Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CATEGORY 1A OR 1B CMR, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): Formaldehyde, oligomeric reaction products with aniline

EC Number: 500-036-1

CAS Number: 25214-70-4

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PUBLIC VERSION: *This version does not include the Confidential Annex referred to in the main report.*

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PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CATEGORY 1A OR 1B CMR, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): Formaldehyde, oligomeric reaction products with aniline

EC Number: 500-036-1

CAS number: 25214-70-4

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (REACH) owing to its classification as carcinogen 1 B[1] which corresponds to classification as carcinogen category 2[2]..

Summary of how the substance(s) meet(s) the CMR (Cat 1A or 1B) criteria

The structurally related substance 4,4'-diaminodiphenylmethane is listed by index number 612-051-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) as carcinogenic: Carc. 1B (H 350: "May cause cancer."). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is Carc. Cat. 2; R45 ("May cause cancer.").

4,4'-diaminodiphenylmethane is a major constituent of the UVCB substance *formaldehyde, oligomeric reaction products with aniline* (CAS-No. 25214-70-4) and therefore the classification for 4,4'-diaminodiphenylmethane applies also for this UVCB substance. The classification of ,4'-diaminodiphenylmethane in Regulation (EC) No 1272/2008 shows that also the UVCB substance *formaldehyde, oligomeric reaction products with aniline* meets the criteria for classification as carcinogenic in accordance with Article 57 (a) of REACH.

Registration dossiers submitted for the substance? Yes

[1] Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

[2] Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

PART I

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	500-036-1
EC name:	Formaldehyde, oligomeric reaction products with aniline
CAS number (in the EC inventory):	25214-70-4
CAS number:	25214-70-4
CAS name:	Formaldehyde, polymer with benzenamine
IUPAC name:	Formaldehyde, oligomeric reaction products with aniline
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	$(C_6H_7N.CH_2O)_x$
Molecular weight range:	> 168 g/mol
Synonyms:	polymeric MDA[3] PMDA MDA, technical grade crude MDA

[3] In Kirk-Othmer [1991] the substance is named polymeric MDA and this name is used in this dossier to refer to Formaldehyde, oligomeric reaction products with aniline. The name is abbreviated as PMDA.

Structural formula:

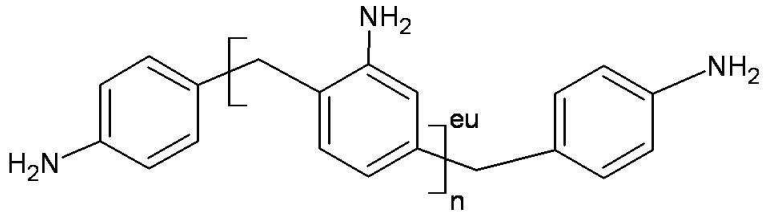

Figure 1: Structural formula with n = 1-5 (according to registration dossiers received) and eu = either unknown

1.2 Composition of the substance

Name: Formaldehyde, oligomeric reaction products with aniline

Description:

Degree of purity: 100%

Formaldehyde, oligomeric reaction product with aniline (Technical-grade MDA) is a UVCB substance with a varying content of tri- and polynuclear amines (so-called „polymers“). A typical standard product with a content of 4,4'-MDA between ca. 47 and < 65 %(w/w) is liquid at room temperature and comprises the following:

Table 2: Generic composition (based on registration dossiers received)

Impurity	Content range[4] % w/w	CAS no.	EC no.	Molecular formular
4,4'-MDA	ca. 47 to < 65	101-77-9	202-974-4	$C_{13}H_{14}N_2$
2,4'-MDA	< 1.4 to ca. 10	1208-52-2	214-900-8	$C_{13}H_{14}N_2$
2,2'-MDA	ca. 0.2 to 3	6582-52-1	229-512-4	$C_{13}H_{14}N_2$
Higher Oligomers of MDA	ca. 38.4 to < 65	-	-	$(C_6H_7N)_2(CH_2)_{(x+1)}(C_6H_6N)_x$ or $C_{(7x+13)}H_{(6x+13)}N_{(x+2)}$
Water	< 1	7732-18-5	231-791-2	H_2O
Aniline	< 0.1	62-53-3	200-539-3	C_6H_7N

The separate identities indicated in the registration dossiers received are confidential and were included in the technical dossier.

