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4,4' - METHYLENEDIANILINE

CAS-No.: 101-77-9

EINECS-No.: 202-974-4

Summary Risk Assessment Report

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4,4´- METHYLENEDIANILINE (MDA)

CAS No. 101 - 77 - 9

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SUMMARY RISK ASSESSMENT REPORT

Final report, November 2000

Germany

The rapporteur for 4,4'-Methylenedianiline (MDA) is the Federal Institute for Occupational Safety and Health.

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PREFACE

This report provides a short summary with conclusions of the risk assessment report of the substance 4,4'-Methylenedianiline (MDA) that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances. For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references, the reader is referred to the original risk assessment report that can be obtained from European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals - http://ecb.ei.jrc.it

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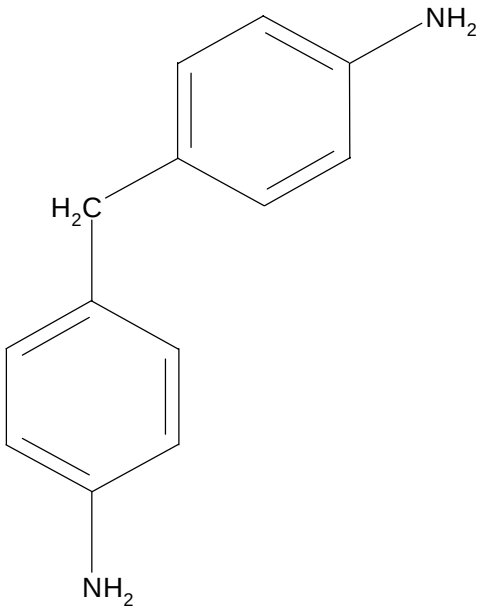
1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS No.: 101-77-9
EINECS No.: 202-974-4
IUPAC Name: Bis (4-aminophenyl)methane
Molecular formula: $C_{13}H_{14}N_2$
Structural formula:



Molecular weight: 198.3 g/mol
Synonyms: 4,4'-Methylenedianiline
4,4'-Diaminodiphenylmethane
4,4’-Diphenylmethane diamine
4,4’-Methylendibenzolamine
4,4’-Methylenebisbenzeneamine
4-(4-Aminobenzyl)aniline
MDA

Purity/impurities, additives

Technical-grade MDA is used as an intermediate in the form of an isomer mixture with a varying content of tri- and polynuclear amines (so-called „polymers“). A typical standard product is liquid at room temperature and comprises the following:

4,4’-MDA:	59- 61% w/w [2]
MDA polymers:	approx. 36% w/w
2,4’-MDA:	approx. 3.5% w/w
2,2’-MDA:	<0.1% w/w
water:	<300 ppm
aniline:	<100 ppm

[2]Depending on the production process the content of 4,4’-MDA can vary, the minimum content produced has been 30- 40%.

Pure 4,4'-MDA is also used as an intermediate and has the following composition:

4,4'-MDA:	≥98% w/w
2,4'-MDA and 2,2'-MDA:	max. 2% w/w
4-amino-4'-methylaminodiphenyl methane:	traces
aniline:	traces

Physico-chemical properties

Pure 4,4'-MDA is at 20 °C and 1013 hPa a colourless to yellowish crystalline powder with a faint amine-like odour.

Melting point	89 °C
Boiling point	398 - 399°C at 1013 hPa
Density	1.056 at 100°C
Vapour pressure	$2.87 \cdot 10^{-8}$ hPa at 20°C
Surface tension	69.5 mN/m
Water solubility	1.25 g/l at 20°C
Partition coefficient (log Pow)	1.59
Flash point	not determined (solid)
Auto flammability	not flammable
Flammability	not flammable
Explosive properties	not explosive
Oxidizing properties	no oxidizing properties

Classification

- (Classification according to Annex I)

T	Carcinogenic Cat. 2	R 45	May cause cancer.
Xn	Harmful	R 20/21/22	Harmful by inhalation, in contact with skin and if swallowed.
		R 48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
	Sensitizing	R 43	May cause sensitization by skin contact.
N	Dangerous	R 51/53	Toxic to aquatic organisms, may cause for the Environment long-term adverse effects in the aquatic environment.

- (adopted classification)

Revision of classification was finalised in the Commission Working Groups on the Classification and Labelling of Dangerous Substances in September 1998 (environment) and in October 1998 (human health):

T	Toxic	R 39/23/24/25	Toxic: danger of very serious irreversible

			effects through inhalation, in contact with skin and if swallowed
	Carcinogenic Cat. 2	R 45	May cause cancer.
Xn	Harmful	R 48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
	Mutagenic Cat 3	R 40	Possible risks of irreversible effects.
	Sensitizing	R 43	May cause sensitization by skin contact.
N	Dangerous	R 51/53	Toxic to aquatic organisms, may cause for the Environment long-term adverse effects in the aquatic environment.

