From studies on repeated exposure effects from irritation of the respiratory tract can be concluded as the most critical effect with a LOAC of 50 mg/m^3 and a NOAC of 10 mg/m^3.

Inhalation

No systemic toxicity was observed in a sub-acute OECD TG 412 inhalation study where Wistar rats were exposed to respirable MEA aerosols at 10, 50 and 150 mg/m^3 for 6 hrs a day, 5 days a week. A NOAEC of 150 mg/m^3 was concluded for systemic effects. However, respiratory irritation including sub-mucosal inflammation and squamous metaplasia in the larynx and trachea was observed at 50 and 150 mg/m^3. Thus, a NOAEC of 10 mg/m^3 for local effects of the respiratory system was found. (REACH-reg., data from anonymous study report, 2010).

Systemic toxicity was reported in connection with 90 days of continuous inhalation exposure at concentration levels above 66 ppm (168 mg/m^3) as this caused neurobehavioral changes in dogs, guinea pigs, and rats. In addition, rats exposed for 2 to 3 weeks to 5 ppm (13 mg/m^3) exhibited lethargy (HSE 2021, data from studies performed in 1960).

Oral intake

A NOAEL of 300 mg/kg bw/day for systemic effects was observed in an oral OECD TG 416 study (two-generation reproduction toxicity study) where rats were dosed with ethanolamine hydrochloride via the diet achieving dose levels of 100, 300 and 1000 mg/kg bw/day. At 1000 mg/kg bw/day effects on body weight and relative organ kidney weight were observed in the parental animals (REACH-reg).

Dermal contact

No data.

Toxicity to reproduction

MEA is not considered to cause adverse effects towards fertility and development below maternal toxic exposure levels.

Fertility

In an oral OECD TG 416 study (Two-generation reproduction toxicity study) rats were dosed with ethanolamine hydrochloride via the diet achieving dose levels of 100, 300 and 1000 mg/kg bw/day. A NOAEL of 300 mg/kg bw/day was concluded for female reproductive performance due to decreased litter size at the highest dose level. No effects were seen in F1 and F2 offspring, i.e., a NOAEL of 1000 mg/kg bw/day (REACH-reg.).

Development

Pregnant Wistar rats were in an OECD TG 414 study exposed to the substance by gavage at dose levels 0, 40, 120, 450 mg/kg bw/day on days 6 - 15 of gestation. No reproductive and developmental toxicity parameters were affected. The NOAEL for developmental effects was established to correspond to

450 mg/kg bw/day; the NOAEL for maternal toxicity was 120 mg/kg bw/day based on decreased body weight at highest level.

Pregnant New Zealand White rabbits were exposed dermally to 0, 10, 25, and 75 mg/kg/day of the test substance for approximately 6 hr/day on days 6 through 18 of gestation. Local dermal effects were noted at the two highest dose levels and a NOAEL of 10 mg/kg bw/day was concluded for maternal toxicity. A NOEAL of 75 mg/kg bw/day was concluded in relation to developmental effects.

Mutagenic and genotoxic effects
No indication of a mutagenic potential of MEA was found in neither *in vitro* nor *in vivo* studies.

In vitro studies
The *in vitro* genotoxicity was 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 in Chinese hamster lung fibroblasts [V79], all of which were negative (HSE 2021).

In vivo studies
Furthermore, negative results were also obtained from an 'in vivo' mouse micronucleus test where clear signs of substance related toxicity were observed at the highest dose (HSE 2021).

Carcinogenic effects
No data.

4. Overall evaluation and identification of critical effect

From the data above – and in agreement with HSE (2021) and MAK (2016) it can be concluded that the critical effect of MEA is the local respiratory tract irritation.

Both expert assessments (HSE 2021 and MAK 2016) identify the OECD TG 412 inhalation study in rats as the basis for derivation for a health-based limit value. In this study groups of 5 male and 5 female Wistar rats were exposed nose-only to 2-aminoethanol aerosol (with a vapour fraction; purity of the test substance: 99.93%) for 28 days, for 6 hrs a day, on 5 days a week. The test concentrations were 0, 10, 50 or 150 mg/m^3 (analysed concentrations: 10.2, 49.1 and 155.9 mg/m^3; Median mass aerodynamic diameter (MMAD) = 1.1 to 1.2 µm, with about 70% of the particles below 3 µm; the aerosol fraction was 0.5, 26.4 and 134.5 and the vapour fraction was 9.8, 22.7 and 21.4 mg/m^3) (MAK 2016 with reference to the original study report from 2010 from the REACH Ethanolamines Consortium SE). The exposure resulted in adverse morphological changes to the epithelium in the larynx (metaplasia of the squamous epithelium, inflammation, and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with an increasing incidence and severity. The resulting local NOAEC for rats after 28-day exposure was 10 mg/m^3.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

According to Danish EPA (2006) the health-based quality criteria (QC) for MEA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III)
QC = 10 mg/m^3 / (2.5 x 10 x 6)
QC = 0.07 mg/m^3

It should be noted that the NOAEC exposure level of 10 mg/m^3 in relation to 6hrs/day is not averaged to a 24hrs exposure level (in this case it would be 2.5 mg/m^3), as it is the daily concentration level and not the daily inhaled amount of substance that is considered critical for developing the local effects in the respiratory tissue.

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the critical effect is local irritation) as no default kinetic factor is used when the critical effect is local irritation in surface tissue.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor, since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.

Thus, **a C-value of 0.07 mg/m^3 is proposed** for MEA.

As a non-carcinogenic substance with a C-value in the range of in the range of 0.01-0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2.

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose [concentration]-response for human health. Link: COVER PAGE (europa.eu)

ECHA (2022). Substance Inforcard on 2-aminoethanol.Link: *Substance Information - ECHA (europa.eu)*

HSE (2021). Appendix C: summary of toxicological evidence for MEA and NDMA. Link: *Appendix C: summary of toxicological evidence for MEA and NDMA - GOV.UK (www.gov.uk)*

MAK (2016). 2-Aminoethanol / monoethanolamine. MAK Value Documentation.Link:2-Aminoethanol [MAK Value Documentation, 2016] (wiley.com)

PubChem database 2022. Compound summary: Ethanolamine. National Library of Medicine. Link: *Ethanolamine | C2H7NO - PubChem (nih.gov)*

REACH-reg (2022). Reach registration dossier on 2-aminoethanol. Link: Registration Dossier - ECHA (europa.eu)

US-NRCCT (1987). National Research Council (US) Committee on Toxicology. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants: Volume 2. Washington (DC): National Academies Press (US); 1984. Ethanolamine.Link*: https://www.ncbi.nlm.nih.gov/books/NBK208294/*

Appendix B

November 2022

Methyldiethanolamine (MDEA) – CAS: 105-59-9

Synonyms: 2-[2-hydroxyethyl(methyl)amino]ethanol; N-Methyldiethanolamine; 2,2'-methyliminodiethanol

C-value (2022): 0.01 mg/m^3, main group 2, class I.

1. General information

1.1 Occurrence and use

Methyldiethanolamine (MDEA) is a tertiary amine and is colourless liquid with an ammonia like odour, miscible with water, ethanol, and benzene. MDEA is widely used as a sweetening agent in chemical, oil refinery, syngas production and natural gas. According to the ECHA database, MDEA is used by consumers in washing and cleaning products, by professional workers (widespread uses: coating products, lubricants and greases, metal working fluids, polymers and laboratory chemicals; building, construction work, and manufacture of plastic products (ECHA 2022). MDEA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

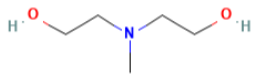
Table A.1 Regulatory overview, MDEA

Regulation	Specification	Reference
CLP-classification	Eye Irrit. 2; H319 (Causes serious eye irritation)	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Eye Irrit. 2; H319 (Causes serious eye irritation)	REACH-reg
REACH **Restrictions** **SVHC**	Registered at the tonnage level of 10 000 – 100 000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	Not listed	AT (2022)-
Danish C-value* 2016	Not listed	Danish EPA (2016)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, MDEA

Parameter	CAS No. 105-59-9	Reference
Structural formula		PubChem database
Chemical formula	$C_5H_{13}NO_2$	REACH-reg
Molecular weight	119.16	PubChem database
Physical state	Liquid at 20°C	REACH-reg
Melting point	-21.3°C	REACH-reg
Boiling point	243.3°C	REACH-reg
Vapour pressure	0.003 hPa at 20°C	REACH-reg
Relative vapour density	1.04	PubChem database
1 ppm = mg/m^3	4.87 mg/m^3	Calculated
Water solubility	1000 g/L at 20°C	REACH-reg
Partition coefficient log POW	-1.16 at 23°C	REACH-reg
Pka / pH	8.52 / pH: 11.5	PubChem database / REACH-reg
Odour threshold	Amine like odor, threshold not determined	PubChem database

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *The REACH-registration dossier (registered at the tonnage level of 10 000 – 100 000 tonnes per year), last modified in 02-Aug-2022*
- *MAK (1998). Methyldiethanolamine. MAK value documentation.*

The toxicological properties of MDEA are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination

Key values used for chemical safety assessment in the REACH-registration of the substance are an oral absorption rate of 100%; dermal absorption rate of 20%; and an inhalation absorption rate of 100%.

A single intravenous dose of 50 or 500 mg/kg bw of radiolabelled [14C] MDEA at a dose volume of 2 mL/kg was administered to four male rats per group and held for 72 hrs in metabolic cages. Distribution of MDEA was relatively uniform throughout the major organs, with the highest concentration found in liver and kidney. The predominant excretion route was in urine, where metabolites constituted the major fraction in urine, indicating that metabolism plays an important role in MDEA elimination. Urinary excretion was slow. Metabolism could be saturated at high dosages since nonlinear kinetic behaviour was observed in rats dosed intravenously with 500 mg/kg bw (REACH-reg).

Topically applied MDEA was well absorbed by both male and female rats, 17-21% and 41-50% after 6 and 72 hrs, respectively. After being retained in the skin and later slowly released into the bloodstream, distribution of MDEA was relatively uniform throughout the major organs, with the highest concentrations being in the liver and kidney. The urinary excretion half-life was in excess of 30 hrs following cutaneous dosing (REACH-reg).

3.2 Human toxicity

No human toxicity data was identified.

3.3 Animal toxicity

Single dose toxicity
MDEA has a low acute toxicity potential by inhalation, oral exposure and dermal exposure and does not meet the CLP-criteria for classification for acute toxicity.

Inhalation
In an inhalation acute toxicity study with rats, no mortality was observed after 6 and 8 hrs exposure to a saturated MDEA vapour atmosphere (REACH-reg).

Oral
The LD50 value for acute oral toxicity is 4680 mg/kg bw in rats (REACH-reg).

Dermal
The LD50 value for acute dermal toxicity is >2000 mg/kg bw in rats (REACH-reg).

Irritation
MDEA can induce irritation to the eyes resulting in the classification of Eye irrit. 2.

Skin irritation
In an acute dermal irritation/corrosion study, conducted according to OECD TG 404, application of undiluted MDEA to rabbit skin did not produce reactions after 1 to 15 min. Wide spanning reddening of the whole dorsal skin area was reported at the end of the observation period, scale formation occurred in one animal after 20 hrs (REACH-reg).

Eye irritation

In an acute eye irritation/corrosion study, similar to an OECD TG 405, 50 µL of the test substance were applied to the conjunctival sac of one eye in 2 rabbits. The animals were observed after 10 min, 1 and 3 hrs on the day of treatment and up to 8 days post-treatment. 50 µL of undiluted MDEA caused redness, swelling and clouding of the cornea as well as conjunctival bleeding. The symptoms disappeared after 8 days (REACH-reg).

Respiratory irritation
No data.

Skin sensitisation
MDEA is not considered to be a skin sensitiser based on animal experiments.

In a skin sensitisation study, equivalent or similar to an OECD TG 406, all 10 animals challenged with 0.1% of the positive control dinitrochlorobenzene showed clear skin response while all the irritation control animals were free of skin response. Of the 20 animals challenged with 100% MDEA 18 exhibited clear dermal responses. However, all 10 irritation control animals exhibited clear dermal responses. Due to the responses seen in the controls, a re-challenge was performed at lower, less irritating concentrations. Animals were re-challenged with 50% and 10% MDEA at separate sites. All test group animals re-challenged with 50% and 10% MDEA were free of dermal responses. In addition, all irritation control animals were free of dermal responses, confirming that non-irritating concentrations were administered. Under conditions of this study, MDEA produced sporadic irritation, but did not produce dermal sensitisation in guinea pigs (REACH-reg).