[4] Based on registration dossiers received

1.3 Physico-chemical properties

Table 3: Overview of physicochemical properties[5]

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	olig. MDA is a yellow, clear, high viscous liquid/wax	
Melting/freezing point	30 — 70 °C	
Boiling point	410.6 °C at 1013.25 hPa	
Vapour pressure	< 0.000001 hPa; 20 °C 0.000016 hPa; 50 °C	
Water solubility	0.36 g/L, Temp. 20 °C; pH 7.1 — 7.4; Remarks: 1 g test item per one liter of water 1.22 g/L, Temp. 20 °C; pH 7.5 — 7.6 Remarks: 10 g test item per one liter of water	
Partition coefficient n-octanol/water (log value)	1.3 - 2.5 at 23°C/pH = 6.2 1.2 -2.7 at 23°C/pH = 10	Key value for chemical safety assessment: Log K_{ow} (Log P_{ow}) 2.5, 23 °C
Dissociation constant	The test item consists of substances with a number of different amine groups. For each of these groups a discrete dissociation constant can be defined, but not determined by titration. The determination of the dissociation constant of an aqueous preparation of the test item is not possible.	

[5] The references of the values reported in Table 3 will be available in the technical dossier. In case references need to be included an additional column could be added manually in Table 3.

2 HARMONISED CLASSIFICATION AND LABELLING

The UVCB substance *formaldehyde, oligomeric reaction products with aniline* is covered by the entry of 4,4'-diaminodiphenylmethane under index number 612-051-00-1 in Annex VI, Part 3 of Regulation (EC) No 1272/2008. as provided in Table 4 and Table 5.

Table 4: Classification for MDA according to part 3 of Annex VI, Table 3.1 (List of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
			Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
4,4'-diamino-diphenylmethane; 4,4'-methylene-dianiline	202-974-4	101-77-9	Carc. 1B Muta. 2 STOT SE 1 STOT RE 2 * Skin Sens. 1 Aquatic Chronic 2	H350 H341 H370 ** H373 ** H317 H411	GHS08 GHS07 GHS09 Dgr	H350 H341 H370 ** H373 ** H317 H411			

Table 5: Classification for MDA according to part 3 of Annex VI, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	Chemical name	Notes related to substances	EC No	CAS No	Classification	Labelling	Concen-tration Limits	Notes related to preparations
ANNEX 1								
612-051-00-1	4,4'-diamino-diphenylmethane; 4,4'-methylene-dianiline		202-974-4	101-77-9	Carc. Cat. 2; R45 Muta. Cat. 3; R68 T; R39/23/24/25 Xn; R48/20/21/22 R43 N; R51-53	R: 45-39/23/24/25-43-48/20/21/22-68-51/53 S: 53-45-61		

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on harmonised classification and labelling.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant

6.2 CMR assessment

The structurally related substance 4,4'-diaminodiphenylmethane is listed by index number 612-051-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) as carcinogenic: Carc. 1B (H 350: "May cause cancer."). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is Carc. Cat. 2; R45 ("May cause cancer.").