2 GENERAL INFORMATION ON EXPOSURE

MDA is synthesized by reaction of formaldehyde and aniline in the presence of hydrochloric acid. In Western Europe, the substance is manufactured at 11 sites. In 1993, the production volume of MDA was about 430,000 t. More than 99% of the total production volume are processed to methylenediphenyl diisocyanate (MDI), exclusively at the same site. MDI is further used for polyurethane production. About 4000 t MDA are annually used as hardener for epoxy resins, hardener in adhesives, intermediate in the manufacture of high-performance polymers, and processed to 4,4'-methylenebis(cyclohexaneamine).

3 ENVIRONMENT

3.1 EXPOSURE

During production, 4,4'-MDA is released into the environment mainly via waste water into the hydrosphere, while releases into the atmosphere are not significant. Polyamines (the minor components of the technical product) are emitted in much lower amounts than diamines. It is unlikely that the polyamines will significantly raise the total emissions.

Environmental releases during processing to MDI as well as during the non-MDI uses are not significant.

General characteristics of MDA which are relevant for the exposure assessment are:

- estimated atmospheric half-life 12.8 h,
- no volatilization because of the low Henry's law constant ($4.4 \cdot 10^{-7} \cdot Pa \cdot m^3 \cdot mol^{-1}$),
- no hydrolysis,
- photolysis in surface waters (estimated half-lives 4 - 190 d),
- biodegradation in adapted treatment plants, possibly not in surface waters,
- reaction with humic substances in soils and sediments. The reaction product accumulates due to the very low biodegradation (estimated half-life 1000 d),
- low bioaccumulation in fish. Possibly accumulation of the reaction product with humic substances in sediment dwelling organisms.

3.1.1 PECs at production sites

For the environmental exposure assessment site-specific scenarios are used for calculating the PECs in surface waters and sediments. The scenarios are based on actual sewage monitoring data from industry.

Local concentrations in sewage treatment plants are all below 500 µg/l. 7 production sites are emitting into rivers, the aquatic PECs range from $8 \cdot 10^{-3}$ to 0.4 µg/l. 4 sites are emitting into the sea, their PECs range from 0.047 to 1.0 µg/l. For sediments, PECs in the range from 0.42 to 150 µg/kg ww are estimated.

Concentrations in the atmosphere and soils are negligible.

3.2 EFFECTS

Short-term toxicity data for 4,4'-MDA are available for fish, daphnia, algae and bacteriae. Long-term tests are available for daphnia with 4,4'-MDA and for algae with the technical-grade MDA. The aquatic PNEC is extrapolated from a long-term study with *Moina macrocopa* (14 d-NOEC = 0.15 mg/l). Although, other results from long term tests with the pure 4,4'-MDA are not available, the assessment factor is set at F = 50, since the NOEC found for the algae with the technical grade product is additionally used. This leads to a PNEC of 3 µg/l for the aquatic environment.

The PNEC for microorganisms is extrapolated from a respiration test with activated sludge (3h-EC50 = >100 mg/l) using an assessment factor of 100. This leads to a PNEC of ≥1 mg/l.

For the terrestrial compartment, valid results from short-term tests with species from 2 trophic levels (plants, earthworms) are available. The lowest acute toxicity was recorded for Avena sativa (14 d-EC_{50} = 128 mg/kg soil, growth). With an assessment factor of 1000, a PNEC of 128 µg/kg is derived.

There are no effect data for the reaction product of MDA with humic substances in sediments. Therefore, a PNEC cannot be derived. A test with sediment organisms is necessary to determine the sediment toxicity.

3.3 RISK CHARACTERISATION

For the aquatic compartment, the risk characterisation based on site-specific scenarios for MDA production leads to PEC/PNEC ratios in the range from $9 \cdot 10^{-4}$ to 0.33. For sewage treatment plants, PEC/PNEC ratios of maximum 0.5 are derived. As no significant releases into the atmosphere and soils are expected, an assessment of these compartments is not necessary.

The risk characterisation for the aquatic compartment, microorganisms, the atmosphere and the terrestrial compartment reveals that there is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already **(conclusion ii)**.

As no information on the toxicity of sediment organisms is available, a risk characterisation for this compartment is not possible. There is need for further information and/or testing **(conclusion i)**. A long-term toxicity test on a sediment-dwelling organism is recommended.