Repeated dose toxicity
In a sub-chronic dermal toxicity study in rats, local and systemic NOAELs of 100 mg/kg bw (corresponding to 0.8 mg/cm^2) and 750 mg/kg bw/day were identified, respectively (REACH-reg).

Inhalation
No data on repeated dose inhalation toxicity.

Oral intake
No data on repeated dose oral toxicity.

Dermal contact
In a sub-chronic dermal toxicity study, equivalent or similar to OECD TG 411 (dermal repeated dose 90-day study), rats were exposed to aqueous dilutions at dose levels of 100, 250, and 750 mg/kg bw for 6 hrs/day, 5 days/week, for 13 weeks. Results showed dose-related irritation in the mid- and high-dose groups; major histopathological features were acanthosis, hyperkeratosis, parakeratosis, dermatitis, dermal fibrosis, eschar, and ulceration. Low-dose group findings were similar to the controls, and probably a consequence of the wrapping procedure. There were no effects on clinical pathological findings or organ weights, and histopathological findings were limited to treated skin. These studies show that recurrent application of MDEA produces a dose-related irritant effect, but there is no evidence for systemic cumulative or specific target organ or tissue toxicity. Based on the sub-chronic study, local and systemic NOAELs of 100 mg/kg bw (corresponding to 0.8 mg/cm^2 based on an exposed body surface area of 25 cm^2 and an assumed body weight of 0.2 kg) and 750 mg/kg bw were established upon dermal exposure, respectively (REACH-reg).

Toxicity to reproduction
MDEA is not subjected for classification on toxicity to reproduction or developmental toxicity according to Regulation (EC) No. 1272/2008 (REACH-reg).

Reproduction
In a reproduction/ developmental toxicity screening study, according to OECD TG 421, the NOAEL for reproductive performance and fertility was 300 mg/kg bw for the F0 parental rats based upon findings such as litter loss, insufficient lactation behaviour, and increased duration of gestation. The NOAEL of 100 mg/kg bw/day was established for parental toxicity, based on body weight loss in both sexes. Reproductive toxicity was only seen in the presence of parental toxicity (REACH-reg).

Development
In a prenatal developmental toxicity study, equivalent or similar to OECD TG 414, occluded cutaneous application of MDEA to pregnant rats during organogenesis resulted in maternal toxicity as indicated by skin irritation and mild anaemia from 500 mg/kg bw/day onwards, but no treatment-related developmental effects were observed (REACH-reg).

Mutagenic and genotoxic effects
No indication of a mutagenic potential of MDEA was found in neither *in vitro* nor *in vivo* studies.

In vitro studies
In a bacterial reverse mutation assay, equivalent or similar to OECD TG 471, no mutagenic activity was observed in any of the 5 strains mutants over the range of concentrations tested (0.1, 0.3, 1, 3, 5, 10 mg/plate) in the absence or the presence of S9 activation (REACH-reg).

In vivo studies
In a mammalian erythrocyte micronucleus test, equivalent or similar to OECD TG 474, there were no significant differences in the polychromatic erythrocyte to normochromatic erythrocyte ratios at any dosage (175, 350, or 560 mg/kg bw). Furthermore, no significant increases in the incidence of micronucleated polychromatic erythrocyte were observed at any sampling time (30, 48 and 72 hrs). Therefore, MDEA is not considered to induce micronuclei under the condition of this test (REACH-reg).

Carcinogenic effects
No data.

4. Overall evaluation and identification of critical effect

Based on the data described above it can be concluded that the critical effect of MDEA is local irritation given that systemic toxicity was not observed at a dermal dose level of 750 mg/kg bw/day for 90 days. However, the study showed that recurrent application of MDEA produced local dermal irritation in a dose-related manner. No adequate data is available for assessing dose-response for irritation of the mucous membranes of the eyes and respiratory tract in relation to airborne exposure.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

It should be recognized that MDEA is an alkaline substance causing irritation to the mucous membranes of the eye. However, no inhalation data is available for assessing the potential for respiratory irritation.

MDEA as a tertiary amine is very similar to another tertiary amine: triethanolamine (TEA), both in relation to chemical structure and the physicochemical properties. However, MDEA according to the classification and Pka value might be considered a slightly more potent irritant than TEA. For triethanolamine (TEA) there is a substantial database including inhalation studies for the toxicological assessment, and thus it is considered relevant to perform a read-across from data on TEA for establishing a C-value for MDEA.

The critical effect of TEA is local respiratory tract irritation. In a subacute inhalation toxicity study, conducted according to OECD TG 412, rats were exposed to the TEA at concentrations of 0.02, 0.1, and 0.5 mg/L, 6 hrs/day, 5 days/week. TEA was administered as a liquid aerosol during the 28-day period. A NOAEC of 0.5 mg/L and 0.02 mg/L was established for systemic effects and for local effects (female), respectively. Since slight local effects were observed in males, this concentration was determined to be the LOAEC for local effects in males (REACH-reg). The LOAEC of 0.02 mg/L corresponds to 20 mg/m^3.

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV x UF V)
QC = 20 mg/m^3 / (2.5 x 10 x 6 x 3 x 3)
QC = 0.014 mg/m^3

It should be noted that the LOAEC exposure level of 20 mg/m^3 in relation to 6h/day is not averaged to a 24h exposure level (in this case it would be 5 mg/m^3) as it is the daily concentration level and not the daily inhaled amount of substance that is considered critical for developing the local effects in the respiratory tissue.

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the critical effect is local irritation) as no default kinetic factor is used when the critical effect is local irritation in surface tissue.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UF IV (dose-response) is set to 3 (values from 3-10 is the default value in REACH-guidance R8 for accounting for the point of departure). A factor 3 is selected based on mild irritant effects at the LOAEC level.

UF V (read-across): As MDEA may be considered slightly more potent as a respiratory irritant it is judged relevant to use an additional uncertainty factor of 3 in relation to the read-across approach and thus, a QC of 0.01 is proposed for MDEA.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure. Thus, a **C-value of 0.01 mg/m^3** is proposed for MDEA.

As a non-carcinogenic substance with a C-value of ≤ 0.01 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class I.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 001

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. Link: https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

ECHA (2022). Substance Inforcard on 2,2'-methyliminodiethanol. Accessed: September 19, 2022. Link: https://echa.europa.eu/da/substance-information/-/substanceinfo/100.003.012

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REACH-reg (2022). Reach registration dossier on 2,2'-methyliminodiethanol. Accessed: September 19, 2022. Link: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/14521

Appendix C

November 2022

2-Amino-2-methyl-1-propanol (AMP) – CAS: 124-68-5

Synonyms: 2-amino-2-methylpropan-1-ol; aminomethyl propanol

C-value (2022): 0.07 mg/m^3, main group 2, class II.

1. General information

1.1 Occurrence and use

2-Amino-2-methyl-1-propanol (AMP) is used by consumers in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing (REACH-reg). AMP is used to produce other chemicals (surface-active agents, vulcanization accelerators, and pharmaceuticals) and as an emulsifying agent for cosmetic creams and lotions, mineral oil and paraffin wax emulsions, leather dressings, textile specialties, polishes, cleaning compounds, and so-called soluble oils. The substance is also used in hair products, Pamabrom (drug), and absorbents for acidic gases. Used as a pigment dispersant for water-based paints, resin solubilizer, corrosion inhibitor, protecting agent for carbonyl groups and in boiler-water treatment (PubChem database). AMP is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

Table A.1 Regulatory overview, AMP

Regulation	Specification	Reference
CLP-classification	Eye Irrit. 2; H319 (Causes serious eye irritation) Skin Irrit. 2 H315 (Causes skin irritation) Aquatic Chronic 3; H412 (Harmful to aquatic life with long lasting effects)	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Eye Irrit. 2; H319 (Causes serious eye irritation) Skin Irrit. 2 H315 (Causes skin irritation)	REACH-reg.
REACH **Restrictions** **SVHC**	Registered at the tonnage level of 1000 – 10 000 tonnes per year none no	Regulation (EC) No 1907/2006
Danish OEL	3 ppm or 10.95 mg/m^3 (value from 1994)	AT (2022)
Danish C-value*	Not listed	Danish EPA (2016)-

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, AMP

Parameter	CAS No. 124-68-5	Reference
Structural formula		PubChem database
Chemical formula	$C_4H_{11}NO$	PubChem database
Molecular weight	89.14	PubChem database
Physical state	Solid at 20°C Colourless liquid above its melting point at 30 - 31°C	REACH-reg
Melting point	30 - 31°C	MAK 2012
Boiling point	165°C	MAK 2012
Vapour pressure	<1 hPa at 20°C	MAK 2012
Relative vapour density	3.0	PubChem database
1 ppm = mg/m³	3.65 mg/m³	Calculated
Water solubility	920 g/L at 20°C	REACH-reg
Partition coefficient log POW	-0.63 at 20°C	REACH-reg
Pka / pH	9.5 / pH: 11.3	Danish Q(SAR) / PubChem database
Odour threshold	Threshold not determined	-

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *The REACH-registration dossier (registered at the tonnage level of 1000 – 10 000 tonnes per year), last modified in 12-Jan-2022*
- *MAK (2012). 2-Amino-2-methyl-1-propanol. MAK value documentation.*

The toxicological properties of AMP are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination
In an OECD TG 417 toxicokinetic study, AMP did not show bioaccumulation potential. AMP is almost completely absorbed following administration of an oral bolus dose and almost 100% of the dose was excreted via the urine and faeces within 168 hrs, most of the dose was excreted within the first 24 hrs. AMP is not metabolised prior to excretion and does not appear to accumulate in any tissues. Dermal dosing led to an absorption of approximately 40% of the dose, the majority of which was excreted in the urine. Of the absorbed dose, approximately a quarter remained in the skin at the exposure site, and it is not clear if this would subsequently have become systemically available. Based on this data there is no concern that AMP would accumulate in the body (REACH-reg).

3.2 Human toxicity

Respiratory irritation
Heated AMP can generate sufficient vapour to cause mucosal irritation (MAK 2012); and AMP has been shown to cause airborne irritative contact dermatitis (REACH-reg).
Two cases of airborne contact dermatitis were noted in a cosmetic company when using AMP. Subjects suffered for months from periorbital oedema and facial erythema which worsened during work hours and improved with time away from work. Eight additional asymptomatic workers from the same company were studied concurrently. The prick and patch tests carried out with substances used in the production line proved negative except for AMP at 10% and 20% dilutions in water and ethyl alcohol. Positive results were recorded for erythema, oedema, and blisters. Positive results at 10% and 20% may be considered as irritative responses. There was lack of response to the lower doses (that would have been considered allergenic responses) noted in both the asymptomatic and symptomatic subjects (REACH-reg).

Repeated dose toxicity
Pamabrom, a bromotheophylline salt of AMP is an over-the-counter pharmaceutical product. Pamabrom is a diuretic, which works by increasing urination and is effective in treating oedema during pregnancy. 800 - 1600 mg daily (25% AMP= 200 - 400 mg/person/day) = 2.86 - 5.7 mg/kg/day (for a 70 kg individual) an oral exposure caused no toxic effects in pregnant women (sensitive population). NOAEL for AMP from the repeated dose oral data in women is 2.86- 5.7 mg/kg/day, for a 70 kg individual (REACH-reg).

3.3 Animal toxicity

Single dose toxicity
AMP has a low acute toxicity potential by inhalation, oral exposure and dermal exposure and does not meet the criteria for classification for acute toxicity.

Inhalation
The LC50 value for acute inhalation toxicity for 6 hrs exposure duration, was established to exceed 1300 mg/m^3 (REACH-reg).

Oral intake
The LD50 value for acute oral toxicity is 2900 mg/kg bw in rats (REACH-reg, MAK 2012).

Dermal contact
The LD50 value for acute dermal toxicity is >2000 mg/kg bw in rabbits (REACH-reg).