4,4'-diaminodiphenylmethane is a major constituent of the UVCB substance *formaldehyde, oligomeric reaction products with aniline* (CAS-No. 25214-70-4) and therefore the classification for 4,4'-diaminodiphenylmethane applies also for this UVCB substance. The classification of ,4'-diaminodiphenylmethane in Regulation (EC) No 1272/2008 shows that also the UVCB substance *formaldehyde, oligomeric reaction products with aniline* meets the criteria for classification as carcinogenic in accordance with Article 57 (a) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

Production volumes and uses

Registration information on production volumes and uses is provided in the confidential Annex to this report. Further background information on production volumes and uses is taken from the ECHA Report "Data on manufacture, import, export, uses and releases of 4,4'-diaminophenylmethane (MDA) as well as information on potential alternatives to its use" [ECHA, 2008]. It has to be noted that the ECHA report only refers to 4,4'-diaminophenylmethane (MDA). Nevertheless the production volumes of MDA and PMDA correspond approximately because the manufacturing process of PMDA and MDA are essentially identical, with the exception of a separation step [Kirk-Othmer, 1991]. Therefore, the production volumes given in the ECHA report apply for PMDA as well.

Manufacture and use for MDI

PMDA is synthesized by reaction of formaldehyde and aniline in the presence of hydrochloric acid. All processes produce polymeric MDA (PMDA), which consists of mixtures of isomers and oligomers of MDA. As 98% of PMDA is used as a precursor to methylene diphenyl-diisocyanate (MDI), the production tonnage of PMDA has been calculated, from the production tonnage of MDI, to be in the region of 1400000 t in 2008.

Other uses
Other uses of PMDA are:

- as a hardener for epoxy resins in
  - adhesives,
  - production of rolls with composite cover,
  - production of chemically resistant pipes
  - production of moulds,
- in the production of high performance polymers and
- as a starting point for the synthesis of 4,4'-methylenebis(cyclohexaneamine) (PACM).

Tonnages involved in use of PMDA as a hardener in epoxy resins are confidential (see Annex III of ECHA Report [2008]) and are unknown for adhesives. The overall EU consumption for use as a hardener in epoxy resins is estimated by one company to be around 200 t, however further confidential information suggests that this figure may be regarded as a

minimum. A number of applications for the use of PMDA as a hardener in adhesives are understood to have been phased out. A producer of high performance polymer using PMDA as a raw material indicated using less than 5000 tpa at a single site. No information on the tonnages involved in the manufacture of PACM has been made available, although PACM is produced in the EU. A summary of uses and indicative volumes for each use based on information gathered for the ECHA study [ECHA, 2008] is presented below.

Figure 2: Mass balance for the manufacture and use of MDA according to ECHA report [ECHA, 2008]