4 HUMAN HEALTH

4.1 EXPOSURE

4.1.1 Occupational Exposure

MDA is employed as a chemical intermediate, as a curing agent in plastics processing for high-performance polymers, as a curing agent for polyurethane elastomers, foams and special-purpose coatings, for epoxy resins and two-component systems.

Occupational exposure scenarios in the chemical industry, in the industrial area and in skilled trade have to be considered.

The exposure assessment is based on measured data (limited), expert judgement and estimations according to the EASE model.

With regard to inhalative exposure, exposure to MDA in dust form is of primary concern here. Inhalative exposure to MDA vapour is not relevant (vapour pressure <<1Pa).

Concerning dermal exposure investigations have shown that glove material is used which does not provide complete protection and materials for which information about the suitability is not available. Therefore dermal exposures are estimated for all exposure situations.

Azodyes in general could release the amine component unintentionally under special conditions (reductive cleavage). For workers the dermal uptake of the azodye itself, that may occur during dying, has to be considered. Because of reductive conditions in the body (e.g. by bacteria of the intestinal) the dye could lead to an unintentionally release of MDA.

The results for the different scenarios are summarized in **Table 4.1**

Table 4.1 Summary of exposure data

Exposure scenario	Form of exposure	Duration and frequency[1]	Inhalative exposure shift average [mg/m³]	Dermal exposure shift average [mg/p/d][2]
Chemical industry				
Manufacturing and further processing as a chemical intermediate	flakes, granules (dust)	shift length, daily	0.52 (workplace measurements)	42 - 420
	liquid (vapour) (approx. 60 %)	shift length, daily	very low (exp. judg.)	25 - 252
Production of preparations mid preparations max. 10 % MDA	powder (dust)	batch processing 2 hours/daily	0.05 - 0.125 (EASE)	4 - 42
Curing formulations max. 60 % MDA	flakes; granules (dust)	batch processing2 hours/daily	lower than above (exp. judg.)	25 - 252
Max. 5 % MDA		batch processing 2 hours/daily	lower than above (exp. judg.)	2 - 21

Table 4.1 continued overleaf

Table 4.1 continued

Exposure scenario	Form of exposure	Duration and frequency[1]	Inhalative exposure shift average [mg/m³]	Dermal exposure shift average [mg/p/d][2]
Industrial area				
Manufacturing of formulations using powdery MDA	powder (dust)	batch processing 2 hours/daily	0.6 (workplace measurements)	42 - 420
Formulating putties using liquid MDA (approx. 60 %)	liquid MDA	batch processing 2 hours/daily	very low (exp. judg.)	25 - 252
Production of preparations				
Imid preparations max. 10 % MDA	powder (dust)	batch processing 2 hours/daily	0.1 - 1.25 (EASE)	4 - 42
Curing formulations max. 60 % MDA	flakes; granules (dust)	batch processing 2 hours/daily	0 - 0.75 (EASE)	25 - 252
Max. 5 % MDA			0 - 0.08 (EASE)	2 - 21
Mixing curing formulations (max. 60 % MDA) with resin for epoxies	flakes, granules (dust)	short-term (0.5 h), daily	0 - 0.2 (EASE, without LEV)	50 - 504
Handling of formulations containing MDA and epoxid resins (4.5 - 30%)	liquids	short-term (0.5 h), daily	very low (exp. judg.)	50 - 504
		shift length, daily	very low (exp. judg.)	25 - 252
Mixing curing formulations (max. 5% MDA) with resin for polyurethanes	flakes, granules (dust)	short-term (0.5 h), daily	0 - 0.02 (EASE, without LEV)	4.2 - 42
Handling of formulations containing MDA and polyurethane (2 - 3%)	liquid, pastes	shift length, daily	very low (exp. judg.)	2.5 - 25
Handling formulations containing MDA (0.1 - 10%) and imid resins	powder	short-term (0.5 h), daily	0.03 - 0.3 (EASE)	8.4 - 84
	paste	shift length, daily	very low (exp. judg.)	8.4 - 84
Skilled trade				
Mixing of formulations containing MDA (9 - 60 %) with epoxid resins	flakes, granules (dust)	short-term (0.5 h), not daily	0 - 0.2 (EASE, without LEV)	504 - 2 520
Handling of formulations containing MDA and epoxid resins (4 - 30 %)		duration and frequency not known assumed: not daily	very low (exp. judg.)	252 - 1 260

[1]Information about frequency and duration of exposure not available
[2]Estimation according to the EASE model (without PPE)

4.1.2 Consumer Exposure

There is no information about the use of MDA in consumer products, hence consumer exposure seems not to exist. Theoretically exposure could be given to residual free MDA through contact with products in whose manufacture process MDA is introduced, but there is no information about levels of free MDA.