Irritation

AMP can induce irritation to skin and mucous membranes including the eyes resulting in the classification as Skin Irrit. 2 and Eye irrit. 2.

Skin irritation
In a study following a protocol similar to the Draize test, AMP was tested for irritation using an occluded application to the shaved backs of 6 rabbits. AMP was found to be highly irritating, producing clear signs of erythema and oedema. In a study to assess the irritancy to skin, AMP diluted at 4.75% in water was applied to the skin of 6 rabbits. None of the rabbits showed any sign of skin irritation (scores of 0 at all time-points). This study is used as a basis for a specific concentration limit of 5% for Skin Irritation. This is very conservative given that no irritation was noted just below this concentration (REACH-reg).

Eye irritation
AMP was applied to the eyes of 12 rabbits undiluted. In six of the rabbits, AMP was washed out 15-30 seconds after dosing. AMP caused serious damage to the eyes and ultimately destroyed the vision. The damage was not mitigated even with an immediate flushing of the eyes. The damage is likely the result of the high pH of the compound instead of any inherent toxicity based on the chemical structure. In a study to assess the irritancy to eyes, AMP diluted at 4.75% in water was applied to the eyes of 9 rabbits. None of the rabbits showed any sign of eye irritation (scores of 0 at all time-points). This study is used as a basis for specific concentration limits of 5% for Eye Irritation 2, and 10% for Eye Damage 1 (as pure AMP warrants Eye Damage 1) (REACH-reg).

Respiratory irritation
Studies of the potential irritant characteristics of inhaled AMP have been performed using the ATSM E981 sensory irritation methodology. Restrained mice were head-only exposed up to 1160 mg/m^3 aerosolized AMP for 3 hrs followed by a 20-minute recovery period. No deaths were recorded but sensory and pulmonary irritation of mice was noted (REACH-reg).

Skin sensitisation
Tested in the Buehler test in guinea pigs, AMP applied topically for provocation as 0.5 ml of a 5 % solution proved not to be sensitizing (MAK 2012).

Repeated dose toxicity
From studies on repeated exposure effects, irritation of the respiratory tract can be concluded as the most critical effect with a LOAC of 700 mg/m^3.

Inhalation
The objective of this study was to determine the toxicity via inhalation exposure by nose-only inhalation during/after five consecutive daily exposures (conducted in 2016). The rats were exposed to three dose levels of AMP (700, 1400, and 2000 mg/m^3) for six hours per day. Adverse histopathological findings seen predominantly in the mid and high dose animals (and to a lesser extent in the low-dose animals) included observations in the skin (necrosis and ulceration; also noted in the clinical observations) and nasal cavity (atrophy of goblet cells), squamous metaplasia (respiratory and transitional epithelium), and ulceration of the turbinates. A NOAEL in male and female rats after exposure for 6 hrs/day for 5 consecutive days via nose-only inhalation was not determined (REACH-reg).

Oral intake
In a reproduction / developmental toxicity screening study, according to OECD TG 421, dietary exposure of male rats to 700 mg/kg bw/day AMP-HCl (70% active AMP) caused increases in absolute and relative liver weights, accompanied by a very slight degree of micro vacuolization of periportal hepatocytes, with or without vacuolization of hepatocytes consistent with fatty change. Females in all treatment groups exhibited similar histopathological changes in the

liver, but in the absence of an organ weight change. Absolute and relative kidney weights were increased in the 700 mg/kg bw/day AMP, but these were not considered toxicologically significant due to the absence of histopathological changes. The NOEL for general toxicity in males was 210 mg/kg bw/day, while the general toxicity NOEL for females could not be determined (i.e., a LOAEL of 70 mg/kg bw/day for females), based upon the presence of very slight microscopic liver effects (REACH-reg.)

In a chronic toxicity study performed on beagle dogs, equivalent to an OECD TG 452, showed no effect at any dose level on general appearance, behaviour, body weight, food consumption, ophthalmoscopic exams, clinical chemistry, haematology, organ weights, or tissue histopathology. Based on the absence of statistically and biologically significant findings a NOAEL for AMP in the diets of Beagle dogs is >2.8 mg/kg bw/day (REACH-reg).

Dermal contact
No data.

Toxicity to reproduction
AMP exposure via the oral route at doses greater than 70 mg/kg bw/day causes an increase in post implantation loss via a specific (yet not fully defined) maternal mediated mechanism. The relevance of this effect observed in rats to humans is unclear given the differences in absorption between humans and rats, the specific nature of the maternal effect, the lack of evidence from other species. Therefore, it is proposed not to classify AMP for reproductive toxicity (REACH-reg).

Reproduction
AMP dose levels of 0, 70, 210 and 700 mg/kg bw/day were used in a reproduction / developmental toxicity screening study, according to OECD TG 421. AMP had no effect on mating performance or conception, but caused marked, dose-related increases in post-implantation loss (embryo resorption). At the high dose level all 12 pregnant females showed evidence of complete litter resorption (100% post-implantation loss), while at 210 mg/kg bw/day, post-implantation loss was 70% (vs. 10% in controls). Effects associated with, or secondary to the post-implantation loss increase at 210 mg/kg bw/day included decreased litter size, increased pup body weight, and decreased gestation body weight and body weight gain. There were no treatment related effects on reproductive performance at 70 mg/kg bw/day that was concluded as a NOAEL for reproductive effects (REACH-reg).

Development
In a prenatal developmental toxicity, according to OECD TG 414, dermal administration of 300 mg/kg bw/day of AMP produced significant effects at the test site, as evidenced by scabbing (77% affected) and moderate to severe scaling (35% affected). The dermal finding of slight scaling at 30 and 100 mg/kg bw/day was not considered adverse, as the observation was transient in nature and relatively low in incidence. There was no evidence of AMP related systemic maternal or developmental toxicity at any dose level tested. Under the conditions of this study, the NOAEL for maternal toxicity based on dermal effects was 100 mg/kg bw/day. The NOEL for developmental toxicity was 300 mg/kg bw/day (REACH-reg).

Mutagenic and genotoxic effects
AMP was not genotoxicity in the bacterial reverse mutation assay, the mammalian cell gene mutation assay, and a mouse micronucleus study.

Mutagenicity tests with AMP have included an OECD TG 471 bacterial reverse mutation assay (1996), an OECD 476 mammalian cell gene mutation assay (1997), and an OECD 474 mouse

micronucleus study (1998). Mutagenicity tests have also been conducted using the Ames assay in Salmonella typhimurium and a mutagenicity assay in Saccharomyces cerevisiae D4 (1976) (REACH-reg).

Carcinogenic effects
No data on carcinogenicity of AMP.

4. Overall evaluation and identification of critical effect

According to the MAK (2012) assessment, a NOEL could not be deduced from the available data on AMP at the time. The available study results are inadequate for the establishment of a MAK value. However, a point of departure could be identified from a more recent repeated dose inhalation study conducted in 2016 and it can be concluded that the critical effect of AMP most likely is local respiratory tract irritation. In a 5-day inhalation study, described as comparable to an OECD guideline study and GLP compliant, rats were exposed to three dose levels of AMP (700, 1400, and 2000 mg/m^3) for 6 hrs/day by nose-only inhalation. Adverse histopathological findings in the nasal cavity were seen at all dose levels. This indicates that local nasal irritation is a critical effect. However, a 5-day study is not considered adequate for derivation of a QC that must protect for chronic exposure as well. Instead, a LOAEL of 70 mg/kg bw/day for systemic exposure will be used. This point of departure is selected based on an OECD TG 421 reproductive study, where no treatment related effects on reproductive performance were observed at 70 mg/kg bw/day but were apparent at higher concentrations (REACH-reg).

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

According to Danish EPA (2006) a health-based quality criteria for systemic effects of AMP can be derived by a LOAEL of 70 mg/kg bw/day for systemic exposure. This point of departure is used as the basis for the calculation.

The first step to derive the quality criteria in air is to convert an oral LOAEL (in mg/kg bw/day) to an inhalation concentration (in mg/m^3). As a default the ECHA guideline uses a daily inhalation rate for rats of 1.15 m^3/ kg bw/day. Also, when no specific data on the oral absorption rate and the inhalation absorption rate, the inhalation rate by default is considered to be twice as high as the oral inhalation rate (ECHA 2012). Thus, a LOAEC can be calculated according to:

LOAEC = LOAEL/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 70 mg/kg bw/day/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 30 mg/m^3

The quality criterion can then be calculated:

QC = N(L)OAEC/ (UF I x UF II x UF III x UF IV)
QC = 30 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.066 mg/m^3 or 0.07 mg/m^3

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the dose metric is expressed in mg/m^3 for inhalation.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UF IV (dose-response): is set to 3 (values from 3-10 is the default value in REACH-guidance R8 for accounting for the point of departure). A factor of 3 for mild effects in the liver at the LOAEL is considered sufficient.

This level is also considered to protect against local effects in relation to the respiratory tract as the substance has a chemical structure closely related to MEA having a QC value of 0.07 mg/m^3.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.
Thus, a **C-value of 0.07 mg/m^3** is proposed for AMP.

As a non-carcinogenic substance with a C-value in the range of in the range of 0.01 -0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

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MAK (2012). 2-Amino-2-methyl-1-propanol. MAK Value Documentation. Link: https://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb12468kske0009

PubChem database 2022. 2-Amino-2-methyl-1-propanol | C4H11NO – PubChem. Accessed: September 18, 2022. Link: https://pubchem.ncbi.nlm.nih.gov/compound/11807

REACH-reg (2022). Reach registration dossier on 2-amino-2-methylpropanol. Link: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/11767

Appendix D

October 2022

Piperazine (PZ) CAS: 110-85-0

Synonyms: Diethylenediamine; 1,4-Diazacyclohexane

C-value (2022): 0.001 mg/m^3, main group 1, class I.

1. General information

1.1 Occurrence and use

PZ is used as salts for different applications or as an intermediate in the chemical industry. In human and veterinary medicine, PZ is used as an anthelmintic to treat parasitic infections; as an antihistaminic and tranquillizer It is also used as a corrosion inhibitor; as an additive in rubber production; and as a vulcanization accelerator (MAK 1998). PZ is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

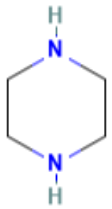
Table A.1 Regulatory overview, PZ

Regulation	Specification	Reference
	Skin Corr. 1B; H314 (Causes sever skin burns and eye damage) Resp. Sens. 1; H334 (may cause allergy or asthma symptoms or breathing difficulties if inhaled) Skin Sens. 1; H317 (May cause and allergic skin reaction) Repr. 2; H361fd (Suspected of damaging fertility)	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
CLP-classification	Skin Corr. 1B; H314 (Causes sever skin burns and eye damage) Eye Damage 1 H318 (causes serious eye damage) Resp. Sens. 1B; H334 (may cause allergy or asthma symptoms or breathing difficulties if inhaled) Skin Sens. 1B; H317 (May cause and allergic skin reaction) Repr. 2 H361 Suspected of damaging fertility or the unborn child	REACH-reg
REACH **Restriction** **SVHC**	Registered at the tonnage level of 1000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL **EU OEL (LTEL)** **EU OEL (STEL)**	0,1 mg/m^3 (value from 2022) 0.1 mg/m^3 0.3 mg/m^3	AT (2022) ECHA info card ECHA info card
Danish C-value* 2016	Not listed	Danish EPA (2016)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, PZ

Parameter	CAS No. 110-85-0	Reference
Structural formula		PubChem database
Chemical formula	$C_4H_{10}N_2$	REACH-reg
Molecular weight	86.14	REACH-reg
Physical state	Solid (at room temperature)	REACH-reg
Melting point	106°C	REACH-reg
Boiling point	147°C	REACH-reg
Vapour pressure	0.39 hPa at 23°C	REACH-reg
Relative vapour density	3	PubChem database
1 ppm = mg/m³	3.5 mg/m³	Calculated
Water solubility	150 g/L 20°C	REACH-reg
Partition coefficient log POW	-1.24 at 25°C	REACH-reg
Pka / pH	9.73 / pH: 10.8 – 11.8	PubChem database
Odour threshold	Ammonia like odour, 0.1 ppm	PubChem database

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *REACH-registration dossier (registered at the tonnage level of above 1000 tonnes per year), last modified in 31-Jan-2022*
- *European Union Risk Assessment Report. PZ (2005)*
- *MAK (1998). PZ. MAK Value Documentation*

The toxicological properties of PZ are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination

PZ is readily absorbed from the gastrointestinal tract in pigs, and major part of the resorbed compound is excreted as unchanged PZ during the first 48 hrs. An oral absorption of 100% is brought forward to the exposure assessment. However, no data on dermal or respiratory uptake have been located. Default absorption values of 100% are assumed for dermal and inhalation exposure. The principal route of excretion of PZ and its metabolites is via urine, with a minor fraction recovered from faeces (16%). However, about one fourth of a single administered oral dose is retained in the tissues after 7 days, some of which seems to consist of unidentified conversion products. Besides *N*-mononitrosoPZ, no other metabolites have been identified. In humans the kinetics of the uptake and excretion of PZ and its metabolites with urine appear to be roughly similar to that in the pig, although the nature and extent of conversion to metabolites remains unknown (ECB 2005).