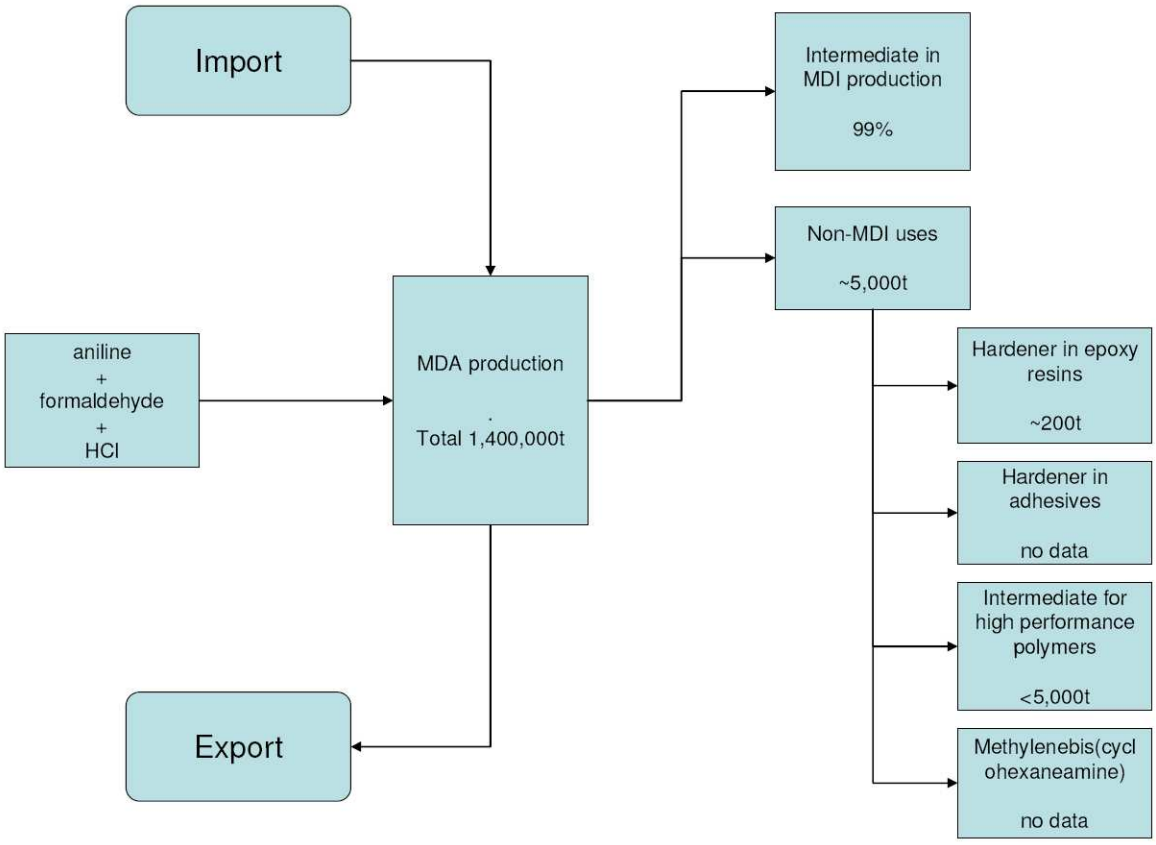

Table 6: Summary on historical use volumes of MDA and relevance to authorisation [ECHA, 2008].

Use	Volume (tonnes per annum)	Intermediate use?	Except from authorisation?
Exported out of the EU	No data	N/A	Y
Production of MDI	1,400,000	Y	Y
Hardener in epoxy resins	**~200**	**N**	**N**
Hardener in adhesives	No data	**N**	**N**
Intermediate for high performance polymers	<5,000	Y	Y
Production of methylenebis (cyclohexaneamine)	No data	Y	Y

Occupational exposure

As previously stated is it very difficult to treat MDA as a single entity because the manufacturing processes of PMDA and MDA are essentially identical, with the exception of a separation step. Therefore the exposure assessment below either relates to MDA as a component of PMDA or to pure MDA where necessary.

Occupational exposure scenarios in the chemical industry and industrial area and in skilled trade have been considered. The exposure assessment is based on measured data from IFA-Institute for Occupational Safety and Health of the German Social Accident Insurance. (limited), expert judgement and the ECETOC TRA worker tool (Version 2).

Since occupational exposure scenarios in the chemical industry and industrial area are taken from the Chemical Safety Report this information can be found in the confidential Annex.

Although the registration information indicates that PMDA is intended to be used only in an industrial setting, a skilled trade scenario has also been included in the modelled exposure assessment. This was done to illustrate that professional use of PMDA must be excluded in any case.

MEASURED OCCUPATIONAL EXPOSURE TO MDA (2000 -2011) IN GERMANY

Introduction

The German worker exposure data were provided by the IFA-Institute for Occupational Safety and Health of the German Social Accident Insurance.

The new data provided by the IFA were measured in industry for the years 2000 to 2011. The data are differentiated into personal sampling data taken while the individual was carrying out

all activities, i.e. active plant work, control room work and break periods and data from static sampling in the different workplaces.

The identification and documentation of the following evaluated data from exposures in the workplace are based on the criteria of the MGU (*Messsystem Gefährdungsermittlung der Unfallversicherungsträger* - measuring hazard identification of accident insurance carrier (formerly BGMG)) [Gabriel, S. et al., 2010]. The standard of the MGU is a quality management system, which essentially implements the requirements of DIN EN ISO 9001. The testing laboratories are operated in accordance with DIN EN ISO 17025.