From the notified new substance Cartasol Yellow under special chemical conditions (reductive cleavage) MDA may be liberated unintentionally. The quantity of the substance imported to the EU market from a Non-EU country amounts more than 10 tones/year. This substance may be used as a dye for paper, leather, writing inks, and textiles. No further quantitative information on the use of the substance nor on the liberation rate of MDA for the different applications is available. At present there are no predictions on the probability of established reductive conditions during the use of Cartasol Yellow which as a consequence might result in liberation of MDA. Therefore from the possible use pattern it is concluded that if any, only negligible exposure of the consumer to MDA may be expected.

There are reports that trace amounts of free MDA might be released by irradiation sterilization of polyurethane materials which are used in medical devices as potting materials in plasma separators and artificial dialyzers. However, no quantitative data can be derived from the reports because of limited information regarding experimental conditions.

4.1.3 Indirect Exposure via the Environment

Man can be exposed indirectly to MDA via emissions into the hydrosphere from production. The main contribution to the intake at both local and regional scale are drinking water and fish with fractions of about 55% and 45%, respectively, to the total daily dose. The total daily dose is estimated to $2.1 \cdot 10^{-5}$ mg/kg/d for the local and to $5.4 \cdot 10^{-7}$ mg/kg/d for the regional scale.

4.2 EFFECTS

The evaluation of the available information shows, that MDA is absorbed by the three routes of intake (dermal, oral, inhalation) in animals and humans. Especially in humans a quantitative assessment of absorption is not possible. There is no evidence for accumulation in the body. MDA and its N-acetylated metabolites are mainly excreted in the urine. The N-acetylation apparently represents the detoxification pathway, whereas the N-hydroxylation being supposed from in vitro studies can lead to potentially toxic intermediates. Although the detection of MDA in the urine gives information on current exposure the formation of adducts with hemoglobin provides the opportunity for biological monitoring of cumulative exposures.

Acute intoxication of humans with MDA is reported after oral, dermal and inhalation exposure, leading to jaundice ("Epping Jaundice"). In addition to acute hepatic illness, in some cases myocardial effects and persistent retinal damage were reported. Acute intoxication of humans did not cause any mortality. Acute toxicity in rats is demonstrated by LD_{50} values of 350-450 mg/kg bw after oral and 1000 mg/kg bw (vehicle dimethylsulfoxide) after dermal exposure; inhalation LC50 for rats (> 0.837 mg/l) is demonstrated exceeding the highest possible concentration of MDA in air at room temperature. Damage to the liver and kidneys has been reported to be the most prominent toxic effects in rats. Cats and dogs seem to be much more sensitive than rats with fatalities observed after oral application of 25-50 mg/kg bw with liver and kidney damage and blindness due to retinal atrophy as the most severe effects. On the basis of these acute toxicity data MDA is classified as "toxic", risk phrases R 39/23/24/25**.**

Human data on local irritation or corrosion caused by MDA are not available. The substance causes slight irritation to the skin and mild to moderate irritation to the eyes of rabbits reversible within 3-7 days. According to EU legislation, MDA is not to be classified because of local corrosive properties.

Animal data on skin sensitization do not result in conclusive evidence on the skin sensitization potential of MDA. However, based on the data on humans there is convincing evidence that MDA is a skin sensitizer. MDA also demonstrates cross-reactivity to substances of the para-substituted compound group. Based on the human data the substance is classified as „sensitizing“ and labeled with the risk phrase R 43.

Main toxic effects in rats and mice after repeated exposure to MDA were degeneration with consequential bile duct hyperplasia and fibrosis in the liver and a hyperplastic lesion of the thyroid. Further treatment-related effects were anemia, irritation of the stomach, basophilic hypertrophy of the pituitary, and kidney toxicity. The LOAEL (7.5 mg/kg bw/d in male rats and 8 mg/kg bw/d in female rats) representing the most sensitive adverse (nonneoplastic) effect after repeated oral application was derived from a subchronic study which was accepted as valid. This LOAEL is corresponding to the LOAEL on nonneoplastic effects from the 2-year study on rats (9 resp. 10 mg/kg bw/d in male, resp. female rats). Although the NTP-studies had not examined parameters of hematology, bioclinical chemistry, and urinalysis, the LOAEL of 9 mg/kg bw/d from this long term study was considered to be the most appropriate value for quantitative risk assessment. No NOAEL could be derived from these studies on rats. The database of MDA-related toxic effects on mice is more limited than that in rat, because only few drinking water studies are available. A NOAEL can be derived from a 90-day study, which was 11.4 mg/kg bw/d in male mice and 14.4 mg/kg in female mice. No valid repeated dose studies with inhalation and dermal application route were available. According to the severe health effects which occurred after repeated dose administration MDA is classified as „harmful“, risk phrase R48/20/21/22.