Four healthy volunteers were exposed to a PZ concentration of 0.29 ± 0.03 mg/m^3 for 8 hrs. The urinary excretion of PZ amounted to 0.37 ± 0.05 mg in 48 hrs. The total dose was 1.1 mg PZ. Thus about 30% of the dose was excreted. The maximum amount of mono-N-nitrosoPZ excreted in the urine by a test person was 0.4 µg in 32 hrs. This suggests that about 5 % of the absorbed PZ is converted to mono-*N*-nitrosoPZ. *N,N'*-DinitrosoPZ was not detected in the urine (ECB 2005).

3.2 Human toxicity

Single dose toxicity

Experience from the pharmaceutical use of PZ indicates a moderate to low acute toxicity. Although no data on the lethal dose have been located, its use against gout at the end of the nineteenth century involved single doses that sometimes exceeded 10 g (corresponding to a dose of 144 mg/kg if assuming a body weight of 70 kg) (ECB 2005).

Irritation

Skin irritation

Application of a 25% aqueous solution of PZ hexahydrate, 25 g PZ hexahydrate/ 100 mL water, equivalent to 11% PZ base, caused primary dermal irritation in 10 out of 12 human volunteers. Concentrations below 50 g/L (< 2.2% PZ base) had no visible adverse effects. Patches soaked with the test solution were applied to skin for up to 48 hrs. There was a significant difference between two sources of the hexahydrate, one source seemed more irritating than the other. The responses varied from no response to erythema and marked vesiculation (ECB 2005).

Sensitisation

Systematic surveys of asthmatic reactions among workers exposed in a factory during production of PZ anhydrate, and a number of salts (adipate, citrate, phosphate, and dihydrochloride) were performed. 131 workers were employed in the production of PZ, potential exposure to several other chemicals also existed, information about work-related respiratory symptoms was obtained by questionnaire, and spirometry was also conducted. Fifteen persons were classified as asthmatic or had symptoms of asthma during work. Sixty-nine potential asthmatic cases could also be traced among 400 former workers. Interviews with 58 of these persons revealed 18 additional cases of occupational asthma of which 13 had supporting medical records. The criteria for the diagnosis of chemically induced asthma were recurrent dyspnoea with wheezing breathing and coughing, and an unequivocal association with exposure to PZ in 29 persons. None of the subjects had a history of attacks before employment, and atopic subjects were not preferentially affected. Specific provocation tests with PZ were positive, whereas bronchial constriction was not provoked in asymptomatic control subjects. The time

lag between first exposure and onset of asthma could vary from months to years, and the asthmatic reactions were mostly of the delayed type, but in some cases there was also an immediate transient reaction that was followed by a prolonged late phase reaction. In conclusion, PZ exposure scores were obtained for each subject expressed as a time-index (sum of time estimates for different work processes) and a time-weighted intensity index (sum of the products of each time estimate and corresponding intensity score, divided by the time index). Airway symptoms were clearly correlated with the PZ time-index but showed a less clear correlation with intensity of exposure. Operations generating the highest exposures were subsequently eliminated, and after more than one year a renewed study was undertaken. The mean TWA for this process was 1.2 mg/m^3, but peak values of about 100 mg/m^3 were found during cleaning. The most recent case of asthma associated with drum flaking was discovered in 1983, when the TWA exposure level for PZ in air was 0.7 mg/m^3, whereas among the personnel manufacturing the hexahydrate, a process characterised by a TWA level of 0.3-0.4 mg/m^3, no cases of asthma were found to have been elicited. For the latter groups, analysis by multiple regressions was included of lung function measures (VC, FEV1, VTG, VTG/TLC), age, height, smoking habits, atopy and PZ exposure. A healthy worker effect cannot be excluded, in as much as some PZ-exposed workers could have been exposed in a manner that favoured those able to tolerate PZ exposure and the true LOAEL and NOAEL applicable to the general population could actually be lower than the reported 0.4 mg/m^3. Some processes had been closed down, the intensity as well as peak exposures could only be roughly estimated for these processes, the LOAEL as well as NOAEL for asthma induction in this cohort is, therefore, associated with too much uncertainty to be brought forward to the risk characterization (ECB 2005).

Overall, human exposure to PZ and its salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation, but no NOAEL can be set as no threshold could be deduced from the studies.

Repeated dose toxicity

Several clinical studies of similar nature have been reported on oral exposure to PZ in relation to medical use. Taken together they offer convincing evidence for PZ neurotoxicity at recommended doses. For previously healthy humans, a LOAEL of about 30 mg PZ base/kg bw/day can be established for a limited 3-7 day's treatment period. Since there is little information on effects at lower doses than the therapeutic dose, the 30 mg/kg bw/day dose should rather be regarded as a 'low OAEL' than a true LOAEL (ECB 2005).

Mutagenic and genotoxic effects

Thirty male workers exposed to PZ and 30 controls were investigated with respect to induction of micronuclei in peripheral lymphocytes. An increased incidence of non-Hodgkin's lymphoma had previously been reported for this cohort. However, potential exposure may have involved over 100 chemicals including many well-known carcinogens, and no apparent significant associations to a specific exposure could be established (ECB 2005).

Carcinogenic effects

In a retrospective cohort study including 664 male workers employed in chemical plant where exposure to PZ as well as to a number of other chemicals, including carcinogens took place - a statistically significant increase in cancer morbidity was observed for malignant lymphoma/myelomatosis. However, due to confounding by mixed exposures, it is not possible to draw any valid conclusions from this observation. A case-control study conducted within the cohort did not reveal any significant association with any specific chemical (ECB 2005).

3.3 Animal toxicity

Single dose toxicity

PZ has a low acute toxic potential by inhalation, oral, and dermal exposure. PZ does not meet the criteria for classification for acute toxicity.

Inhalation
No LC50 value has been established as 4 hrs exposure at 2 mg/L did not result in any lethal outcome (REACH-reg).

Oral intake
The LD50 value for acute oral toxicity is 2600 mg/kg bw in rats (REACH-reg).

Dermal contact
The LD50 value for acute dermal toxicity is 8300 mg/kg bw in rabbits (REACH-reg).

Irritation
PZ is corrosive to skin and mucous membranes including the eyes resulting in the classification as Skin Corr. 1B; H314 (Causes sever skin burns and eye damage).

Skin irritation
The available skin irritation studies with rabbits, performed according to OECD TG 404, showed severe erythema and necrosis (ECB 2005).

Eye irritation
The available eye irritation studies with rabbits, performed according to methods similar to OECD guidelines, indicate that PZ causes necrosis covering up to 90% of the cornea (ECB 2005).

Respiratory irritation
Slight mucosal irritation reported in an inhalation hazard test (See acute toxicity, inhalation)

Sensitisation
Dermal
The available skin sensitisation test on guinea pigs, performed according to OECD guideline 406, showed mild sensitisation potential (REACH-reg).

Inhalation
No experimental animal data was found regarding inhalation and provocation of respiratory tract reactions.

Repeated dose toxicity

Inhalation
No relevant *in vivo* data was identified.

Oral intake
In a dietary study with PZ in beagle dogs, a dose 50 mg/kg/day (equivalent to 25 mg/kg/day of PZ base) was considered as a NOAEL in dogs by the EU Committee for Veterinary Medicinal Products (1999) (ECB 2005).

Dermal contact
No data.

Toxicity to reproduction
In a two-generation reproduction study in rats, performed according to OECD TG 416, with respect to effects on reproduction 125 mg/kg/day (PZ base) was considered as a NOAEL, with 300 mg/kg bw/day as a LOAEL for this study (ECB 2005).

Development
A study performed according to GLP assessed the effects of PZ phosphate on the embryonic and foetal development in New Zealand white rabbit. The study does not fulfil the requirements of the present OECD TG 414, as the exposure period only covers the period of organogenesis. Groups of 16 animals were dosed by oral intubation with 0, 100, 225, and 500 mg/kg bw/day PZ phosphate suspended in 1% w/v methyl cellulose. The doses correspond to 0, 42, 94, or 210 mg/kg bw/day PZ base. The females were treated from days 6 to 18 of pregnancy. Although borderline, 94 mg/kg bw/day PZ base may be considered to constitute the maternal LOAEL in this study. At 210 mg/kg bw/day, - a highly toxic maternal dose level - PZ base was highly embryotoxic and demonstrated teratogenicity. Post-implantation loss was high with 100% resorptions in four litters. Foetal weights were reduced and there was a slight retardation of ossification. In addition, 15 of 56 (23%) foetuses (in a total of 8 litters produced) exhibited major abnormalities (6 cases of cleft palate and 9 cases of umbilical hernia) as compared with two (1.7%) in controls. At 94 as well as at 42 mg/kg bw/day PZ base post-implantation loss, foetal weights, extent of ossification, and foetal sex ratios were unaffected by the treatment. Also, there was no significant increase in foetal abnormalities at the two lowest dose levels. Overall, the effects observed at 210 mg/kg bw/day PZ base are considered secondary to maternal toxicity.

Mutagenic and genotoxic effects
PZ tested on TA 1535, TA 1537, TA 98, and TA 100, at 33, 100, 333, 1000, or 2167 µg/plate was found to be negative in the Salmonella typhimurium reverse mutation test with and without metabolic activation. Upon dosing groups of CD-1 mice orally with 5000 mg/kg bw/day of PZ phosphate, no significant increase in the level of micronuclei of polychromatic or normochromatic erythrocytes of the bone marrow could be detected in an adequately performed GLP study. No lethality was observed at 5000 mg/kg bw/day, a dose that was subsequently utilised in this micronucleus test.

Carcinogenic effects
Groups of 15 MRC rats/sex were given 0.025% of PZ in the drinking water (20-25 mg/kg bw/day), 5 days/week, during 75 weeks after which the animals were kept until death and subjected to complete pathological examination. The dosed animals did not exhibit any increase of tumours in comparison with 15 male and 15 female controls.

4. Overall evaluation and identification of critical effect

Experience from the pharmaceutical use of PZ indicates a moderate to low acute toxicity in humans. Exposure to PZ and its salts to humans can cause allergic dermatitis as well as respiratory sensitisation. Dermal sensitisation is also shown by LLNA in mice.

The critical effect in humans in relation to inhalation of PZ was identified as respiratory sensitisation. In the European Union Risk Assessment Report, it is indicated that the true LOAEL and NOAEL applicable to the general population could actually be lower than the reported NOAEL of 0.4 mg/m^3 for occupational exposure. ECB (2005) concluded that the data on skin and respiratory tract sensitisation do not allow for evaluation of a threshold, so no adequate NOAEL/ LOAEL can be set.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

The critical effect is respiratory sensitisation as observed from occupational exposure. No specific health-based quality criteria value can be calculated for this effect as no threshold can be set for respiratory sensitisation.

5.2 Proposal for C-value

As a respiratory sensitizing substance with a C-value of 0.001 mg/m^3 the substance should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 1. Furthermore, the C-value of 0.001 mg/m^3 ensures low emission as a class I substance.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001.

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

ECB (2005). European Union Risk Assessment Report Cas No: 110-85-0, EINECS No: 203-808-3, PZ.