All data collected will be merged into the exposure database MEGA (measurement data to exposure to hazardous substances at work). The MEGA exposure database is maintained and evaluated for the institutions for statutory accident insurance and prevention by Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, formerly BGIA; German: *Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung*).

If individual measurements are below the limit of quantification (LOQ) of the applied analytical method, half of this value is taken into account within the statistical evaluation. The MEGAPRO software, developed by IFA, allows the statistical analysis of the data of the exposure database MEGA according to different selection criteria and evaluation strategies.

Evaluation Strategy and selection criteria

Table 7 – Table 14 show the evaluated German worker exposure data (expressed as MDA) collected in the years 2000-2011.

The evaluation is made in the form of industry (branch groups) and work area groups and further differentiated by the sampling strategy (static or on the person) and the presence of a LEV (Local Exhaust Ventilation). A general overview of the branch groups, which are in correlation to the main uses mentioned at the beginning of chapter “Information on Manufacture and uses” is given in Table 7 to Table 10.

A deeper analysis of the exposure of workers in the main work area group (foundry) representing more than 57% of the whole data collective, separated into exposure relevant processes, is considered separately in the same way in the Table 11 to Table 14.

Table 7: Overview Branch-Groups

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Total	all	86	36	78 (90.7 %)	8	0.006	LOQ (!)	LOQ (!)	LOQ (!)	0.0035 (+)
Plastic and foam material, processing, production	all	13	6	12 (92.3 %)	4	0.002	LOQ (!)	LOQ (!)	LOQ (!)	0.001 (+)
Steel foundry, mixed steel foundry	all	47	18	43 (91.5 %)	2	0.006	LOQ (!)	LOQ (!)	LOQ (!)	0.0073 (+)

Within the evaluation tables the following abbreviations and indexes are used:

LOQ Limit of quantification

(!) The specification of a cumulative frequency concentration in the results table is not made, as there are more measurement values below the analytical limit of quantification (LOQ) , as measurement values are represented by this cumulative frequency value

(+) Distribution value is below the largest limit of quantification (LOQ) of the data collective.

Perc. Percentile

Table 8: Overview Branch-Groups – personal and static

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Total	personal	28	16	24 (85.7 %)	5	0.006	LOQ (!)	LOQ (!)	0.0036 (+)	0.0072
	static	58	28	54 (93.1 %)	8	0.005	LOQ (!)	LOQ (!)	LOQ (!)	0.0025 (+)
Plastic and foam material, processing, production	personal	2	1	2 (100 %)	1	0.002				
	static	11	5	10 (90.9 %)	4	0.002	LOQ (!)	LOQ (!)	LOQ (!)	0.001 (+)
Steel foundry, mixed steel foundry	personal	16	8	13 (81.3 %)	2	0.006	LOQ (!)	LOQ (!)	0.0068	0.0524
	static	31	14	30 (96.8 %)	2	0.005	LOQ (!)	LOQ (!)	LOQ (!)	LOQ (!)

Table 9: Overview Branch-Groups with LEV

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Total	all	52	21	46 (88.5 %)	7	0.006	LOQ (!)	LOQ (!)	0.0025 (+)	0.0054(+)
Plastic and foam material, processing, production	all	8	2	8 (100 %)	2	0.002				
Steel foundry, mixed steel foundry	all	21	9	18 (85.7 %)	2	0.006	LOQ (!)	LOQ (!)	0.0075	0.0413

Table 10: Overview Branch-Groups without LEV

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Total	all	26	14	24 (92.3 %)	4	0.005	LOQ (!)	LOQ (!)	LOQ (!)	0.0025 (+)
Plastic and foam material, processing, production	all	4	3	3 (75 %)	3	0.001				
Steel foundry, mixed steel foundry	all	21	10	20 (95.2 %)	1	0.005	LOQ (!)	LOQ (!)	LOQ (!)	LOQ (!)