MDA induces gene mutations in bacteria. In mammalian cell cultures MDA is an inducer of chromosomal aberrations in the presence of an exogenous metabolisation system. Inconclusive or weak effects were obtained in other cell culture assays. In vivo, slight increases of micronuclei frequencies were found in mice after treatment to high doses. Furthermore, a high MDA dose led to DNA fragmentation in rat liver cells. Weak marginal effects were obtained for induction SCE (mouse bone marrow) and DNA binding (rat liver). In vivo DNA repair tests (UDS) were negative for livers of rats and mice. MDA causes concern for man owing to possible mutagenic effects. There is evidence from in vivo micronucleus tests (although only weakly positive) which is supported by the induction of DNA fragmentation in vivo and chromosomal aberrations in vitro. According to the classification criteria MDA has been classified as category 3 mutagen, risk phrase R 40.

MDA is carcinogenic in experimental animals. Long term studies on rats and mice indicated that oral MDA treatment was associated with tumors of the thyroid and the liver. From animal data there is a concern on a carcinogenic potential of MDA in humans. The results from the reports on human exposure did not show clearly a carcinogenic activity in humans. The available data are not sufficient to justify the classification as an human carcinogen (cat. 1) However, they warrant the classification as category 2 carcinogen, risk phrase R 45.

The mechanism of MDA carcinogenicity is not yet known. Based on the results of carcinogenicity studies in animals and the results of genotoxicity studies and also in absence of evidence that the appearance of thyroid and liver tumors in rats and mice is a consequence of chronic tissue-damaging (liver) or tissue-stimulating (thyroid) effects a genotoxic mechanism cannot be excluded.

There are no data available in humans or animals on fertility or on developmental effects caused by MDA.

4.2.1 Risk Characterisation

4.2.2 Workplace

4.2.2.1 General remarks on calculations and extrapolations relevant for workplace risk assessment

For several estimations human data are not available. The necessary adjustments of animal data to humans follow the idea of central tendency estimate using the default values and assessment factors given in the **Table 4.2** The assessment factors are generated from substance specific toxicity data supported by plausibility considerations. Interspecies adjustment is based on metabolic rate scaling.

Table 4.2 Assessment factors and default values for extrapolation of effect data

Body weight, human	70 kg
Respiratory volume, human	10 m^3/8 h
Factor for route-to-route extrapolation	
- Oral to dermal	>2
- Oral to inhalation	1
Factor for species extrapolation rat, oral to human, oral	1/10
LAEL to NAEL	1/3

4.2.2.2 Occupational risk assessment

Inhalation of dust and skin exposure are the relevant routes of exposure at workplaces.

The following report concentrates on the main points of concern with regard to the risk characterisation at workplaces.

Acute toxicity

Dermal contact

The starting point for the estimation of the NAEL (human, dermal, acute) is the LOAEL of 3 mg/kg (human, oral, acute). A NAEL of greater than 140 mg/person for acute dermal exposure was calculated. A total dermal dose of greater than 420 mg/person is anticipated to result in liver toxicity.

Dermal exposure of a relevant level is assumed for all applications even with PPE. For all workplace scenarios acute dermal exposure is of concern (see **Table 4.3**).

Conclusion: iii)

Sensitization

Dermal contact

MDA is considered to be a human skin sensitizer. There are no valid data on its sensitization potency. Relevant dermal exposure and contact allergies are expected even with use of PPE. There is concern with regard to all workplaces.

Conclusion: iii)

Repeated dose toxicity (systemic)

Risk assessment for repeated dose toxicity relies upon two essential results: Based on a 2-year rat study with liver and thyroid toxicity a LOAEL of 9 mg/kg/d was determined. Human experience of acute liver toxicity at 3 mg/kg proves a higher sensitivity of humans in response to MDA. Based on acute oral toxicity in rats and humans, a rat-to-human extrapolation factor of 1/10 is assumed.

Inhalation

The starting point for the NAEC calculation is the LOAEL of 9 mg/kg/d (rat, oral, chronic). For inhalation risk assessment an extrapolated NAEC in the range of 2 mg/m^3 was estimated.

The NAEC is compared with the exposure information. Most MOS values are considered of concern (see **Table 4.3**)

Conclusion: iii)

Dermal contact

The basis for the extrapolated NAEL is the LOAEL of 9 mg/kg/d (rat, oral, chronic). For dermal risk assessment an extrapolated NAEL of greater than 40 mg/p/d was estimated.