MAK. 1998. “PZ. MAK Value Documentation.”

PubChem database 2022. PZ | C4H10N2 – PubChem. Accessed: September 5, 2022. Link: https://pubchem.ncbi.nlm.nih.gov/compound/4837

REACH-reg (2022). Registration Dossier - ECHA - PZ CAS No. 110-85-0. Accessed: September 5, 2022. Link: https://echa.europa.eu/registration-dossier/-/registered-dossier/14941

Appendix E

November 2022

N-methyl-1,3-propanediamine (MAPA) CAS: 6291-84-5

Synonyms: 3-aminopropylmethylamine; methylaminopropylamine (MAPA)

C-value (2022): 0.04 mg/m^3, main group 2, class II.

1. General information

1.1 Occurrence and use

N-methyl-1,3-propanediamine (MAPA) is a primary diamine and used in formulation or re-packing and at industrial sites. MAPA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

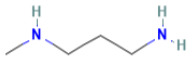
Table A.1 Regulatory overview, N-methyl-1,3-propanediamine (MAPA)

Regulation	Specification	Reference
CLP-classification	No harmonized classification	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Skin Corr. 1 H314 Causes severe skin burns and eye damage Eye Damage 1 H318 Causes serious eye Damage	REACH-reg
REACH **Restriction** **SVHC**	Registered at the tonnage level of 1 – 10 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	Not listed	AT (2022)
Danish C-value* 2016	Not listed	Danish EPA (2016)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, MAPA

Parameter	CAS No. 6291-84-5	Reference
Structural formula		PubChem database
Chemical formula	$H_2NCH_2CH_2OH$	PubChem database
Molecular weight	88.15	PubChem database
Physical state	Liquid	REACH-reg
Melting point	-19.53	Danish Q(SAR)
Boiling point	140°C	REACH-reg
Vapour pressure	1.333 kPa at 39.37°C	REACH-reg
Relative vapour density	Not identified	PubChem database
1 ppm = mg/m^3	3.61 mg/m^3	Calculated
Water solubility	1 000 g/L at 25°C	REACH-reg
Partition coefficient log POW	-0.66	REACH-reg
Pka / pH	Not identified / pH: 13.5 at 20ºC and 100 g/L concentration	PubChem database
Odour threshold	Odourless	

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *REACH-registration dossier (registered at the tonnage level of 1 - 10 tonnes per year), last modified in 27-Feb-2019*

The toxicological properties of MAPA are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination
No data.

3.2 Human toxicity

No data

3.3 Animal toxicity

Single dose toxicity
MEA has a moderate toxic potential in relation to oral exposure while specific lethal exposure levels has not been determined for dermal and inhalation exposure.

Inhalation
The LC50 value for acute inhalation toxicity is >189.3 mg/m^3 (REACH-reg).

Oral intake
The LD50 value for acute oral toxicity is 951 mg/kg bw in rats (REACH-reg).

Dermal contact
The LD50 value for acute dermal toxicity is >844 mg/kg bw in guinea pigs (REACH-reg).

Irritation
No data was identified for irritation. However, MAPA is a strong base (pH=13.5), and no testing has been made in the REACH-reg. because of this. Strong bases are considered corrosive to the eyes and skin.

Skin irritation
No data

Eye irritation
No data

Respiratory irritation
No data

Skin sensitisation
No data

Repeated dose toxicity
From studies on repeated exposure, irritation of the respiratory tract can be considered as the most critical effect with a LOAC of 61 mg/m^3.

Inhalation
In a repeated inhalation study for MAPA in rats by inhalation, animals (4 /group) were exposed to the test material at concentrations of 0, 61, and 189.3 mg/m^3 for 6 hrs/day for 13 days. Exposure was to aerosols with a MMAD of 7.2 µm. No statically significant effects were observed for clinical sign, gross pathology, and histopathology in the treated animal. Nasal irritation was observed, likely due to irritant nature of the substance, and the substance was indicated as a severe irritant. However, a NOAEC was considered to be 189.3 mg/m^3 for MAPA in rats by inhalation. (This may be in relation to systemic toxicity and not as an irritant).

Oral intake

In a Repeated dose study for MAPA in rats by oral gavage, the animals were exposed 12 times over a 16-day period, at dose levels of 0, 10 and 50 mg/kg bw/day. No statically significant effects were observed for clinical sign, food intake, body weight, haematology, clinical chemistry, gross pathology and histopathology of the treated male and female rats compared to control. Therefore, the NOAEL was considered to be 50 mg/kg bw/day for MAPA in rats by oral gavage in a 16-day study.

Dermal contact
No data.

Toxicity to reproduction

Fertility
No data

Development
No data

Mutagenic and genotoxic effects
MAPA was evaluated for its mutagenic potential in Salmonella typhimurium LT2 strains TA 1950 TS24, TA1537, TA1538, TA1952 and mutant hisG46. No mutagenic effects were observed.

Carcinogenic effects
No data.

4. Overall evaluation and identification of critical effect

MAPA is considered to have a low toxicity. However, due to the fact that MAPA is a strong base, irritation may occur when in contact with the skin, eyes or the airways. In a repeated dose study in rats by inhalation, animals were exposed to the MAPA at concentrations of 0, 61, and 189.3 mg/m^3 for 6 hrs/day for 13 days. No statically significant effects were observed for clinical sign, gross pathology, and histopathology in the treated animal. Although a NOAEC of 189.3 mg/m^3 was reported for systemic effects, no NOAEC for severe nasal irritation was reported, even though irritation was noted at all doses. As the substance is considered as a severe irritant a LOAEC of 61 mg/m^3 is considered for the local effects.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

According to Danish EPA (2006) the health-based quality criteria for MAPA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV)
QC = 61 mg/m^3 / (2.5 x 10 x 6 x 10)
QC = 0.04 mg/m^3

It should be noted that the NOAEC exposure level of 61 mg/m^3 in relation to 6h/day is not averaged to a 24h exposure level (in this case it would be calculated to 15.2 mg/m^3) as it is the daily concentration level and not the daily inhaled amount of substance that is considered critical for developing the local effects in the respiratory tissue.

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the critical effect is local irritation) as no default kinetic factor is used when the critical effect is local irritation in surface tissue.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from sub-acute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from sub-acute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UFIV: a further uncertainty factor of 10 due to poor reporting of the data and to consider the indication of severe irritation in the study.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.
Thus, a **C-value of 0.04 mg/m^3** is proposed for MAPA.

As a non-carcinogenic substance with a C-value in the range of in the range of 0.01 -0.2 mg/m^3 the substances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class II.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health.Link: COVER PAGE (europa.eu)

ECHA (2022). Substance Inforcard on 3-aminopropylmethylamine
Link: https://echa.europa.eu/da/substance-information/-/substanceinfo/100.025.950

PubChem database 2022. N-Methyl-1,3-propanediamine | C4H12N2 – PubChem. Accessed: 21, 2022. Link: https://pubchem.ncbi.nlm.nih.gov/compound/80511

REACH-reg (2022). Registration Dossier - ECHA - N-Methyl-1,3-propanediamine CAS No. 6291-84-5. Accessed: September 21, 2022. Link: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/20668

Appendix F

November 2022

Triethanolamine (TEA) CAS: 102-71-6

Synonyms: 2-[bis(2-hydroxyethyl)amino]ethanol; 2,2',2''-nitrilotriethanol

C-value (2022): 0.04 mg/m^3, main group 2, class II.

1. General information

1.1 Occurrence and use

Triethanolamine (TEA) is a tertiary amine and a triol. It is a bifunctional compound that exhibits both properties of alcohols and amines. TEA contains small amounts of diethanolamine and may also act as an antioxidant against the auto-oxidation of animal and vegetable fats. It is commonly used as a pH adjuster and surfactant in industrial and cosmetic products such as skin and hair conditioning products. TEA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

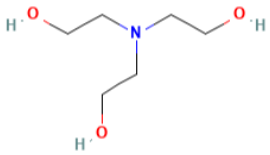
Table A.1 Regulatory overview, TEA

Regulation	Specification	Reference
CLP-classification	Not listed	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	No classification	REACH-reg
REACH **Restriction** **SVHC**	Registered at the tonnage level of 100 000 – 1 000 000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	3,1 mg/m^3 (value from 1994)	AT (2022)
Danish C-value* 2016	0,01 mg/m^3 (value from 1991)	Danish EPA 2016

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, TEA

Parameter	CAS No. 102-71-6	Reference
Structural formula		PubChem database
Chemical formula	$C_6H_{15}NO_3$	PubChem database
Molecular weight	149.19	PubChem database
Physical state	Liquid (viscous)	REACH-reg
Melting point	20.5°C	REACH-reg
Boiling point	336.1°C	REACH-reg
Vapour pressure	<0.0003 hPa at 21°C	REACH-reg
Relative vapour density	5.1	PubChem database
1 ppm = mg/m³	6.1 mg/m³	Calculated
Water solubility	>1000 g/L at 20°C	REACH-reg
Partition coefficient log POW	-2.3 at 25°C	REACH-reg
Pka / pH	7.76 / pH 10.5 (0.1 N solution)	PubChem database
Odour threshold	Mild ammonia like odour, 0.1 to 0.48 ppm	PubChem database

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *REACH-registration dossier (registered at the tonnage level of 100 000 – 1 000 000 tonnes per year), last modified in 05-May-2022*
- *MAK (2018). Triethanolamine / 2-[Bis(2-hydroxyethyl)amino]-ethanol. MAK value documentation.*

The toxicological properties of TEA are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination

Studies in experimental animals indicated that TEA is absorbed through the skin. No data on oral and inhalation exposure is available (REACH-reg).

3.2 Human toxicity

Respiratory sensitisation

A total of 3 cases of respiratory diseases caused by TEA have been reported. All cases were immediate-type reactions in the form of asthma or rhinitis. The workers were exposed to heated and thus increasingly vaporized triethanolamine. First symptoms were observed in 2 metal workers after they had used metal-working fluids containing triethanolamine for 8 to 10 years.

In an exposure chamber, provocation with the metal-working fluid that contained 14% TEA and had been heated to 100°C provoked an immediate reaction with a 17% decrease in the peak expiratory flow (PEF) rate. After exposure to undiluted, cold TEA, the PEF decreased by 21%. After provocation with a metal-working fluid that contained 85% TEA and had been heated to 100°C, the second patient reacted immediately, and the PEF was decreased by a maximum 21% for up to 20 hrs and the forced expiratory volume in one second (FEV1) was decreased by 13%. Exposure to the cold product led to an 18% decrease in the PEF. One control person with asthma and mild bronchial hyperreactivity and another with asthma and moderate bronchial hyperreactivity did not react to the provocation with heated TEA or a TEA aerosol (no other details).

An abstract reported allergic rhinitis caused by triethanolamine in an 8-year-old girl who reacted to 10^{-7} M to 10^{-4} M TEA in prick tests. The author also reported, without giving further documentation, a positive result in the test for passive cutaneous anaphylaxis with 10^{-7} M to 10^{-4} M triethanolamine and the detection of specific IgE to triethanolamine.

3.3 Animal toxicity

Single dose toxicity

TEA has a low acute toxic potential for oral and dermal exposure. Due to the low volatility of the substance, an acute inhalation toxicity has not been performed (REACH-reg)

Inhalation

No LC50 value has been determined for this compound (REACH-reg).

Oral intake

The LD50 value for acute oral toxicity is 6400 mg/kg bw in rats (REACH-reg).

Dermal contact

The LD50 value for acute dermal toxicity is >2000 mg/kg bw in rats (REACH-reg).

Irritation

TEA is not irritating to skin or eyes, and therefore does not meet the GHS criteria for classification.

Skin irritation
In a study equivalent or similar to an OECD TG 404, Acute Dermal Irritation / Corrosion study, application of undiluted TEA to rabbit skin did not produce a reaction (REACH-reg).

Eye irritation
In a study equivalent or similar to an OECD TG 405, Acute Eye Irritation / Corrosion study, 50 µL of the test substance were applied to rabbits. The animals were observed for 1 hr, 24 hrs and 8 days post-treatment. No effects where observer for TEA 24 hrs and 8 days post exposure (REACH-reg).

Respiratory irritation
No data.