Table 11: Work-area-group – Foundry

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Moulding-area	All	14	3	13 (92.9 %)	1	0.006	LOQ (!)	LOQ (!)	LOQ (!)	0.015
Foundry	All	23	11	20 (87 %)	1	0.005	LOQ (!)	LOQ (!)	0.005 (+)	0.0077
Mixing	All	11	3	8 (72.7 %)	3	0.002	LOQ (!)	0.001 (+)	0.002 (+)	0.003

Table 12: Work-area-group – Foundry – personal and static

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Moulding-area	personal	3	1	3 (100 %)	1	0.006				
	static	11	3	10 (90.9 %)	1	0.005	LOQ (!)	LOQ (!)	LOQ (!)	0.0207
Foundry	personal	9	5	6 (66.7 %)	1	0.005				
	static	14	9	14 (100 %)	1	0.005	LOQ (!)	LOQ (!)	LOQ (!)	LOQ (!)
Mixing	personal	1	1	0	1					
	static	10	2	8 (80 %)	2	0.002	LOQ (!)	LOQ (!)	0.002 (+)	0.003

Table 13: Work-area-group – Foundry with LEV

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Moulding-area	All	11	1	10 (90.9 %)	1	0.006	LOQ (!)	LOQ (!)	LOQ (!)	0.021
Foundry	All	5	4	3 (60 %)	1	0.005				
Mixing	All	11	3	8 (72.7 %)	3	0.002	LOQ (!)	0.001 (+)	0.002 (+)	0.003

Table 14: Work-area-group – Foundry without LEV

Groups	Type	Number of samples	Enterprises	Frequency of samples < LOQ	Number UVT	Limit of quantification (mg/m³)	50th-perc. (mg/m³)	75th-perc. (mg/m³)	90th-perc. (mg/m³)	95th-perc. (mg/m³)
Moulding-area	All	3	2	3 (100 %)	1	0.005				
Cast-process	All	16	9	15 (93.8 %)	1	0.005	LOQ (!)	LOQ (!)	LOQ (!)	0.005 (+)
Mixing	All	0	0	0	0					

Summary of the IFA-Data

The data presented above reveal that airborne concentrations of MDA in the area of plastic and foam material processing and production are below the analytical limit of quantification (LOQ). Relevant airborne concentrations of MDA have only been observed in the branch group of steel foundry. The overall statistics for the steel foundry area (Table 8) estimates the 95^{th} percentile to 0,0524 mg/m^3 (90^{th} percentile 0,0068 mg/m^3) in case of personal sampling. Although the number of personal samples are quite small (n = 16) the IFA data reveal that inhalation exposure to MDA may occur in the steel foundry area.

INFORMATION ON ALTERNATIVES

Alternative substances

For alternatives for the uses that could be subject to authorisation (i.e. when MDA is considered not to be an intermediate), reference is made to [ECHA, 2008]. It is understood that other aromatic amines or aliphatic amines can be used as alternatives as curing agents in some circumstances although information on alternatives for specific applications has not been found.

Based on the literature review undertaken in [ECHA, 2008], it has not been possible to gain a good overview of the current status of development of alternatives for the remaining non-MDI uses (particularly as hardener in epoxy resins and adhesives). Some promising alternatives have obviously been identified (as evidenced by a number of patents), though the actual market suitability of these alternatives is unknown.

RISK-RELATED INFORMATION

Risk related information for MDA is taken from the exposure-risk-relationship (ERB), published by the German Committee on Hazardous Substances (AGS) (AGS, 2010). The information from the ERB is reduced in this Annex XV document to the most critical endpoint, the carcinogenicity after inhalation and dermal contact. In the table below, all exposure scenarios are listed and compared with the calculated acceptance risk (4:10000). The quotient of exposure and acceptance risk is expressed as Risk Characterisation Ratio (RCR) and is calculated by the German Competent Authority. An RCR < 1 implicates an acceptable risk whereas an RCR > 1 is associated with an unacceptable risk.