Repeated dermal exposure is assumed in the chemical industry, in all industrial applications even in case of use of PPE. For skilled trade applications intermittent exposure is assumed. However, because shift average values are rather high, conclusion iii is drawn. All MOS are considered to be of concern. In case of relatively low MOS values chronic liver toxicity is anticipated to occur.

Conclusion: iii)

Combined exposure

For most exposure situations the MOS values for combined exposure show that dermal contact to MDA to a high degree determines risk assessment concerning liver toxicity.

Conclusion: iii) (according to conclusion iii for dermal contact)

Carcinogenicity

MDA is classified as carcinogenic. Carcinogenicity of MDA was established in rodents. The mechanism of tumour development is not clearly demonstrated. It has to be assumed that a genotoxic mechanism is involved in MDA carcinogenicity.

Inhalation

For workplace risk assessment a T25 of 12 mg/m^3 was calculated. The starting point for the calculation is the T25-value of 8.4 mg/kg/d for MDA dihydrochloride (continuous life time exposure in animals). For duration adjustment to workplace conditions an adjustment factor of 2.8 is used. It was assumed that the higher sensitivity of humans concerning liver toxicity applies to carcinogenic potency as well. There are no further data to clarify species differences concerning carcinogenicity. If there is no species difference at all the T25 might be up to one order of magnitude greater than calculated.

For purposes of carcinogenic risk assessment a MOE is calculated.

Assuming the involvement of a genotoxic mechanism most MOE values are of concern (**Table 4.3**). However it should be kept in mind that humans might be less sensitive than assumed.

Conclusion: iiib)

Dermal contact

For workplace risk assessment a dermal T25 of greater than 250 mg/person/d was calculated. The calculation is based on the T25-value of 8.4 mg/kg/d for MDA dihydrochloride (continuous life time exposure in animals). For duration adjustment to workplace conditions an adjustment factor of 2.8 is used. Again, it was assumed that humans are more sensitive than rats and that there may be a genotoxic mechanism.

Repeated dermal exposure is assumed in the chemical industry, in all industrial and skilled trade applications, even in case of use of PPE.

Most MOE values calculated for dermal exposure are very low resulting in high concern for carcinogenicity due to dermal contact. All scenarios are considered of concern.

Conclusion: iiib)

Combined exposure

Carcinogenic risk for combined exposure nearly exclusively is determined by the estimates of dermal exposure.

Conclusion: iiib) (according to **conclusion iiib**) for dermal contact)

The risk characterisation for acute toxicity (inhalation), irritation/corrosivity, sensitization (inhalation), repeated dose toxicity (local, inhalation and dermal) and mutagenicity reveals that there is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already (**conclusion ii**).

MDA is classified as a carcinogenic agent. Reproductive toxicity testing is not complete. Because of relevant data gaps a corresponding risk assessment cannot be performed.

Risk reduction measures are required in view of the carcinogenic properties of this substance, the need for a test to evaluate the reproductive toxicity will be revisited in the light of the risk reduction strategy.

In the following **Table 4.3** results of the occupational risk assessment are presented. Only toxicological endpoints and scenarios leading to conclusion iii are listed.

Table 4.3 Results of the occupational risk assessment (conclusion iii)