Skin sensitisation
In study conducted according to OECD TG 406, skin sensitisation, no sensitisation potential was reported for TEA in guinea pigs upon dermal sensitisation and challenge. Although allergic reactions to TEA have been reported, the substance is judged to have a very low sensitisation potential in both humans and animals (REACH-reg).

Repeated dose toxicity
From studies on repeated exposure, irritation of the respiratory tract can be considered as the most critical effect with NOAEC of 20 mg/m^3.

Inhalation
In a Subacute inhalation toxicity study, conducted according to OECD TG 412, rats were exposed to the TEA at concentrations of 0.02, 0.1, and 0.5 mg/L, 6 hrs/day, 5 days/week. TEA was administered as a liquid aerosol during the 28-day period. A NOAEC of 0.5 mg/L was established for systemic effects. Local effects were characterized histopathologically by focal inflammatory changes in the submucosa of the larynx region with a tendency of concentration dependent increase in incidence and severity of the lesion from mid to high concentration in both sexes. Since slight local effects were observed in males at 0.02 mg/L, this was considered as a LOAEC (REACH-reg). The LOAEC of 0.02 mg/L corresponds to 20 mg/m^3.

Oral intake
In a subchronic oral toxicity study, conducted similar to OECD TG 408 (oral repeated dose 90-day study), rats were fed 250, 500 or 1000 mg/kg bw/day of TEA. No treatment related effects were observed in the study. Therefore, a NOAEL of 1000 mg/kg bw/day was established for both males and females.

Dermal contact
In a subchronic oral toxicity study, conducted similar to OECD TG 411 (dermal repeated dose 90-day study), rats were exposed to 1.125, 0.25, 0.5, 1 or 2 g/kg bw/day of TEA. The compound-induced skin lesions, chronic-active inflammation and acanthosis. The incidence, severity, and morphology of the lesions were similar between sexes. In males, however, the compound effect extended to one dose lower than in females. Although there was increased incidence of nephropathy from low to high dose in female rats, the severity of this lesion did not vary between dose groups, and, therefore, it was regarded as incidental. A NOAELs of 125 and 250 mg/kg bw/day were established for local effects for males and females.

Toxicity to reproduction
TEA decreased the number of implants and delivered pups. Regardless, TEA is not subjected for classification on toxicity to reproduction or developmental toxicity according to Regulation (EC) No. 1272/2008.

In a reproduction / developmental toxicity screening test, according to OECD TG 421 study, rats were dosed with TEA at 100, 300 and 1000 mg/kg bw/day. A NOAEL of > 1000 mg/kg bw/day was established for systemic toxicity and reproductive performance and fertility as no adverse effect were observed up to the highest dose tested. In the F1 generation, decreased numbers of implants and delivered pups was recorded, and an increase of post-implantation loss. Thus, a NOAEL of 300 mg/kg bw/day was established for developmental toxicity.

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) has been conducted in rats orally exposed to 0, 100, 300 and 1000 mg/kg bw/day. In the high-dose F0 and F1 generation females (1000 mg/kg bw/day), decreased numbers of implants and increased resorption rates resulted in significantly smaller litters, giving evidence for an adverse effect of the test compound on fertility and/or reproductive performance at high doses. It has to be noted that a dose of 1000 mg/kg bw/day also caused systemic toxicity in these females, as was indicated by reduced food consumption and/or body weight gain during gestation/lactation.

Mutagenic and genotoxic effects
No indication of a mutagenic potential of TEA was found in *in vitro* studies.

In vitro studies
In an OECD TG 473 (in vitro mammalian chromosome aberration test), CHO cells were exposed to TEA at 1510 - 4030 µg/mL (without S9) and 6040 - 10100 µg/mL (with S9). The test results showed negative results for mutagenicity with and without metabolic activation.

In vivo studies
No data

Carcinogenic effects
In a 2-year carcinogenicity study performed in rats, 667 mg/kg bw/day or 1333 mg/kg bw/day were administered daily via the drinking water. A variety of tumours developed in all groups, including the control group, and all tumours observed were histologically similar to spontaneous tumours in this strain of rats. No statistically significant increase of the incidence of any tumour was observed in the treated groups of both sexes by the chi-square test. In this study, however, there was an increase in nephrotoxicity, which appeared to have an adverse effect on the life expectancy of the treated animals, especially of females. Therefore, an age-adjusted statistical analysis on incidences of main tumours or tumour groups of both sexes was also done. The result showed that a positive trend was noted in the occurrence of hepatic tumours (neoplastic nodule/hepatocellular carcinoma) in males and of uterine endometrial sarcomas and renal-cell adenomas in females. These tumours, however, have been observed spontaneously in this strain of rats, and their incidences in the control group of the present study were lower than those of our historical controls. These results may indicate that a positive trend in the occurrence of these tumours is not attributable to triethanolamine administration. Increased incidence of renal tumours in the female high-dose group may have related to renal damage. Histological examination of renal damage observed in the treated groups, especially in the female high-dose group, revealed acceleration of so-called chronic nephropathy. In addition, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis with or without papillary necrosis were also observed. Thus, it is concluded that under these experimental conditions triethanolamine is not carcinogenic in F344 rats but is toxic to the kidneys. A NOAEL of 1333 mg/kg bw/day was established in this study.

4. Overall evaluation and identification of critical effect

From the data above –it can be concluded that the critical effect of TEA is the local respiratory tract irritation. In a Subacute inhalation toxicity study, conducted according to OECD TG 412, rats were exposed to the TEA at concentrations of 0.02, 0.1, and 0.5 mg/L, 6 hrs/day, 5 days/week. TEA was administered as a liquid aerosol during the 28-day period. A NOAEC of 0.5 mg/L and 0.02 mg/L was established for systemic effects and for local effects (female), respectively. Since slight local effects were observed in males, this concentration was determined to be the LOAEC for local effects in males (REACH-reg). The LOAEC of 0.02 mg/L corresponds to 20 mg/m^3.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

According to Danish EPA (2006) the health-based quality criteria for TEA can be derived by:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV)
QC = 20 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.044 mg/m^3

It should be noted that the LOAEC exposure level of 20 mg/m^3 in relation to 6h/day is not averaged to a 24h exposure level (in this case it would have been 5 mg/m^3) as it is the daily concentration level and not the daily inhaled amount of substance that is considered critical for developing the local effects in the respiratory tissue.

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the critical effect is local irritation) as no default kinetic factor is used when the critical effect is local irritation in surface tissue.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UF IV (dose-response): is set to 3 (values from 3-10 is the default value in REACH-guidance R8 for accounting for the point of departure). A factor 3 is selected based on mild irritant effects at the LOAEC level.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.
Thus, a **C-value of 0.04 mg/m^3** is proposed for TEA.

As a non-carcinogenic substance with a C-value in the range of 0.01 -0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose [concentration]-response for human health. Link: https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897. Accessed: October 21, 2022
Link: https://echa.europa.eu/da/substance-information/-/substanceinfo/100.002.773

PubChem database 2022. Triethanolamine| C6H15NO3 – PubChem. Accessed: October 21, 2022. Link: https://pubchem.ncbi.nlm.nih.gov/compound/7618

REACH-reg (2022). Registration Dossier - ECHA - 2,2',2"-nitrilotriethanol CAS No. 102-71-6. Accessed: October 21, 2022. Link: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/15134/1/2

Appendix G

November 2022

Monoisopropanolamine (MIPA) CAS: 78-96-6

Synonyms: 1-aminopropan-2-ol; 1-amino-2-propanol; Isopropanolamine

C-value (2022): 0.02 mg/m^3, main group 2, class II.

1. General information

1.1 Occurrence and use

Monoisopropanolamine (MIPA) is a primary amine with an alcohol group at the C2 position. (PubChem database). MIPA is a precursor of vitamin B12 and/or an intermediary in the production of propionaldehyde in many microbial genera (CIR 1987). As industrial chemical MIPA is used in the following products: washing & cleaning products, biocides (e.g., disinfectants, pest control products), fuels and cosmetics and personal care products (REACH-reg). MIPA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

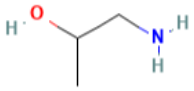
Table A.1 Regulatory overview, MIPA

Regulation	Specification	Reference
CLP-classification	Skin Corr. IB; H314 Causes severe skin burns and eye damage	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Skin Corr. IB; H314 Causes severe skin burns and eye damage Acute Tox 4 H312 Harmful in contact with skin Eye Damage 1 H318 Causes serious eye damage	REACH-reg.
REACH **Restriction** **SVHC**	Registered at the tonnage level of ≥ 1000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	Not listed	AT (2022)
Danish C-value* 2016	Not listed	Danish EPA (2016)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, MIPA

Parameter	CAS No. 78-96-6	Reference
Structural formula		PubChem database
Chemical formula	C_3H_9NO	PubChem database
Molecular weight	75.11	PubChem database
Physical state	Colourless liquid	REACH-reg
Melting point	1.74°C	REACH-reg
Boiling point	159.5°C	REACH-reg
Vapour pressure	0.63 hPa at 25°C	REACH-reg
Relative vapour density	2.6	PubChem database
1 ml/m³ (ppm) = mg/m³	3.12 mg/m³	MAK 1998
Water solubility	miscible	REACH-reg
Partition coefficient log POW	-0.93 at 23°C	REACH-reg
Pka / pH	9.62 at 20°C/ Ca. pH at 12 at 20 g/L and at 20°C	REACH-reg / Sasol (2019)
Odour threshold	Mild ammonia like odour, threshold not determined	PubChem database

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *REACH-registration dossier (registered at the tonnage level of ≥ 1000 tonnes per year), last modified in 01-Sept-2022*
- *MAK (1998). 1-Amino-2-propanol. MAK value documentation.*
- *CIR (1987) Final Report on the Safety Assessment of Diiopropanolamine, Isopropanolamine, and mixed Isopropanolamine.*

The toxicological properties of MIPA are described in the following sections. Information on the substances was retrieved from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination
MIPA has been detected in the urine of man and rat as a naturally occurring amino alcohol. It is formed via aminoacetone from L-threonine. MIPA is a precursor in the biosynthesis of vitamin B12, and in micro-organisms it is a precursor of propionaldehyde (MAK 1998).

3.2 Human toxicity

Irritation
Questioning industrial workers who were exposed to MIPA yielded a few reports of contact dermatitis. As the substance is alkaline, the described effects are more likely to be a result of skin irritation than of sensitisation (MAK 1998).

Sensitisation
A 2 % aqueous solution of MIPA was tested for sensitising and photo-sensitising potential in a modified Draize test. The test solution (0.2 mL) was applied to the dorsal skin of 150 male and female persons for a period of 48 to 72 hrs, 9 times within 3 weeks. During the provocation treatment two weeks later, MIPA did not induce allergic dermatitis. In another test, 0.2 mL of a 0.2 % solution of MIPA was applied to the skin of 25 male and 25 female persons on three consecutive days, weekly for three weeks. Each time the patch was removed, the application site was irradiated with UVA and UVB light (three times the minimal erythema-inducing dose). MIPA did not induce photoallergic reactions (MAK 1998).

3.3 Animal toxicity

Single dose toxicity
MIPA has a low acute toxic potential for oral and dermal exposure (REACH-reg).

Inhalation
No LC50 value has been determined for this compound, an acute inhalation exposure study in rats for 6 hrs at a concentration of 3460 mg/m^3 failed to cause any deaths in rats (REACH-reg).

Oral intake
The LD50 value for acute oral toxicity is 2813 mg/kg bw in rats (REACH-reg).

Dermal contact
The LD50 value for acute dermal toxicity is 1851 mg/kg bw in rabbits (REACH-reg).

Irritation
MIPA can cause severe burns and eye damage, therefore MIPA is categorized as Skin Corr. 1B; H314.