Carcinogenicity

The following clause summarises the relevant parts of the ERB for MDA which was announced by the AGS in 2010 [AGS, 2010] and shows the German approach in terms of calculating risk estimates for carcinogenic substances at the workplace.

As starting point for deducing the exposure-risk-relationship the chronic NTP studies are chosen in which MDA hydrochloride was administered by drinking water to F344 rats and $B6C3F_1$ mice. The most sensitive carcinogenic effects observed in these studies are neoplastic nodes as well as carcinomas in the liver of male rats [Weisburger et al., 1984, Lamb et al., 1986]. According to the AGS concept [AGS, 2008] and the below mentioned formula a T25

is calculated based on the summarised incidences of carcinogenic liver effects in the male rat. This results in an hT25 of 45.7 mg/m^3.

$$hT25 = C \cdot \frac{reference\ incidence}{(incidence\ at\ significance - control\ incidence)} \cdot \frac{(1 - control\ incidence)}{1}$$

With C: lowest concentration with a significant carcinogenic effect: 44.8 mg/m^3
Reference incidence: 0.25
Incidence at significance: 0.26 (12/50)
Control incidence: 0.02 (1/50)

The mechanism of carcinogenicity of MDA is still not clarified. Genotoxic mechanism as well as non-genotoxic mechanism could be assumed. It is supposed that reactive metabolites of MDA directly interact with the DNA of the target organ. Therefore, the AGS conservatively decided to assume a genotoxic mode of action for the carcinogenicity of MDA. Consequently a linear extrapolation to the low dose is carried out. From these considerations the exposure-risk-relationship for MDA results in following nominal excess risks:

Tolerance risk (4:1000)	731 µg/m^3
Acceptance risk (4:10000)	73 µg/m^3
Acceptance risk (4:100000) after 2013 at the latest 2018	7.3 µg/m^3

Within the process of registration two derived minimum effect levels (DMELs) are calculated. The values are: $DMEL_{dermal}$ 0.004 mg/kg/d and $DMEL_{inhalation}$ 0.014 mg/m^3 (ECHA website, 22.08.2011). These DMELs are consistent with the above mentioned nominal excess risks determined by the AGS [AGS, 2010].

To have an overview the RCRs are calculated by the German Competent Authority with the according DMEL as well as with the acceptance risk (see Table 15 and confidential annex).

Inhalation

No modification of the acceptance risk (4:10000) is necessary as this nominal risk is relevant to humans. The required extrapolation for workplace time, respiratory volume, higher sensitivity of humans, and route-to-route was carried out within the ERB.

No modification of the $DMEL_{inhalation}$ is necessary as this value is relevant to humans.

As the evaluation of the IFA-data shows inhalation exposure to workers, the RCR for purpose of carcinogenic risk assessment is calculated by the German Competent Authority (see Table 15). The RCR express the quotient of exposure (IFA-data) and acceptance risk or DMEL and implicates an acceptable risk if the value is < 1.

Table 15: RCR values calculated by the German Competent Authority for inhalation exposure scenarios of MDA taken from the IFA-data