Exposure scenario	Acute toxicity, dermal, MOS (conclusion)	Sensitization, dermal (conclusion)	RDT systemic, inh., MOS (concl.)	RDT systemic, dermal, MOS (conclusion)	Carcinogenicity, inh., MOE (concl.)	Carcinogenicity, dermal, MOE (concl.)
Chemical industry						
Manufacturing and further processing as a chemical intermediate (Methylene diphenyl di-isocyanate, MDI) - Dust -Vapour	 >0.3 - 3.3 (iii) >0.5 - 5.6 (iii)	 iii iii	 4 (iii)	 >0.1 - 1 (iii) >0.2 - 2 (iii)	 23 (iiib) iiia	 >0.6 - 6 (iiib) >1 - 10 (iiib)
Production of powdery preparations - Imid preparations, max. 10% MDA (dust) - Curing formulations, max. 60% MDA (dust) - Max. % MDA (dust)	 >3.3 - 35 (iii) >0.5 - 5.6 (iii) >6.7 - 70 (iii)	 iii iii iii		 >1 - 10 (iii) >0.2 - 2 (iii) >2 - 20 (iii)	 96 - 240 (iiib) >96 - 240(iiib) >96 - 240(iiib)	 >6 - 62 (iiib) >1 - 10 (iiib) >12 - 125(iiib)
Industrial area						
Manufacturing of formulations using powdery MDA (dust) Formulating putties: using liquid MDA (approx. 60 %) (vapour)	>0.3 - 3.3 (iii) >0.5 - 5.6 (iii)	iii iii	3 (iii)	>0.1 - 1 (iii) >0.2 - 2 (iii)	20 (iiib) iiia	>0.6 - 6 (iiib) >1 - 10 (iiib)
Production of powdery preparations - Imid preparations, max. 10% MDA (dust) -Curing formulations, max. 60% MDA (dust) - Max. 5% MDA (dust)	 >3.3 - 35 (iii) >0.5 - 5.6 (iii) >6.7 - 70 (iii)	 iii iii iii	 1.6 - 20 (iii) >3 (iii)	 >1 - 10 (iii) >0.2 - 2 (iii) >2 - 20 (iii)	 10 - 120 (iiib) >16 (iiib) >150 (iiib)	 >6 - 62 (iiib) >1 - 10 (iiib) >12 - 125(iiib)
Mixing curing formulations (max. 60% MDA) with resins for epoxies (Dust) Mixing (vapour) Handling of formulations containing MDA and epoxid resins (4.5 - 30%) (Vapour)	>0.3 - 2.8 (iii) >0.3 - 2.8 (iii) >0.5 - 5.6 (iii)	iii iii iii		>0.1 - 1 (iii) >0.1 - 1 (iii) >0.2 - 2 (iii)	>60 (iiib) iiia iiia	>0.5 - 5 (iiib) >0.5 - 5 (iiib) >1 - 10 (iiib)
Mixing curing formulations (max. 5% MDA) with resin for polyurethanes (Dust) Handling of formulations containing MDA and polyurethane (2 -3%) (Vapour)	>3.3 - 33.3 (iii) >5.6 - 56 (iii)	iii iii		>1 - 10 (iii) >2 - 16 (iii)	>600 (iiib) iiia	>6 - 60 (iiib) >10 - 100(iiib)

Table 4.3 continued overleaf

Table 4.3 continued

Exposure scenario	Acute toxicity, dermal, MOS (conclusion)	Sensitization, dermal (conclusion)	RDT systemic, inh., MOS (concl.)	RDT systemic, dermal, MOS (conclusion)	Carcinogenicity, inh., MOE (concl.)	Carcinogenicity, dermal, MOE (concl.)
Handling of formulations containing MDA (0.1 - 10 %) and imid resins - Dust - Vapour	 >1.7 - 16.7 (iii) >1.7 - 16.7 (iii)	 iii iii	7 - 67 (iii)	 >0.5 - 5 (iii) >0.5 - 5 (iii)	40 - 400 (iiib) iiia	>3 - 30 (iiib) >3 - 30 (iiib)
Skilled trade						
Mixing formulations containing MDA (9 - 60 %) with epoxid resins (dust) Handling of formulations containing MDA and epoxid resins (4.5 - 30%) (Vapour)	>0.05 - 0.3 (iii) >0.1 - 0.5 (iii)	iii iii		> 0.02 - 0.08 (iii) >0.03 - 0.16 (iii)	>60 (iiib) iiia	>0.1 - 0.5(iiib) >0.2 - 1 (iiib)

4.2.3 Consumers

Risk characterization with respect to a possible impairment of reproduction by MDA cannot be performed due to lack of valid data for the hazard assessment.

Risk reduction measures are required in view of the carcinogenic properties of this substance, the need for a test to evaluate the reproductive toxicity will be revisited in the light of the risk reduction strategy.

Following the exposure assessment, consumer exposure to MDA is generally not expected.

In case of using products, colored with the notified new azodye Cartasol Yellow an exposure of consumers cannot be excluded due to the possibility of liberation of MDA. A health risk regarding Acute toxicity, Irritation, Corrosivity, Sensitization, Repeated dose toxicity, and Mutagenicity is not expected (**conclusion ii**). Because MDA is considered as a non-threshold carcinogen, for Carcinogenicity **conclusion iiib**) is assigned.

There may be a liberation of MDA from polyurethane-containing medical devices after sterilization by gamma irradiation which cannot be quantified. Therefore, a potential risk of exposure to free MDA cannot excluded for uremic patients or patients who receive blood transfusions frequently**.** Because MDA is considered as a non-threshold carcinogen, for Carcinogenicity **conclusion iiib**) is assigned.