Skin irritation
Animals were treated for 1, 5, 15 min and 20 hrs using occlusive conditions. An application site of 2.5x2.5 cm was covered with the liquid test substance. After the application time (1, 5 and 15 min) the skin was washed with Lutrol (50%). The animals were observed for 8 days, and skin changes were recorded daily. During the application of the test substance, a 5-minute application period resulted in severe oedema and erythema and caused grey-blackish, relocatable necrosis beyond the application. Besides bleeding was observed for 3/6 animals (MAK 1998)

Eye irritation
Animals were treated with 50 µL of MIPA to the conjunctival sac of one eye in 2 rabbits. The animals were observed after 10 min, 1 and 3 hrs on the day of treatment and up to 8 days afterwards. Findings were recorded daily. The eyes were not washed out after 24 hrs. The report

describes findings after 1 and 24 hrs and at the end of the observation period. The application of the test substance caused corrosion to the exposed eyes predominantly expressed by severe corneal opacity, severe erythema and iritis. After 48 hrs crusty eyelids, suppuration and staphyloma were noted. Severe corneal opacity and staphyloma are considered to be irreversible effects to ophthalmic tissue.

Respiratory irritation
Sensory irritation was induced in mice exposed during 3 hours to an aerosol with concentrations of 230 to 1005 mg/m3 MIPA. Little pulmonary irritation (delayed onset) occurred.

Skin Sensitisation
Testing for skin sensitisation has not been performed because of the corrosivity of the substance.

Repeated dose toxicity
From studies on repeated exposure, irritation of the respiratory tract can be considered as the most critical effect with NOAEC of 75 mL/m^3.

Inhalation
In a sub-acute study, groups of 4 to 6 male and 4 to 6 female B6C3F1 mice and F344 rats were exposed to MIPA concentrations of 0, 25, 50 or 75 mL/m^3 for 6 hrs daily, 9 times within 2 weeks. MIPA had no effect on body or organ weights. Gross pathological and microscopic examinations revealed no changes; haematological, serological and urinary parameters were not affected by the exposures (MAK 1998).

Oral intake
In a sub-chronic study, groups of 10 rats were given MIPA in the diet for 90 days at doses between 140 and 2200 mg/kg bw/day. The high dose caused changes in kidneys and liver weight. The NOEL was established as 600 mg/kg bw/day (MAK 1998).

Dermal contact
A single application of MIPA to the shaved abdominal skin of a rabbit for one hr caused moderate corrosion. Repeated application caused marked erythema and very slight swelling of the skin, and moderate corrosion after 7 applications (MAK 1998).

Toxicity to reproduction
No significant data was identified.

Mutagenic and genotoxic effects
No indication of a mutagenic potential of MIPA was found in *in vitro* studies.

In vitro studies
In a mutagenicity study with Salmonella typhimurium, MIPA (purity 97 %) was tested in the concentration range between 1 and 5000 µg/plate in the S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of an exogenous metabolizing system (S9 from the livers of rats pre-treated with Kanechlor500). Cytotoxicity was seen at the highest concentration. MIPA proved not to be mutagenic. In another Salmonella mutagenicity test, MIPA (purity 96.4 %) was tested in the concentration range between 33 and 4000 µg/plate in the strains TA98, TA100, TA1535 and TA1537 with and without an exogenous metabolizing system (S9 from the livers of rats and hamsters pre-treated with Aroclor 1254). In the strains TA98, TA100 and TA1537 no mutagenicity could be detected. In TA1535 at concentrations of about 1800 to 2800 µg/plate and more in the presence of S9 from either rat or hamster liver, in each case in 2 of 4 tests, significant increases in the number of revertant (2.7 to 5.8 times the control values) were found. Reasons for the inconsistency of the results were

not discussed. Cytotoxicity was seen at concentrations of 2800 or 3333 µg/plate. In Escherichia coli WP2uvrA, MIPA was not mutagenic in the concentration range between 1 and 5000 µg/plate either with or without S9 from the livers of rats treated with Kanechlor 500 (MAK 1998).

In vivo studies
No data

Carcinogenic effects
No data.

4. Overall evaluation and identification of critical effect

From the data above it is concluded that MIPA is of low acute, subchronic and chronic systemic toxicity. The substance in its liquid form is a severe eye irritant and as for other amino alcohols (e.g., the structural closely related MEA) local irritation of mucous membranes may be considered as the critical effect in relation to airborne exposure to the substance. As no specific data is available from which to estimate the quality criterion it is considered justified to use read-across from the data on MEA that is a very closely related substance with respect to chemical structure, physicochemical data and toxicological profile.

In an OECD TG 412 inhalation study groups of 5 male and 5 female Wistar rats were exposed nose-only to MEA aerosol (with a vapour fraction; purity of the test substance: 99.93%) for 28 days, for 6 hours a day, on 5 days a week. The test concentrations were 0, 10, 50 or 150 mg/m^3 (analysed concentrations: 10.2, 49.1 and 155.9 mg/m^3; MMAD = 1.1 to 1.2 µm, with about 70% of the particles below 3 µm; the aerosol fraction was 0.5, 26.4 and 134.5 and the vapour fraction was 9.8, 22.7 and 21.4 mg/m^3). The exposure resulted in adverse morphological changes to the epithelium in the larynx (metaplasia of the squamous epithelium, inflammation and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with an increasing incidence and severity. The resulting local NOAEC for rats after 28-day exposure was 10 mg/m^3.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC

The QC for MIPA is based on read-across data from MEA:

QC = N(L)OAEC / (UF I x UF II x UF III x UF IV)
QC = 10 mg/m^3 / (2.5 x 10 x 6 x 3)
QC = 0.02 mg/m^3

It should be noted that the NOAEC exposure level of 10 mg/m^3 in relation to 6h/day is not averaged to a 24h exposure level (in this case it would be 2.5 mg/m^3) as it is the daily concentration level and not the daily inhaled amount of substance, that is considered critical for developing the local effects in the respiratory tissue.

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the critical effect is local irritation) as no default kinetic factor is used when the critical effect is local irritation in surface tissue.

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UF IV (read-across): it is judged relevant to use an additional uncertainty factor of 3 in relation to the read-across.

Based on a read across from MEA data, a QC of 0.02 mg/m^3 can be set for MIPA.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.
Thus, **a C-value of 0.02 mg/m^3** is proposed for MIPA.

As a non-carcinogenic substance with a C-value in the range of 0.01 – 0.2 mg/m^3 the substances should, according to *Luftvejledningen* (Danish EPA 2001), be placed in main group 2, class II.

6. References

AT (2022). Bilag 2 til Arbejdstilsynets bekendtgørelse nr. 1054 af 28. juni 2022 om grænseværdier for stoffer og materialer (kemiske agenser) i arbejdsmiljøet.

CIR (1987) Final Report on the Safety Assessment of Diiopropanolamine, Isopropanolamine, and mixed Isopropanolamine.

Danish EPA (2001). Luftvejledningen Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen Nr. 2 2001

Danish EPA (2006). Metoder til fastsættelse af kvalitetskriterier for kemiske stoffer I jord, luft og drikkevand med henblik på at beskytte sundheden. Vejledning fra Miljøstyrelsen Nr. 5.

Danish (EPA (2016). Vejledning om B-værdier. Vejledning nr. 20. Miljøstyrelsen.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose [concentration]-response for human health.
Link: https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

ECHA (2022). Substance Inforcard on 1-aminopropan-2-ol. Accessed: November 11, 2022.
Link: https://echa.europa.eu/da/substance-information/-/substanceinfo/100.001.057

PubChem database 2022. 1-aminopropan-2-ol | C3H9NO – PubChem. Accessed: November 11, 2022. Link: https://pubchem.ncbi.nlm.nih.gov/compound/4

REACH-reg (2022). Registration Dossier - ECHA - 1-aminopropan-2-ol CAS No. 76-96-6. Accessed: November 11, 2022. Link: https://echa.europa.eu/da/registration-dossier/-/registered-dossier/13935

MAK (1998). 1-Amino-2-propanol. MAK value documentation.

Sasol (2019). MONOISOPROPANOLAMINE. SAFETY DATA SHEET. Version 11.01, 2019

Appendix H

November 2022

2-(methylamino)ethanol (MMEA), CAS: 109-83-1

Synonyms: N-Methylethanolamine; Ethanol, 2-(methylamino)-

C-value (2022): 0.01 mg/m^3, main group 2, class I.

1. General information

1.1 Occurrence and use

2-(methylamino)ethanol (MMEA) is a secondary amine. This substance is used by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing (REACH-reg). MMEA is also used in the carbon capture technology and emission to air may result from this use.

1.2 Regulation

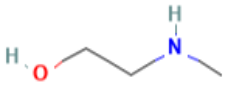
Table A.1 Regulatory overview, MMEA

Regulation	Specification	Reference
CLP-classification	Acute tox. 4; H302 + H312 (Harmful if swallowed, in contact with skin) Skin Corr. 1B; H314 (Causes severe skin burns and eye damage)	Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)
	Acute tox. 4; H302 + H312 (Harmful if swallowed, in contact with skin) Skin Corr. 1B; H314 (Causes severe skin burns and eye damage) Eye Damage 1 H318 (Causes serious eye damage) Repr.. 2 H361 (Suspected of damaging fertility or the unborn child) STOT SE 3 H335 (May cause respiratory irritation) STOT RE 2 H373 (May cause damage to organs through prolonged or repeated exposure) organs: kidney, testes, epididymides, ovaries, liver, and spleen	REACH-reg
REACH **Restriction** **SVHC**	Registered at the tonnage level of 1000 – 10 000 tonnes per year no no	Regulation (EC) No 1907/2006
Danish OEL	3 ppm or 9.36 mg/m^3	AT (2022)
Danish C-value* 2016	No listed	Danish EPA (2016)

*In Danish = B-værdi

2. Physicochemical properties

Table A.2 Physicochemical properties, MMEA

Parameter	CAS No. 109-83-1	Reference
Structural formula		PubChem database
Chemical formula	C_3H_9NO	PubChem database
Molecular weight	75.11	PubChem database
Physical state	Clear colourless liquid	PubChem database
Melting point	-3 °C - -5°C	REACH-reg. PubChem database
Boiling point	160°C	REACH-reg
Vapour pressure	2.01 hPa at 30.6°C	REACH-reg
Relative vapour density	2.6	PubChem database
1 ppm = mg/m^3	3.12 mg/m^3	Calculated
Water solubility	1 000 g/L at 20°C	REACH-reg
Partition coefficient log POW	-0.91 at 25°C	REACH-reg
Pka / pH	9.95 at 20°C / pH 13.6	REACH-reg
Odour threshold	Fishy odour, threshold not determined	PubChem database

3. Toxicology

Data considered most relevant for the toxicological evaluation of the substance in relation to derivation of a C-value:

- *the REACH-registration dossier (registered at the tonnage level of 1000 –10 000 tonnes per year), last modified in 24-May-2022*

Below the toxicological properties of MMEA is described based on the description from the above sources. Data from the REACH-registration was assessed carefully for quality and validity before use as the data reported by the registrant may not have undergone any expert check.

3.1 Toxicokinetics

Absorption, distribution, elimination

Key values used for chemical safety assessment in the REACH-registration of the substance are an oral, dermal and inhalation absorption rates of 100%.

Based on physico-chemical properties and on the effects observed in animal studies, absorption of MMEA into the body is favoured via all exposure routes. MMEA produced clinical signs pointing to systemic availability. Due to a molecular weight of 75.1, negative log Pow (-0.91), high water solubility (1000 g/L), and pronounced clinical signs observed in animals treated orally, oral absorption is considered to be extensive and therefore set to 100 %. According to the criteria outlined in Guidance on Toxicokinetics (Chapter R.7C), absorption by inhalation is considered to be low due to the vapour pressure of 201 Pa (< 500 Pa), high water solubility and negative log Pow (the substance may be retained in the mucus). However, 100 % absorption by inhalation (worst-case) is taken for hazard assessment due to the absence substance-specific experimental data. Dermal absorption is considered to be low. Molecular weight of 75.1 (< 100) favours dermal uptake while negative log Pow and high-water solubility do not. For oral-to-dermal extrapolation, dermal absorption is set to equal to oral absorption (100 %, worst case). (REACH-reg)

3.2 Human toxicity

Respiratory irritation
There is no evidence that exposure to MMEA may result in a pattern of symptoms and signs which involves different organs as well as stimulation of the central nervous system. There is possible relationship between the reported exposure by inhalation and by skin and the irritation of the mucous membranes. Human injuries have been reported after inhalation (REACH-reg)

3.3 Animal toxicity

Single dose toxicity
MMEA has acute toxic potential and has a classification as Acute tox. 4; H302 + H312 (Harmful if swallowed, in contact with skin)

Inhalation
No mortalities occurred during the observation period. Eye and nose discharge were the only abnormalities noted. Gross pathology revealed no signs of toxicity. LC50 was not identified. (REACH-reg).