Groups	95th-perc. [mg/m³]	traffic light model		DMEL-concept	
		acceptance risk [mg/m³]	RCR acceptance risk	DMEL [mg/m³]	RCR DMEL
overview branch-groups (see Table 7)					
total	0.0035 (+)	0.07	0.05	0.014	0.25
plastic and foam material, processing, production	0.001 (+)	0.07	0.01	0.014	0.07
steel foundry, mixed steel foundry	0.0073 (+)	0.07	0.10	0.014	0.52
overview branch-groups – personal and static (see Table 8)					
total (personal)	0.0072	0.07	0.10	0.014	0.51
total (static)	0.0025 (+)	0.07	0.04	0.014	0.18
plastic and foam material, processing, production (static)	0.001 (+)	0.07	0.01	0.014	0.07
steel foundry, mixed steel foundry (personal)	0.0524	0.07	0.75	0.014	3.74
overview branch-groups with LEV (see Table 9)					
total	0.0054 (+)	0.07	0.08	0.014	0.39
steel foundry, mixed steel foundry	0.0413	0.07	0.59	0.014	2.95
overview branch-groups without LEV (see Table 10)					
total	0.0025 (+)	0.07	0.04	0.014	0.18
work-area-group – foundry (see Table 11)					
moulding area	0.015	0.07	0.21	0.014	1.07
foundry	0.0077	0.07	0.11	0.014	0.55
mixing	0.003	0.07	0.04	0.014	0.21
work-area-group – foundry – personal and static (see Table 12)					
moulding-area (static)	0.0207	0.07	0.30	0.014	1.48
mixing (static)	0.003	0.07	0.04	0.014	0.21
work-area-group – foundry with LEV (see Table 13)					
moulding-area	0.021	0.07	0.30	0.014	1.50
mixing	0.003	0.07	0.04	0.014	0.21
work-area-group – foundry without LEV (see Table 14)					
cast-process	0.005 (+)	0.07	0.07	0.014	0.36

(+): Distribution value is below the largest limit of quantification (LOQ) of the data collective

While the given data provided by the IFA may not contradict the safe use of PMDA in industry as indicated by the registration dossiers, they clearly allocate that inhalation exposure to MDA does arise even under relatively controlled conditions as in industrial settings. All RCR calculated by the German Competent Authority with the acceptance risk (0.07 mg/m^3) show values below 1 and therefore an acceptable risk level. The column with RCRs calculated with $DMEL_{inhalation}$ (0.014 mg/m^3) shows four values > 1 and one borderline scenario. It has to be mentioned that the current acceptance risk will be lowered at the latest in 2018 to 0.007 mg/m^3, thus being in the same range as the $DMEL_{inhalation}$.

Dermal

The acceptance risk (4:10000) of 0.07 mg/m^3 is extrapolated to a modified value assumed to be relevant to humans (dermal exposure) by the following steps. The implication of a respiratory volume (10 m^3) and a body weight of 70 kg results in a modified acceptance risk (4:10000) for dermal exposure of 10 µg/kg/d.

No modification of the $DMEL_{dermal}$ is necessary as this value is relevant to humans.

The RCR for all dermal exposure scenarios are calculated by the German Competent Authority, for details see confidential Annex.

Some of the calculated RCR-values are very high resulting in high concern for carcinogenicity due to dermal contact.

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ABBREVIATIONS

AGS	German Committee on Hazardous Substances
CSR	chemical safety report
DMEL	derived minimal effect level
ECB	(Ex-)European Chemicals Bureau.
ERB	exposure-risk-relationship
ES	exposure scenario
hT25	human equivalent T25
IFA	Institute for Occupational Safety and Health of the German Social Accident Insurance
IFA	formerly BGIA; German: *Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung*
LEV	local exhaust ventilation
LOQ	limit of quantification
MGU	measuring hazard identification of accident insurance carrier (***M**esssystem **G**efährdungsermittlung der **U**nfallversicherungsträger* - (formerly BGMG)
PACM	4,4'-methylenebis(cyclohexaneamine)
PPE	personal protection pquipment
RCR	risk characterisation ratio
T25	tumourigenic dose at which 25 % additional incidence is expected
tpa	tons per anno
UVCB substances	substances of **u**nknown or, **v**ariable, **c**omplex composition or **b**iological origin
UVT	accident insurance carrier (**U**nfall**v**ersicherungs**t**räger)