4.2.4 Man indirectly exposed via the environment

Indirect exposure via the environment which is calculated using data for oral intake via drinking water and food results in an intake of a total daily dose of $2.1 \cdot 10^{-5}$ resp. $5.4 \cdot 10^{-7}$ mg/kg bw (local resp. regional scenario). For the derivation of the margin of safety (MOS) the total calculated internal dose at a local exposure of $2.1 \cdot 10^{-5}$ mg/kg bw/d and at a regional exposure of $5.4 \cdot 10^{-7}$ mg/kg bw is compared with the oral LOAEL of 9.0 mg/kg bw/d from a long term study. The MOS is considered to be sufficient regarding the non-neoplastic effects (**conclusion ii**). However, there remains concern due to the carcinogenic properties of MDA (**conclusion iiia**).

5 OVERALL RESULT OF THE RISK ASSESSMENT

5.1 ENVIRONMENT

i) There is need for further information and/or testing

This conclusion is reached for sediments. As no information on the toxicity of sediment organisms is available, a risk characterisation for this compartment is not possible. A long-term toxicity test on a sediment-dwelling organism is recommended.

ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already

This conclusion is reached for the aquatic compartment (excluding sediment), microorganisms in treatment plants, the atmosphere and the terrestrial compartment. The environmental risk assessment revealed that a risk related to these compartments is not expected.

5.2 HUMAN HEALTH

The substance MDA has not been tested for the reproductive toxicity, consequently the risk assessment does not evaluate the risks to any human population for this endpoint.

Risk reduction measures are required in view of the carcinogenic properties of this substance, the need for a test to evaluate the reproductive toxicity will be revisited in the light of the risk reduction strategy.

5.2.1 Workers

iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The main problems are the carcinogenic property of the substance and the dermal exposure situations. Dermal exposure for all scenarios is anticipated at relevant levels because proper use of suitable tested PPE cannot be assumed.

5.2.2 Consumers

iii) There is need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The **conclusion iiia**) is reached because of the risk assessment shows that risks cannot be excluded as the substance is to be considered as a non-threshold carcinogen.

The **conclusion iiib**) is reached because

- sterilization of medical devices consisting of polyurethane components by gamma irradiation should be avoided.
- exposure of consumers should be avoided by including the notified new substance Cartasol Yellow in the regulation to restrict azodyes.

5.2.3 Man exposed via the environment

iii) There is need for limiting the risks; risk reduction measures which are already being applied shall betaken into account

This **conclusion iiia**) is reached because of the risk assessment shows that risks cannot be excluded as the substance is to be considered as a non-threshold carcinogen.

GLOSSARY

Standard term / Abbreviation	Explanation / Remarks and Alternative Abbreviation(s)
Ann.	Annex
AF	assessment factor
BCF	bioconcentration factor
bw	body weight / *Bw*, *b.w.*
°C	degrees Celsius (centigrade)
CAS	Chemical Abstract System
CEC	Commission of the European Communities
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
d	day(s)
d.wt.	dry weight / *dw*
DG	Directorate General
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{50lab}	period required for 50 percent dissipation under laboratory conditions (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
$DT_{90field}$	period required for 90 percent dissipation under field conditions (define method of estimation)
EC	European Communities
EC	European Commission
EC_{50}	median effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
EU	European Union
EUSES	European Union System for the Evaluation of Substances
f_{oc}	organic carbon factor (compartment depending)
g	gram(s)
gw	gram weight
GLP	good laboratory practice
h	hour(s)
ha	Hectares / *h*
HPLC	high pressure liquid chromatography
IARC	International Agency for Research on Cancer
IC_{50}	median immobilisation concentration or median inhibitory concentration 1 / *explained by a footnote if necessary*
ISO	International Standards Organisation
IUPAC	International Union for Pure Applied Chemistry
kg	kilogram(s)
kPa	kilo Pascals
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	solid-water partitioning coefficient of suspended matter

l	litre(s) / *L*
log	*logarithm to the basis 10*
$L(E)C_{50}$	lethal concentration, median
m	meter
µg	microgram(s)
mg	milligram(s)
MOS	margins of safety
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
pH	potential hydrogen -*logarithm* (to the base 10) of he hydrogen ion concentration $\{H^+\}$
pKa	-*logarithm* (to the base 10) of the acid dissociation constant
pKb	-*logarithm* (to the base 10) of the base dissociation constant
Pa	Pascal unit(s)
PEC	predicted environmental concentration
PNEC(s)	predicted no effect concentration(s)
$PNEC_{water}$	predicted no effect concentration in water
(Q)SAR	quantitative structure activity relation
STP	sewage treatment plant
TGD	Technical Guidance Document[1]
UV	ultraviolet region of spectrum
UVCB	Unknown or Variable composition, Complex reaction products or Biological material
v/v	volume per volume ratio
w/w	weight per weight ratio

[1] Commission of the European Communities, 1996. Technical Guidance Document in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Commission of the European Communities, Brussels, Belgium. ISBN 92-827-801[1234]