Oral intake
The LD50 value for acute oral toxicity is 1880 mg/kg bw in rats (REACH-reg).

Dermal contact
The LD50 value for acute dermal toxicity is >2000 mg/kg bw in rats (REACH-reg). However, the substances have a harmonised classification as Acute Tox 4 in relation to dermal contact.

Irritation
MMEA is corrosive to skin and mucous membranes including the eyes resulting in the classification as Skin Corr. 1B; H314 (Causes severe skin burns and eye damage).

Skin irritation
In an irritation study, three animals were treated for 3 min, 1 hr or 4 hrs using occlusive conditions. An application site of 2.5 x 2.5 cm was covered with the liquid test substance (0.5 mL). After the application time the skin was washed with Lutrol and Lutrol/water (1:1). The animals were observed for 8 days, skin changes were recorded daily. The following outcomes were observed: 24 hrs after 3 min application slight erythema were observed and 1 animal showed

distinct oedema. At the end of the observation period of 8 days the irritations eased under scaling. Immediately after 1 hr exposure wide spanning erythema and distinct spanning oedema was observed. After 24 hrs parchment-like necrosis was noted. At the end of the observation period of 8 days, persistent oedema and leathery-like necrosis was observed. This is considered to be a full thickness necrosis. Immediately after a 4 hrs exposure necrosis and wide spanning oedema was noted. At the end of the observation period of 8 days irreversible necrosis was observed. This is considered to be a full thickness necrosis (REACH-reg)

Eye irritation
In an eye irritation test, 50 µL of the test substance were applied to the conjunctival sac of one eye in 2 rabbits. The animals were observed after 10 min, 1 hr and 3 hrs on the day of treatment and up to 8 days post-treatment. The eyes were not washed out after 24 hrs as specified in OECD Guideline 405. Within 10 min the application of the test substance caused severe corneal opacity and corrosions of the mucous membrane. After 3 days purulent exudate was noted. At the end of the observation period of 8 days symptoms were still persistent. Severe corneal opacity is considered to be irreversible effect to ophthalmic tissue.

Respiratory irritation
Based on the results of the acute toxicity and irritation studies and taken into account physical-chemical properties of MMEA, there is sufficient reason to suppose that the test substance may be a respiratory hazard.

Skin sensitisation
The skin sensitisation potential of MMEA was evaluated in a guinea pig maximization procedure by the method of Magnusson and Kligman. Pre-test screening allowed the selection of test concentrations for induction and challenge phases. Intradermal injection of 5 % MMEA in propylene glycol produced only minor local reaction, 25 % MMEA was the highest concentration that produced only mild irritation and was used for the epi-cutaneous induction. 5 % of MMEA was the highest concentration which did not produce irritation and was used for the percutaneous challenge. Eighteen of the 20 animals challenged with a 5 % concentration of MMEA were free of skin response, and the 2 remaining animals had clear skin response (scores of 1) at 24 hrs but not at 48 hrs following dosing. The failure to observe a response at 48 hrs is suggestive of irritation and not sensitisation in these animals. Moreover, no skin response occurred in the irritation control animals treated at the same concentration. In conclusion, MMEA is considered to have a mild potential to produce skin sensitisation in guinea pigs (REACH-reg).

Repeated dose toxicity
From a combined repeated dose and reproductive/ developmental toxicity testing, effects were observed at the lowest dosed group for reproductive performance and fertility, therefore a NOAEL of 50 mg/kg bw/day was established for the parental rats. The NOAEL for general, systemic toxicity of the test substance was 50 mg/kg bw/day for females and less than 50 mg/kg bw/day for male animals based on the tubular degeneration in the kidneys (REACH-reg).

Inhalation
No data.

Oral intake
In a combined repeated dose and reproductive/ developmental toxicity testing, conducted according to OECD TG 422, rats were dosed by oral gavage to 0, 50, 150 and 450 mg/kg bw/day. Signs of general systemic toxicity were only observed at dose level of 450 mg/kg bw/day as there were significantly lower body weights in male and female parental animals accompanied with reduced food consumption and reduced general condition. In the spleen, a dose-related increase in incidence and severity of extramedullary hematopoiesis occurred in

males and females dosed at 150 and 450 mg/kg bw/day. In addition, in females of these test groups the severity of hemosiderin storage was increased. These findings are associated with the increased relative spleen weights in females dosed at 150 mg/kg bw/day as well as in males and females dosed at 450 mg/kg bw/day. They were induced in response to anaemia and related to treatment. The liver weights were dose-related increased in males and females of all treatment groups. The liver was enlarged in three males and one female dosed at 150 mg/kg bw/day as well as in three males and five females dosed at 450 mg/kg bw/day. In females, the liver enlargement correlated with a minimal central hepatocellular hypertrophy that was observed in five animals dosed at 150 mg/kg bw/day and in 9 animals dosed at 450 mg/kg bw/day. In males, a minimal fatty change of hepatocytes was observed in two animals dosed at 50 mg/kg bw/day, in 8 animals dosed at 150 mg/kg bw/d, and in 7 animals dosed at 450 mg/kg bw/day. The liver findings were related to treatment and considered to be adaptive. Although, there were no clear histopathological correlates for the increased liver weights in males of all treatment groups and in females dosed at 50 mg/kg bw/day, a test substance-related effect could not be ruled out. There was no correlation between erosion/ ulcer in the stomach and erythrocytosis of the mesenteric lymph node (findings occurred in different animals). However, a treatment-related effect could not be ruled out but was assessed as non-adverse. All further findings occurred either singly or were biologically equally distributed over the control group and the treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment. The NOAEL for general, systemic toxicity of the test substance was 50 mg/kg bw/day for females and less than 50 mg/kg bw/day for male animals based on the tubular degeneration in the kidneys of six males, i.e., a LOAEL of 50 mg/kg bw/day. (REACH-reg).

Dermal contact
No data.

Toxicity to reproduction
MMEA may cause adverse effects towards fertility when dosed orally. Developmental effects were not observed when exposed via inhalation.

Fertility
In a combined repeated dose and reproductive/ developmental toxicity testing, conducted according to OECD TG 422, rats were dosed by oral gavage to 0, 50, 150 and 450 mg/kg bw/day. Signs of general systemic toxicity were only observed at dose level of 450 mg/kg bw/day as there were significantly lower body weights in male and female parental animals accompanied with reduced food consumption and reduced general condition.
Fertility was severely impaired by test-substance administration at dose levels of 150 and 450 mg/kg bw/day. Although mating (male and female mating indices) was not influenced, no live pups were delivered for both test groups (150 and 450 mg/kg bw/day). Target organs were the kidney, testes, epididymides, ovaries, liver, and spleen. In kidneys and testes, tubular degeneration was dose dependent and assessed as an adverse effect. In ovaries, the occurrence of cysts and vacuolization of sex cord stroma was related to treatment and was considered to be adverse. In the high-dose group, infertility was linked to reduced number of sperms (oligospermia) caused by tubular degeneration in testes. In addition, the occurrence of ovarian cysts and vacuolization of the sex cord stroma in females may have influenced fertility. In animals dosed at 150 mg/kg bw/day, the severity of the findings in testes or ovaries was only minimal or slight and the findings did not occur in all infertile animals. Nevertheless, these lesions may have affected fertility. Under the conditions of the present reproduction/developmental toxicity screening test the NOAEL for reproductive performance and fertility was 50 mg/kg bw/day for the parental rats (REACH-reg).

Development
MMEA was vaporized and administered (near the saturation point) to 18 pregnant rats at 150 +/- 15.2 ppm for 7 hrs/day on gestation days 7 to 15. The dams were sacrificed on day 20 of gestation. Foetuses were individually weighed, and two-thirds of them were fixed in Bouin's solution and examined for soft-tissue anomalies. The other one-third were fixed in alcohol, stained with Alizarin Red and examined for skeletal defects. As overall result for the substance MMEA, neither maternal nor foetal toxicity were found. No teratogenicity was observed. The NOAECs were ≥ 460 mg/m^3, the highest dose tested for both, dams and foetuses (REACH-reg)

Mutagenic and genotoxic effects
No indication of a mutagenic potential of MMEA was found in *in vitro* studies.

In vitro studies
In a chromosome-aberration test performed according to OECD guideline 473, the test substance MMEA is not a chromosome-damaging (clastogenic) substance under in vitro conditions using V79 cells in the absence and the presence of metabolic activation (REACH-reg).

In vivo studies
No data

Carcinogenic effects
No data.

4. Overall evaluation and identification of critical effect

There are no repeated dose inhalation toxicity studies in animals. In humans, local irritation and injuries have been reported after inhalation. Taking into account the physical-chemical properties of MMEA (i.e., a pH of 13.6), there is sufficient reason to suppose that the test substance may be a strong irritant to the airways and to the mucous membranes of the eye. For systemic toxicity an oral LOAEL of 50 mg/kg bw/day was set based on adverse effects in the kidneys of male rats.

5. Derivation of QC and proposal for C-value

5.1 Derivation of QC
According to Danish EPA (2006) a health-based quality criteria for systemic effects of MMEA can be derived from a LOAEL of 50 mg/kg bw/day for systemic exposure. This point of departure is used as the basis for the calculation.

The first step to derive the quality criteria in air is to convert an oral LOAEL (in mg/kg bw/day) to an inhalation concentration (in mg/m^3). As a default the ECHA guideline uses a daily inhalation rate for rats of 1.15 m^3/ kg bw/day. Also, when no specific data on the oral absorption rate and the inhalation absorption rate, the inhalation rate by default is considered to be twice as high as the oral inhalation rate (ECHA 2012). Thus, a LOAEC can be calculated according to:

LOAEC = LOAEL/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 50 mg/kg bw/day/ (1.15 m^3/ kg bw/day x 2)
LOAEC = 22 mg/m^3

The quality criterion can then be calculated:

QC = N(L)OAEC/ (UF I x UF II x UF III x UF IV)
QC = 22 mg/m^3 / (2.5 x 10 x 6 x 10)
QC = 0.014 mg/m^3 or 0.01 mg/m^3

UF I (interspecies factor): is set to 2.5 (is the default value in REACH-guidance R8 when the dose metric is expressed in mg/m3 for inhalation

UFII (intraspecies factor): is set to 10 (is the default value in REACH-guidance R8 for accounting for human variability).

UF III (duration factor): is set to 6 (is the default value in REACH-guidance R8 when the extrapolation a NOAEL from subacute to chronic exposure. It is considered justified to use this factor) since it generally acknowledged that NOAELs from chronic studies are lower than NOAEL from subacute studies. This may be due to higher sensitivity of the study (more animals per dose groups in the chronic studies, more detailed examinations of the animals, and/or lower effect levels due to much longer periods with daily exposure.

UF IV (dose-response): is set to 10 (values from 3-10 is the default value in REACH-guidance R8 for accounting for the point of departure). A factor 10 as tubular degeneration in kidneys is considered a severe effect at the LOAEC level.

This level is also considered to protect against local effects in relation to the respiratory tract as the substance has a chemical structure closely related to monoethanolamine having a QC value of 0.07 mg/m^3. However, as MMEA has a methyl group attached to the nitrogen atom compared to MEA, the substance is more alkaline as indicated by the higher pH value, which again justify the lower QC value of 0.01 mg/m^3.

5.2 Proposal for C-value

According to Danish EPA (2016) the C-value should be identical to the QC when the QC value is based on effects in relation to acute or subchronic exposure.
Thus, a C-value of 0.01 mg/m^3 is proposed for MMEA.

As a non-carcinogenic substance with a C-value ≤ 0.01 mg/m^3 the substances should according to *Luftvejledningen* (Danish EPA 2001) be placed in main group 2, class I.

6. References

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Selected amines and amino alcohols - Evaluation of health hazards and proposal of health-based quality criteria and C-values for ambient air

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to selected amines and amino alcohols. This resulted in the present report, which includes a health-based quality criterion for the substances in ambient air.

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